Originak Article

Consumption of antibiotics within ambulatory care in Malta

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Abstract

Background: Antibiotic use is recognised as the most important driver for the development of antimicrobial resistance in community pathogens. Surveillance is therefore critical for improvement programmes.

Methods: Antimicrobial distribution data for the years 2007 to 2009 were collected retrospectively by the National Antibiotic Committee from all licensed wholesale distributors (WSL) in Malta and analysed according the World Health Organization Anatomical Therapeutic Chemical classification (ATC) level 4 criteria.

Results: Overall consumption increased from 18.6 defined-daily-doses/1000-inhabitant-days (DID) in 2007 to 22.7 DID in 2008 and reached 24.4 DID in 2009 - an increase of more than 30% over the three years, Penicillins with beta-lactamase inhibitor increased in volume (7.1 to 8.8 DID) but decreased in proportion (38.4% to 36.0%) between 2007 and 2009. On the other hand, second generation cephalosporins increased in both volume and proportion (2.8 to 5.4 DID; 15.0% to 22.0%). The proportion for macrolides remained stable at approximately 16% but the volume of use again increased (2.9 DID to 3.9 DID). Fluoroquinolone proportion decreased from 9.1% to 6.8%, maintaining a stable volume of use in the region of 1.7 DID.

Conclusions: Antibiotic consumption in Malta has shown a consistent increasing trend over the past three years, despite a reduction in over-the-counter acquisition. Furthermore, there is evidence of a strong, and possibly unjustified, prescription of wide spectrum antibacterials. This is potentially an important driver for documented resistance in *Streptococcus pneumoniae* and *Escherichia coli* and needs to be addressed at a national level.

Keywords

Antimicrobial consumption, surveillance, ambulatory care, Malta

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Introduction

Antimicrobial consumption is recognised as an important driver for resistance amongst community pathogens, especially *Streptococcus pneumoniae* and *Escherichia coli*.[1] For this reason, surveillance of antibiotic use has been undertaken within most of the countries of the European Union.[2] The data sources for these surveillance systems have normally been either reimbursement or sales statistics. Malta has been participating in the European Surveillance of Antimicrobial Consumption (ESAC) since its inception in 2001 but has only managed to contribute hospital statistics. Indeed, in a 2006 publication, Vander Stichele and colleagues commented on the lack of availability of ambulatory care in Malta stating that "for 14 of the 15 sets of valid hospital data (all except Malta) the ambulatory care data were also available within the ESAC data collection systems, and hence total antibiotic exposure could be calculated, as well as the mix between ambulatory and hospital care."[3]

Due to the absence of a reimbursement system in ambulatory medical care in Malta, the majority of antibiotic prescriptions are purchased out-of-pocket from private community pharmacies. In addition, pharmacies do not keep an electronic database of prescriptions dispensed and, therefore, data at prescription level is not available either. For this reason, it is not possible to utilise the usual methods adopted in EU countries to perform ambulatory care antibiotic consumption. As a result, the only feasible way of collecting antimicrobial use data is through wholesalers' distribution records to pharmacy outlets. This became possible following national legislation establishing the National Antibiotic Committee in 2008 (legal notice 122/2008) as an intersectoral mechanism (ISM) with a legal mandate to undertake antibiotic use surveillance (https://ehealth.gov.mt/healthportal/others/regulatory_councils/national_antibiotic_committee/introduction.aspx). The presence of such a national ISM, as well as continuous consumption surveillance, is mandated by European Council Recommendation of 15.11.2001

on the Prudent Use of Antimicrobial Agents in human medicine (2002/77/EC)(http://europa.eu/legislation_summaries/public_ health/threats_to_health/c11569_en.htm).

It is well established that up to 50% of antimicrobial agents prescribed in the community setting are often inappropriate.[4] This is often the result of addressing the wrong pathogen (e.g. use for viral upper respiratory tract infections) or the wrong drug (inappropriate choice of antimicrobial and/or inadequate dose). Wide spectrum antibiotics are well known to predispose towards resistance much more strongly than narrow spectrum equivalents.[5] Indeed unjustified perceptions of resistance, based on inadequate knowledge of the local epidemiology, may result in unnecessary prescription of wide spectrum agents.[6] Antimicrobials prescribed in the community setting, especially for respiratory infections, account for the biggest proportion of antibiotics in any country.[6] It is therefore critical to identify and address inappropriate prescribing patterns. This can be undertaken by quantifying antimicrobial use in the ambulatory care sector in order to identify any apparent or significant changes in consumption trends, both overall as well as for different drug classes.

Methods

Licensed wholesale distributors (WSL) were requested to submit their antimicrobial distribution records for the year 2007, 2008 and 2009. Data were submitted in a format compatible with Microsoft Excel 2003® using the World Health Organization (WHO) anatomical therapeutic chemical (ATC) classification and defined daily dose (DDD).[7] Information was only requested about systemic agents in line with the ESAC methodology.[8] Information collected included: international non-proprietary name (iNN), dosage form, number of doses per package (for oral suspensions this is equivalent to total volume divided by 5ml unit dose), unit dose (in grams per tablet/capsule/phial/5ml dose), and route of administration (oral/rectal/parenteral). Data were sent via email to nac.mhec@gov.mt. Following submission, data were cleaned and validated to remove any errors in data entry. When such inaccuracies were minimal these were edited centrally. If the extent of incorrect data entered was more complex, the WSL was informed about the necessary steps to be taken for correcting the issues identified. The Government Health Services database was utilized in order to extract data for public community pharmacies. Such entitlement was related either to schedule II (Pink Card holders) and/or specified chronic medical conditions (Schedule V conditions with entitlement to antibiotics). Data for the public sector included distribution data of the Government Pharmaceutical Services (GHPS) to both Health-centre dispensaries, out-patients dispensary of St. Luke's Hospital (only for 2007) and subsequently Mater Dei Hospital out-patient dispensing from 2008 including the Pharmacy of your choice (POYC) scheme.

Special attention was paid to avoid duplicate entries from WSLs who distribute to private community pharmacies as well as the GHPS and/or other WSL's. Therefore, distribution by one WSL to another WSL or GHPS were excluded from the analyses; only distribution data to 'private community pharmacies' were included from the data provided by WSL, in addition to the GHPS distribution data.

Annual returns were analysed separately using a metadata set on Microsoft Excel 2003®. Data were aggregated at ATC level 5 (ATC5), i.e., generic name, but reported only at the fourth ATC level (ATC4 e.g., penicillin with beta-lactamase inhibitor – J01CR) to maintain confidentiality about specific products and brands. For the sake of comparison between public and private sector, data were aggregated at ATC level 3 (ATC3 e.g., penicillins – J01C). Data were expressed as DDD per 1000-inhabitant days (DID) to take into account demographic changes from year to year.

Results

All the licensed wholesale Maltese distributors replied to the respective notification letters by submitting either distribution data for the respective years (2007-2009) or a nil return stating that no antimicrobial agents were included in their distribution portfolio for the local market. Table 1 shows the consumption in DID and the proportion (%) per year for the six most utilised antimicrobial classes (ATC4) and the total annual DID. It also shows the percentage change in DID from 2007 to 2009. Overall consumption of antimicrobial agents for systemic use increased from 18.6 DID in 2007 to 24.4 DID in 2009. This corresponds to a 30% increase in consumption over the three years. Penicillins with beta-lactamase inhibitor (J01CR) increased in volume (7.1 to 8.8 DID) but decreased in proportion (38.4% to 36.0%) between 2007 and 2009. On the other hand, second generation cephalosporins (J01DC) increased in both volume and proportion over the three years (2.8 to 5.4 DID; 15.0% to 22.0%). The proportion for macrolides (J01FA) remained stable at approximately 16% but the actual use volume increased from 2.9 DID to 3.9 DID. Fluoroquinolone use decreased from 9.1% to 6.8% maintaining a stable volume of use around 1.7 DID.

Analysis of the data by distribution type (public versus private community pharmacies) showed a great disparity in drug classes utilised (Table 2). More than 90% of antibiotics distributed [mean: 91.8%; 95% CI: 88.4-95.2%] were procured by private pharmacies (Figure 1), indicating that the vast majority of national consumption in Malta is very much dependent on private sector dispensing.

The proportion of antibiotic classes at ATC level 4 differed considerably between the private and public sector as shown in Table 2. Despite these differences the most used drug-class in both sectors was penicillin with beta-lactamase inhibitor (J01CR), specifically co-amoxiclav. Narrower spectrum penicillins (J01CE) and nitrofuran derivatives (J01XE) were used rarely in the private sector and appeared in the top 12

Table 1. *Total consumption in ambulatory care for the years 2007-2009 and changes between 2007 and 2009*

Year	2007		2008		2009		% Δ in DID*	Δ in proportion
ATC4	**DID***	**%**	**DID***	**%**	**DID***	**%**	**(2007-9)**	**(2007-9)**
J01CR (penicillin + beta-lactamase inhibitor)	7.1	38.4	8.3	36.5	8.8	36.0	23.0%	-2.3%
J01DC (2nd generation cephalosporins)	2.8	15.0	4.7	20.7	5.4	22.0	93.2%	7.1%
J01FA (macrolides)	2.9	15.7	3.5	15.5	3.9	15.8	32.0%	0.1%
J01MA (fluoroquinolones)	1.7	9.1	1.8	7.8	1.7	6.8	-1.3%	-2.2%
J01CA (extended spectrum penicillins)	1.4	7.4	1.4	6.0	1.3	5.3	-6.4%	-2.1%
J01AA (tetracyclines)	0.9	5.0	1.1	4.8	1.1	4.6	20.7%	-0.4%
Others (30 classes)	1.8	9.5	2.0	8.7	2.3	9.4	29.5%	-0.1%
Total consumption	18.6	100	22.7	100	24.4	100	31.0%	-

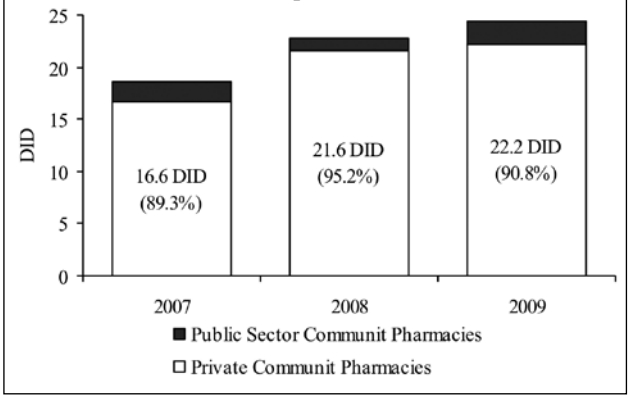
Key: *DID = defined daily doses per 1000 inhabitant days: Δ = change

most used antibiotics only for the public sector. On the contrary extended-spectrum drugs like 2nd generation cephalosporins (J01DC) and fluoroquinolones (J01MA) ranked high in the private pharmacies.

Data from the Microbiology Laboratory of Mater Dei Hospital indicated that the increase in consumption of 2nd generation cephalosporins during the study period was accompanied by an increase in resistance to the same class of drugs in *Escherichia coli* isolates of likely community origin (Health-centres and Accident & Emergency Department) as shown in Figure 2.

The drug class that showed the highest increase in consumption between 2007 and 2009 were the neuraminidase inhibitors. This increase coincides with the H1N1 pandemic influenza during 2009, and was observed in both the private as well as the public sector.

Figure 1: Distribution of consumption by private and public sectors respectively. The DID and percentage of total DID is shown for the private sector



Discussion

Our surveillance data confirm that consumption of antibiotics in ambulatory care within Malta shows clear evidence of a consistent increase over the past years, which seems to be predominantly attributable to an increase in the use of second generation cephalosporins. Nevertheless, penicillins with beta-lactamase inhibitor, despite decreasing in the proportion, still showed a net increase in DID. This data are very worrying. Penicillins with beta lactamase inhibitors, cephalosporins and fluoroquinolones are well recognised drivers for *Clostridium difficile* enterocolitis even in community settings.[9] Above all, it is a matter of grave concern that ambulatory care consumption in Malta relies almost exclusively on four antimicrobial classes - all of which are highly broad spectrum. Penicillins with beta-lactamase-inhibitor, second generation cephalosporins, macrolides and fluoroquinolones have all been strongly linked with the development of resistance. Cephalosporin and fluoroquinolone use is a major driver for methicillin resistance in *Staphylococcus aureus* (MRSA).[5] Macrolide resistance and penicillin non-susceptibility in *Streptococcus pneumoniae* poses major challenges in the treatment of community associated pneumonia and meningitis; in both cases, emergence has been correlated with consumption patterns.[9-11] Macrolide resistance is also a concern in *Streptococcus pyogenes,* where again macrolide consumption has been implicated.[12] The latest emerging threat is the development of resistance within *Escherichia coli* to cephalosporins and fluoroquinolones[5,9] Indeed, the reported local increase in use of 2nd generation cephalosporins was accompanied by a corresponding increase in resistance within community *E. coli* isolates. This association between consumption of cephalosporins and extended-spectrum-beta-

Table 2. *Proportion of antibacterials within private and public settings (Showing the top 12 drug classes)*

Private Community Pharmacies			
Antimicrobial class (ATC4 level)	2007	2008	2009
J01CR (penicillin + beta-lactamase inhibitor)	36.0%	35.4%	33.2%
J01DC (2nd generation cephalosporins)	16.7%	21.8%	24.3%
J01FA (macrolides)	17.0%	16.2%	17.2%
J01MA (fluoroquinolones)	9.9%	8.2%	7.5%
J01CA (extended spectrum penicillins)	7.2%	5.7%	4.3%
J01AA(tetracyclines)	5.4%	5.0%	4.9%
P01AB (oral/rectal metronidazole)	1.0%	2.0%	1.7%
D01BA (systemic antimycotics for dermatological use)	1.7%	1.5%	1.4%
J01FF (lincosamides)	1.4%	0.9%	0.8%
J01EE (sulphanamides/trimethoprim)	0.8%	0.7%	0.6%
J01DD (3rd generation cepholosporins)	0.5%	0.7%	0.9%
J05AH (neuraminidase inhibitor)	0.4%	0.1%	1.2%
Others	2.1%	1.8%	2.0%
Public Community Pharmacies			
Antimicrobial class (ATC4 level)	2007	2008	2009
J01CR (penicillin + beta-lactamase inhibitor)	58.0%	59.3%	64.1%
J01CA (extended spectrum penicillins)	9.4%	11.4%	15.6%
P01AB (oral/rectal metronidazole)	5.2%	4.3%	2.9%
J01FA (macrolides)	4.4%	2.1%	1.7%
J01CE (narrow spectrum penicillins)	4.0%	3.3%	1.2%
J01DB (1st generation cephalosporins)	3.1%	3.3%	1.7%
J01EE (sulphanamides/trimethoprim)	3.2%	3.1%	1.4%
D01BA (systemic antimycotics for dermatological use)	1.5%	1.1%	1.6%
J01XE (nitrofuran derivatives)	1.7%	1.5%	1.4%
J05AH (neuraminidase inhibator)	0.0%	0.0%	3.2%
J01FF (lincosamides)	1.5%	1.3%	0.9%
J01AA(tetracyclines)	1.6%	0.7%	1.0%
Others	6.7%	8.4%	1.99%

lactamases (ESBL) has already been documented in other countries.[13] This resistance originating from the community has a potential knock-on effect on hospitals as it predisposes to subsequent nosocomial cross-transmission of resistant Gram negative bacteria. This in turn has significant patient safety repercussion due to potential ineffective empiric antibiotics and requirement for parenteral third line antimicrobials following therapeutic failure in the community.[14] Indeed, ESBL producing bacteria which initially originated in the community are now recognised as important pathogens responsible for healthcare associated infections.[15]

It should additionally be remarked that systemic agents are not the only pharmaceuticals that induce antibiotic resistance. Topical antibiotics are equally problematic in this respect. The National Antibiotic Committee's newsletter issued for the 2010 European Antibiotic Awareness Day (EAAD) (https://ehealth.gov.mt/ download.aspx?id=4904) highlighted the increase in fusidic acid resistance in community *Staphylococcus aureus* strains which is almost certainly attributable to over and misuse of fusidic acid topical preparations in Malta. Indeed a novel strain of MRSA has been identified in Malta that differs from previously identified strains only by the presence of a fusidic acid resistant gene.[16] This type of MRSA is increasingly being isolated even in patients without a previous history of hospitalisation.

Maltese antimicrobial consumption for 2007 was close to the median reported by the European Surveillance of Antimicrobial

Figure 2. *Trends in consumption of 2nd generation cephalosporins and percentage resistance (%R) in Escherichia coli isolates obtained from Health Centres (HC) and Accident & Emergency Dept – St. Luke's/Mater Dei Hospital (A&E) for the years 2007 to 2009*

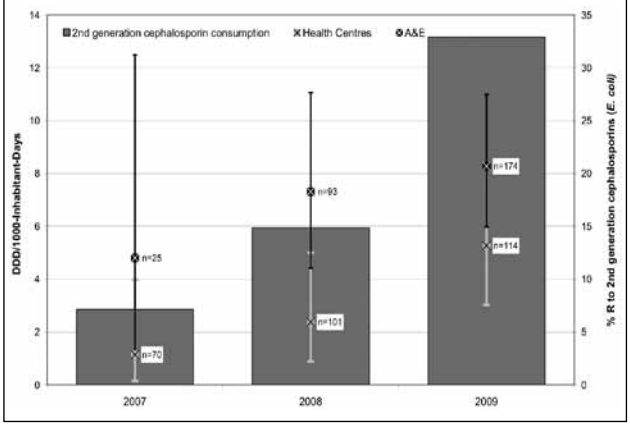
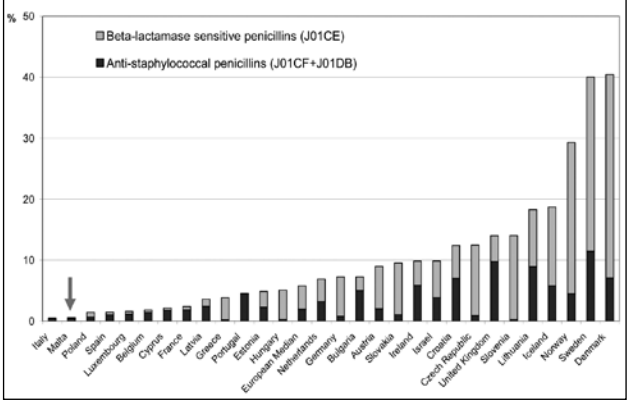


Figure 3. *Proportion of narrow spectrum antibacterials in ambulatory care across 28 European countries and Israel (arrow indicates Malta data)*[23]



Consumption (ESAC) network for 24 European countries during the same time period.[17] This was rather surprising because previous publications had suggested a high level of antibiotic consumption in the country.[18] The 2009 'Special Eurobarometer 338' survey (http://ec.europa.eu/public_ opinion/archives/ebs/ebs_338_en.pdf) showed that 55% Maltese respondents said that they had taken an antibiotic in the previous year; this was the second highest figure in the whole EU.[19] This discrepancy could be explained in a number of ways. WSLs could have underreported distribution sales; we do not believe this to be the case since the patterns of the notified over the three years are consistent and credible. A more likely explanation could be that inadequately lower doses are utilised in Malta. A typical example would be co-amoxiclav 375mg being prescribed where the 625mg would be more appropriate, as is the norm in EU countries. The 2009 Eurobarometer study also confirmed that the vast majority of antibiotic consumption in Malta is the result of medical prescription. Indeed a consistent and credible reduction in over the counter dispensing has been seen in the past decade. The self-medication rate of 19% that was reported in 2001,[20] had already fallen to 5.6% by 2003;[21] the 2009 Eurobarometer study confirmed a further reduction to 4%, which falls practically within the EU median. This improvement can be attributed to annual campaigns and initiative for better antibiotic use addressed at the public as well as doctors and pharmacists, especially related to the annual EAAD.[22] Comparison with European ambulatory care data also highlights the negligible consumption in Malta of narrow spectrum drugs such as first generation cephalosporins, narrow-spectrum penicillins and anti-staphylococcal penicillins (Figure 3).[23] It is not a coincidence that Scandinavian countries have managed to avoid significant resistance problems over the past three decades when up to half of their ambulatory care antibiotics prescribed are still phenoxymethyl- and benzyl- penicillins.[24]

Our healthcare-system is different from that found in most European countries where individual prescription and indication data are available as they are linked to reimbursement. Therefore, Eurobarometer provides the only possible information linking antimicrobial use for inappropriate indications (colds and influenza); Malta had one of the higher proportion of respondents (26%) who were prescribed antibiotics for "influenza".[19]

This first effort to collect national antibiotic consumption statistics in Malta has collected, for the first time, validated national statistics for use of these pharmaceuticals. One possible limitation of these data lies in the fact that some WSL ceased operation since the start of the ongoing surveillance and were therefore included only in the initial years whilst some others started operations and were included in later years. However, we do not believe this influenced significantly the overall consumption as antimicrobial agents are dispensed from licensed pharmacies, the number of which did not change considerably. Neither did trends in the Maltese population with an average estimated population for the 3 years of 412,290 inhabitants (source: http://www.nso.gov.mt/demographic reviews: 2007 [410,290]; 2008 [413,609] and; 2009 [412,970]). Therefore, any change in volume of antibiotic use per 1000-inhabitant days cannot be attributed to changes in population over the years. Furthermore, the increase can neither be due to seasonality since time scales are equal.

An unavoidable limitation of the data collection was our inability to breakdown the data into monthly or quarterly periods to assess seasonal variations in prescribing. Indeed seasonal variation has been strongly reported from the high consuming countries of Southern Europe.[25] This could be equally relevant in the local setting and suggests the need for more detailed surveillance to assess the degree of seasonal variability in antibiotic prescribing in Malta.

In conclusion, our results confirm a heavy reliance on antibiotics, especially those of broad spectrum formulation, by

local prescribers. Indeed, the most striking characteristic of the local data was the negligible consumption of narrow spectrum and penicillinase resistant penicillins as well as first generation cephalosporins. This heavy dependence on wide spectrum antibiotics at the expense of narrow spectrum products is not justified by evidence based international guidelines nor by local resistance epidemiology. It is arguably the most likely driver for the documented local increase in resistance in macrolide resistant *Streptococcus pneumoniae,* ESBL producing *Escherichia coli* and MRSA.[26] It also highlights the challenge facing the National Antibiotic Committee to foster better antibiotic prescribing habits in local medical practitioners. This is not an easy task, especially as national culture is a key driver behind inappropriate prescribing.[27] It is nevertheless a challenge that needs to be addressed since continuation of current trends risks a vicious cycle of ever increasing and expanding resistance that will have a direct patient safety repercussion on the Maltese population.

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