Μελέτη των επιπτώσεων της εφαρμογής Προγράμματος Διαχείρισης της Ορθολογικής Χρήσης Αντιβιοτικών (Antibiotic Stewardship) για ενήλικες ασθενείς σε πανεπιστημιακό νοσηλευτικό ίδρυμα της Ελλάδας

ΝΙΚΟΛΑΟΣ ΣΠΕΡΝΟΒΑΣΙΛΗΣ

Παθολόγος – Λοιμωξιολόγος

Διδακτορική διατριβή

Ιατρική Σχολή, Πανεπιστήμιο Κρήτης

Ηράκλειο, 2023

A study on the impact of the Implementation of an Antibiotic Stewardship Program for adult patients in a Greek academic hospital

NIKOLAOS SPERNOVASILIS

Internist – Infectious Diseases Specialist

PhD Dissertation

School of Medicine, University of Crete

Heraklion, 2023

ΙΠΠΟΚΡΑΤΟΥΣ ΟΡΚΟΣ

Ὄμνυμι Ἀπόλλωνα ἰητρὸν, καὶ Ἀσκληπιὸν, καὶ Ὑγείαν, καὶ Πανάκειαν, καὶ θεοὺς πάντας τε καὶ πάσας, ἵστορας ποιεύμενος, ἐπιτελέα ποιήσειν κατὰ δύναμιν καὶ κρίσιν ἐμὴν ὅρκον τόνδε καὶ ξυγγραφὴν τήνδε. ἡγήσασθαι μὲν τὸν διδάξαντά με τὴν τέχνην ταύτην ἴσα γενέτῃσιν ἐμοῖσι, καὶ βίου κοινώσασθαι, καὶ χρεῶν χρῄζοντι μετάδοσιν ποιήσασθαι, καὶ γένος τὸ ἐξ αὐτέου ἀδελφοῖς ἶσον ἐπικρινέειν ἄῤῥεσι, καὶ διδάξειν τὴν τέχνην ταύτην, ἢν χρῄζωσι μανθάνειν, ἄνευ μισθοῦ καὶ ξυγγραφῆς, παραγγελίης τε καὶ ἀκροήσιος καὶ τῆς λοιπῆς ἁπάσης μαθήσιος μετάδοσιν ποιήσασθαι υἱοῖσί τε ἐμοῖσι, καὶ τοῖσι τοῦ ἐμὲ διδάξαντος, καὶ μαθηταῖσι συγγεγραμμένοισί τε καὶ ὡρκισμένοις νόμῳ ἰητρικῷ, ἄλλῳ δὲ οὐδενί. διαιτήμασί τε χρήσομαι ἐπ' ὠφελείῃ καμνόντων κατὰ δύναμιν καὶ κρίσιν ἐμὴν, ἐπὶ δηλήσει δὲ καὶ ἀδικίῃ εἴρξειν. Οὐ δώσω δὲ οὐδὲ φάρμακον οὐδενὶ αἰτηθεὶς θανάσιμον, οὐδὲ ὑφηγήσομαι ξυμβουλίην τοιήνδε. ὁμοίως δὲ οὐδὲ γυναικὶ πεσσὸν φθόριον δώσω. Ἁγνῶς δὲ καὶ ὁσίως διατηρήσω βίον τὸν ἐμὸν καὶ τέχνην τὴν ἐμήν. Οὐ τεμέω δὲ οὐδὲ μὴν λιθιῶντας, ἐκχωρήσω δὲ ἐργάτῃσιν ἀνδράσι πρήξιος τῆσδε. Ἐς οἰκίας δὲ ὁκόσας ἂν ἐσίω, ἐσελεύσομαι ἐπ' ὠφελείῃ καμνόντων, ἐκτὸς ἐὼν πάσης ἀδικίης ἑκουσίης καὶ φθορίης, τῆς τε ἄλλης καὶ ἀφροδισίων ἔργων ἐπί τε γυναικείων σωμάτων καὶ ἀνδρώων, ἐλευθέρων τε καὶ δούλων. Ἃ δ' ἂν ἐν θεραπείῃ ἢ ἴδω, ἢ ἀκούσω, ἢ καὶ ἄνευ θεραπηίης κατὰ βίον ἀνθρώπων, ἃ μή κρή ποτε ἐκλαλέεσθαι ἔξω, σιγήσομαι, ἄῤῥητα ἡγεύμενος εἶναι τὰ τοιαῦτα. Ὅρκον μὲν οὖν μοι τόνδε ἐπιτελέα ποιέοντι, καὶ μὴ ξυγχέοντι, εἴη ἐπαύρασθαι καὶ βίου καὶ τέχνης δοξαζομένῳ παρὰ πᾶσιν ἀνθρώποις ἐς τὸν αἰεὶ χρόνον. παραβαίνοντι δὲ καὶ ἐπιορκοῦντι, τἀναντία τουτέων

DOCTORAL DISSERTATION

A study on the impact of the Implementation of an Antibiotic Stewardship Program for adult patients in a Greek academic hospital

By Nikolaos Spernovasilis

ADVISORY COMMITTEE

Professor Diamantis Kofteridis (supervisor)

Professor Emeritus Achillleas Gikas

Professor Georgios Chamilos

EXAMINATION COMMITTEE

Professor Diamantis Kofteridis (supervisor)

Professor Emeritus Achillleas Gikas

Professor Georgios Chamilos

Professor Ekaterini Antoniou

Associate Professor Evangelos Kritsotakis

Assistant Professor Theodosios Filippatos

Assistant Professor Petros Ioannou

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

Μελέτη των επιπτώσεων της εφαρμογής Προγράμματος Διαχείρισης της Ορθολογικής Χρήσης Αντιβιοτικών (Antibiotic Stewardship) για ενήλικες ασθενείς σε πανεπιστημιακό νοσηλευτικό ίδρυμα της Ελλάδας

Νικολάου Σπερνοβασίλη

ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ

Καθηγητής Διαμαντής Κοφτερίδης (επιβλέπων)

Ομότιμος Καθηγητής Αχιλλέας Γκίκας

Καθηγητής Γεώργιος Χαμηλός

ΕΞΕΤΑΣΤΙΚΗ ΕΠΙΤΡΟΠΗ

Καθηγητής Διαμαντής Κοφτερίδης (επιβλέπων)

Ομότιμος Καθηγητής Αχιλλέας Γκίκας

Καθηγητής Γεώργιος Χαμηλός

Καθηγήτρια Αικατερίνη Αντωνίου

Αναπληρωτής Καθηγητής Ευάγγελος Κριτσωτάκης

Επίκουρος Καθηγητής Θεοδόσιος Φιλιππάτος

Επίκουρος Καθηγητής Πέτρος Ιωάννου

Στους παππούδες μου, Ευάγγελο Διαλυνά και Νικόλαο Σπερνοβασίλη,

Στη γιαγιά μου, Μαρία Διαλυνά,

Στη μητέρα μου, Ελευθερία Διαλυνά

Στη θεία μου, Δόξα Διαλυνά

Acknowledgments

This doctoral thesis was conducted in the adult wards and units of the University General Hospital of Heraklion, in collaboration with the hospital's Laboratory of Microbiology and Department of Pharmacy, and the Laboratory of Biostatistics of the School of Medicine of the University of Crete, under the supervision of Professor Diamantis Kofteridis (principal supervisor) and Professors Georgios Chamilos and Achilleas Gikas (co-supervisors).

I would like to express my deepest gratitude to all those who helped in this project:

a) Professor Diamantis Kofteridis for the opportunity he gave me to be involved with the concept of antimicrobial stewardship, and for his continuous guidance and active participation to complete this clinical project during my fellowship in Infectious Diseases under his supervision.

b) Professor Georgios Chamilos for introducing me in the world of Infectious Diseases as his resident doctor for approximately four of the five years of my residency in Internal Medicine.

c) Professor Emeritus Achilleas Gikas for connecting me with the Network of the Infectious Diseases Doctors in Greece and Europe and for his continuous support and counselling.

d) Associate Professor Evangelos Kritsotakis for his significant contribution in the analysis of the data related to this project.

e) The staff of the Microbiological Laboratory and the Department of Pharmacy of the University Hospital of Heraklion for their contribution.

f) All doctors of the adult wards and units of the University Hospital of Heraklion for their cooperation.

Ευχαριστίες

Η παρούσα διδακτορική διατριβή εκπονήθηκε στις κλινικές και στις μονάδες νοσηλείας ενηλικών στο Πανεπιστημιακό Γενικό Νοσοκομείο Ηρακλείου (Πα.Γ.Ν.Η.) σε συνεργασία με το Μικροβιολογικό Τμήμα και το Φαρμακείο του Νοσοκομείου, υπό την επίβλεψη του Καθηγητή κ. Διαμαντή Κοφτερίδη και με συνεπιβλέποντες τον Καθηγητή κ. Γεώργιο Χαμηλό και τον Ομότιμο Καθηγητή κ. Αχιλλέα Γκίκα.

Θα ήθελα να εκφράσω τη βαθιά μου ευγνωμοσύνη σε όλους όσους βοήθησαν στην πραγματοποίηση της διατριβής:

α) Στον Καθηγητή κ. Διαμαντή Κοφτερίδη για την ευκαιρία που μου παρείχε να εμπλακώ στην έννοια της διαχείρισης/επιμελητείας της ορθολογικής χρήσης των αντιμικροβιακών και για τη συνεχή καθοδήγηση και ενεργό συμμετοχή του προς την ολοκλήρωση της συγκεκριμένης διατριβής κατά τη διάρκεια της εξειδίκευσής μου στη Λοιμωξιολογία υπό την επίβλεψή του.

β) Στον Καθηγητή κ. Γεώργιο Χαμηλό, ο οποίος με εισήγαγε στον κόσμο της Λοιμωξιολογίας, όντας ειδικευόμενός του για περίπου τέσσερα από τα πέντε χρόνια της ειδικότητάς μου στην Εσωτερική Παθολογία.

γ) Στον Ομότιμο Καθηγητή κ. Αχιλλέα Γκίκα για τις ευκαιρίες διασύνδεσης που μου παρείχε με τα ελληνικά και ευρωπαϊκά δίκτυα Λοιμωξιολόγων, καθώς επίσης και για τη συνεχή υποστήριξη και καθοδήγησή του.

δ) Στον Αναπληρωτή Καθηγητή κ. Ευάγγελο Κριτσωτάκη για την εξαιρετικά σημαντική συμβολή του στην ανάλυση των δεδομένων τα οποία σχετίζονται με την παρούσα διατριβή.

ε) Στο προσωπικό του Μικροβιολογικού Εργαστηρίου και του Φαρμακείου του Πα.Γ.Ν.Η. για τη συνεισφορά τους.

στ) Σε όλους τους ιατρούς των κλινικών και μονάδων νοσηλείας ενηλίκων του Πα.Γ.Ν.Η. για τη συνεργασία τους.

Table of Contents

Abbreviations (in alphabetical order)

AMR: antimicrobial resistance

ASP: antimicrobial stewardship program

BMI: body mass index

CAI: community-acquired infection

CDC: Centers for Disease Control and Prevention

CDI: *Clostridioides difficile* infection

COVID-19: Coronavirus Disease 2019

cpCRA: carbapenemase-producing CR *Acinetobacter*

cpCRE: carbapenemase-producing carbapenem-resistant *Enterobacteriaceae*

cpCRP: carbapenemase-producing CR *Pseudomonas*

CR: carbapenem-resistant

CRBSI: catheter-related blood stream infection

DDD: Define Daily Doses

DHP-1: dehydropeptidase 1

ECDC: European Centre for Disease Prevention and Control

EMA: European Medicines Agency

ESBL: extended-spectrum beta-lactamase

FDA: Food and Drug Administration

GNB: Gram-negative bacteria

HAI: hospital-acquired infection

HAP: hospital-acquired pneumonia

HGT: horizontal gene transfer

ICU: intensive care unit

ID: infectious diseases

IDSA: Infectious Diseases Society of America

IMP: imipenemase

IPC: infection prevention and control

LRTI: lower respiratory tract infection

MDR: multi-drug resistance (or resistant)

MDRO: multidrug-resistant organism

MexAB-OprM: multidrug efflux system AB-outer membrane protein M

MRSA: methicillin-resistant *Staphylococcus aureus*

NDM: New Delhi metallo-β-lactamase

OXA: oxacillin-hydrolyzing

PBP: penicillin-binding protein

PD: patient-days

PDR: pan-drug resistance (or resistant)

PPS: point prevalence survey

QI: quality indicators

SHEA: Society for Healthcare Epidemiology of America

SP: surgical prophylaxis

SSI: surgical site infection

UTI: urinary tract infection

VIM: Verona integron-encoded metallo-β-lactamase

VRE: vancomycin-resistant enterococci

XDR: extremely-drug resistance (or resistant)

List of Figures

List of Tables

Summary

***Introduction*:** Antimicrobial resistance (AMR) is one of the most important public health problems worldwide. The misuse and overuse of antimicrobials, mainly antibiotics, is one of the main drivers of the AMR. Greece is among the countries characterized by high rate of multidrug-resistant organisms (MDROs) in the community and the hospital sector, and by increased use of broad-spectrum antibiotics, including carbapenems. The aim of this dissertation was to evaluate the impact of a carbapenem-focused antimicrobial stewardship program (ASP) for adult patients in a Greek academic hospital on the quality of antimicrobial prescribing, the overall consumption of last-line antibiotics with activity against Gram-negative bacteria, patient outcomes, and on the behavior of the treating physicians regarding the management of infections caused by MDROs.

***Methods*:** This dissertation included three different studies conducted in the University Hospital of Heraklion, in Greece. A carbapenem-focused ASP was implemented between 1st of January 2020 and 31st of December 2020 in all adult wards of the hospital. A repeated point prevalence survey (PPS) was performed among all adult inpatients before and after implementing the ASP to assess its impact on the quality of antimicrobial prescribing. Furthermore, a quasi-experimental, before–after cohort study was undertaken, comparing the 12-month pre-intervention period with the 12-month intervention period regarding the consumption of broad-spectrum antibiotics with activity against Gram-negative bacteria and patient outcomes. Finally, a cross-sectional study was conducted among all resident and specialist doctors of our hospital's adult wards to evaluate the impact of this carbapenem-focused ASP on their perceptions, attitudes, and practices towards the management of infections caused by difficult-to-treat bacteria.

Results: The repeated PPS showed a statistically significant improvement in several quality indicators (QIs) related to antimicrobial prescribing after the implementation of the ASP. Specifically, the rate of documentation in patient files of the reason and of the stop/review date of antimicrobial administration was significantly higher ($p < 0.001$) in the second PPS, while full compliance to national or international treatment guidelines was also significantly increased from 61.8% to 73.6% ($p = 0.003$). The quasi-experimental cohort study demonstrated a statistically significant decrease of −4.9 Define Daily Doses (DDD)/100 patient-days (PD) (95% CI −7.3 to −2.6; $P = 0.007$) in carbapenem use and a statistically significant increase only in the use of piperacillin/tazobactam [+2.1 DDD/100 PD (95% CI 1.0–3.3; $P = 0.010$)], while the consumption of ceftolozane/tazobactam, ceftazidime/avibactam, tigecycline, and colistin had no statistically significant shifts. Thirty-day mortality following initiation of carbapenem treatment and all-cause in-hospital mortality remained unaltered after ASP implementation. In contrast, the length of hospital stay increased (median 17.0 versus 19.0 days; $P < 0.001$), while the risk of infection related readmission within 30 days of hospital discharge decreased (24.6% versus 16.8%; $P = 0.007$). Importantly, in the post-implementation period, acceptance of the ASP intervention by the treating physicians was associated with lower daily hazard of in hospital death [cause-specific HR (csHR) 0.49; 95% CI 0.30–0.80], lower odds of 30-day mortality (OR 0.36; 95% CI 0.18–0.70) and higher rate of treatment success (csHR 2.45; 95% CI 1.59–3.77). Regarding the impact of the stewardship intervention on the behavior of our hospital's doctors when managing infections caused by MDROs, ASP implementation prompted most of them to monitor the continuously evolving microbiological data of their patients more closely. It also shifted them towards a multidisciplinary and personalized care of patients with infections caused by MDROs and towards a more rigorous implementation of infection prevention and control (IPC) measures.

The vast majority of our colleagues (98.5%) wanted the ASP to be continued and further developed, even though at that time they were under the pressure of the COVID-19 pandemic.

Conclusions: This dissertation demonstrated the favorable effect of a carbapenem-focused ASP on the use of last-line antimicrobials with activity against Gram-negative MDROs on the overall quality of antimicrobial prescribing, even during the COVID-19 pandemic. Notably, the intervention described here was correlated with improved patient outcomes. Finally, the implementation of the ASP in our hospital had a positive impact on doctors' perceptions, attitudes, and practices towards the management of patients with difficult-to-treat infections.

Περίληψη

***Εισαγωγή*:** Η μικροβιακή αντοχή αποτελεί ένα από τα σημαντικότερα προβλήματα Δημόσιας Υγείας παγκοσμίως. Η λανθασμένη και η υπερβολική χρήση των αντιμικροβιακών, κυρίως των αντιβιοτικών, είναι ένας από τους κύριους αιτιολογικούς παράγοντες της μικροβιακής αντοχής. Η Ελλάδα βρίσκεται μεταξύ των χωρών οι οποίες χαρακτηρίζονται από υψηλή συχνότητα πολυανθεκτικών μικροοργανισμών στην κοινότητα και στον νοσοκομειακό τομέα και από αυξημένη χρήση ευρέος φάσματος αντιβιοτικών, συμπεριλαμβανομένων των καρβαπενεμών. Σκοπός της παρούσας διατριβής ήταν να αξιολογήσει τον αντίκτυπο ενός εστιασμένου στις καρβαπενέμες προγράμματος διαχείρισης της ορθολογικής χρήσης αντιβιοτικών σε ενήλικες ασθενείς ενός ελληνικού πανεπιστημιακού νοσοκομείου στην ποιότητα της συνταγογράφησης των αντιμικροβιακών, στη συνολική κατανάλωση προωθημένων αντιβιοτικών με δραστικότητα έναντι των Gram-αρνητικών βακτηρίων, στις εκβάσεις των ασθενών, και στη συμπεριφορά των θεραπόντων ιατρών σε σχέση με τη διαχείριση λοιμώξεων προκαλούμενων από πολυανθεκτικούς μικροοργανισμούς.

Μέθοδοι: Η παρούσα διατριβή συμπεριέλαβε τρεις διαφορετικές μελέτες εκτελεσμένες στο Πανεπιστημιακό Νοσοκομείο Ηρακλείου, στην Ελλάδα. Ένα εστιασμένο στις καρβαπενέμες πρόγραμμα διαχείρισης της ορθολογικής χρήσης των αντιβιοτικών εφαρμόστηκε μεταξύ 1^{ης} Ιανουαρίου 2020 και 31^{η} Δεκεμβρίου 2020 σε όλες τις κλινικές ενηλίκων του νοσοκομείου. Προκειμένου να προσεγγιστεί ο αντίκτυπός του στην ποιότητα της συνταγογράφησης αντιμικροβιακών, μια επαναλαμβανόμενη μελέτη σημειακού επιπολασμού έλαβε χώρα μεταξύ όλων των ενηλίκων ασθενών πριν και μετά την εφαρμογή του προαναφερθέντος προγράμματος. Επιπρόσθετα, μια οιονεί-πειραματική, προ και μετά μελέτη κοόρτης έλαβε χώρα, συγκρίνοντας τη δωδεκάμηνη περίοδο προ της παρέμβασης με τη δωδεκάμηνη

περίοδο μετά την παρέμβαση αναφορικά με την κατανάλωση ευρέος φάσματος αντιβιοτικών με δραστικότητα έναντι των Gram-αρνητικών βακτηρίων και αναφορικά με τις εκβάσεις των ασθενών. Τέλος, τελέστηκε μια συγχρονική μελέτη μεταξύ όλων των ειδικευόμενων και ειδικών ιατρών των κλινικών ενηλικών του νοσοκομείου μας προκειμένου να εκτιμηθεί η επίδραση του προγράμματος στις αντιλήψεις, στάσεις και πρακτικές τους σχετικά με τη διαχείριση των λοιμώξεων οι οποίες προκαλούνται από δύσκολα να θεραπευθούν βακτήρια.

Αποτελέσματα: Η επαναλαμβανόμενη μελέτη σημειακού επιπολασμού έδειξε στατιστικά σημαντική βελτίωση σε αρκετούς ποιοτικούς δείκτες που σχετίζονται με τη συνταγογράφηση των αντιμικροβιακών. Συγκεκριμένα, η συχνότητα της γραπτής αποτύπωσης στους φακέλους των ασθενών της αιτιολόγησης και της ημερομηνίας διακοπής/επανεκτίμησης της χορήγησης αντιμικροβιακών ήταν σημαντικά υψηλότερη ($p < 0,001$) στη δεύτερη μελέτη σημειακού επιπολασμού, ενώ η πλήρης συμμόρφωση με τις εθνικές ή διεθνείς οδηγίες θεραπείας επίσης αυξήθηκε σημαντικά, από 61,8% σε 73,6% ($p = 0,003$). Η οιονεί-πειραματική μελέτη κοόρτης ανέδειξε στατιστικά σημαντική ελάττωση -4,9 καθορισμένων ημερήσιων δόσεων (Define Daily Doses, DDD)/100 ασθενοημέρες (Patient-Days, PD) (95% CI −7,3 to −2,6; $p = 0,007$) στη χρήση των καρβαπενεμών και στατιστικά σημαντική αύξηση μόνο στη χρήση της πιπερακιλλίνης/ταζομπακτάμης [+2,1 DDD/100 PD (95% CI 1,0–3,3; $p = 0,010$)], ενώ οι καταναλώσεις της κεφτολοζάνης/ταζομπακτάμης, της κεφταζιδίμης/αβιμπακτάμης, της τιγεκυκλίνης, και της κολιστίνης δεν εμφάνισαν στατιστικά σημαντικές μεταβολές. Η θνητότητα 30 ημερών μετά την έναρξη χορήγησης καρβαπενέμης και η ενδονοσοκομειακή θνητότητα ανεξαρτήτως αιτιολογίας παρέμειναν αμετάβλητες μετά την εφαρμογή του προγράμματος. Αντιθέτως, η διάρκεια νοσηλείας αυξήθηκε (διάμεσος 17.0 έναντι 19.0 ημέρες; $p < 0,001$) ενώ ο κίνδυνος επανεισαγωγής εντός 30 ημερών από το

εξιτήριο λόγω λοίμωξης ελαττώθηκε (24,6% έναντι 16,8%; p = 0,007). Αξιοσημείωτα, κατά την περίοδο εφαρμογής του προγράμματος, η αποδοχή της παρέμβασης του προγράμματος από τους θεράποντες ιατρούς σχετίστηκε με χαμηλότερο ημερήσιο κίνδυνο για ενδονοσοκομειακή θνητότητα [cause-specific HR (csHR) 0,49; 95% CI 0,30–0,80], χαμηλότερες πιθανότητες για θάνατο εντός 30 ημερών μετά την έναρξη χορήγησης καρβαπενέμης (OR 0,36; 95% CI 0,18–0,70) και υψηλότερη συχνότητα επιτυχούς έκβασης (csHR 2,45; 95% CI 1,59–3,77). Αναφορικά με την επίδραση του προγράμματος στη συμπεριφορά των ιατρών του νοσοκομείου μας σε σχέση με τη διαχείριση λοιμώξεων από πολυανθεκτικούς μικροοργανισμούς, η παρέμβαση της εστιασμένης στις καρβαπενέμες επιμελητείας των αντιβιοτικών συνετέλεσε στη στενότερη παρακολούθηση από τους θεράποντες ιατρούς των διαρκώς προκυπτόντων μικροβιολογικών δεδομένων των ασθενών. Επίσης, τους ώθησε προς την κατεύθυνση της διεπιστημονικής και εξατομικευμένης φροντίδας των ασθενών οι οποίοι εμφάνιζαν λοιμώξεις από πολυανθεκτικούς μικροοργανισμούς, καθώς επίσης και προς την κατεύθυνση της αυστηρότερης εφαρμογής μέτρων πρόληψης και ελέγχου λοιμώξεων εντός του νοσηλευτικού ιδρύματος. Η συντριπτική πλειοψηφία των συναδέλφων μας (98,5%) επιθυμούσε το πρόγραμμα να συνεχιστεί και να εξελιχθεί περαιτέρω, παρόλο που εκείνη την περίοδο οι συνάδελφοι αυτοί ευρισκόντουσαν υπό την πίεση της πανδημίας COVID-19.

Συμπεράσματα: Η παρούσα διατριβή ανέδειξε την ευνοϊκή επίδραση ενός εστιασμένου στις καρβαπενέμες προγράμματος διαχείρισης της ορθολογικής χρήσης αντιβιοτικών στη χρήση των προωθημένων αντιβιοτικών με δραστικότητα έναντι των Gram-αρνητικών βακτηρίων, και στην ποιότητα της συνταγογράφησης αντιμικροβιακών γενικότερα, ακόμα και κατά τη διάρκεια της πανδημίας της COVID-19. Αξιοσημείωτα, η παρέμβαση η οποία περιγράφηκε εδώ σχετίστηκε με βελτιωμένες εκβάσεις των ασθενών. Τέλος, η εφαρμογή του

προγράμματος στο νοσοκομείο μας είχε θετικό αντίκτυπο στις αντιλήψεις, στάσεις και πρακτικές των ιατρών σε σχέση με τη διαχείριση ασθενών με δύσκολες στη θεραπεία λοιμώξεις.

CHAPTER I

General Introduction

1. Introduction

The continuously rising antimicrobial resistance (AMR) poses a major threat to public health worldwide [1]. Regardless of the socioeconomic status, AMR is associated with increased deaths, health issues, and medical expenses in all countries [2]. It is well known that exposing bacteria to antibiotics promotes the development of resistant bacterial strains, thus the irrational use of antibiotics is a significant driver of the global spread of AMR [3, 4]. Among the existing different classes of antibiotics, carbapenems represent important components of the antibiotic arsenal due to their broad-spectrum of antibacterial activity, making the preservation of their effectiveness through their judicious use a priority of high importance [5].

2. Carbapenems

2.1 Chemical structure

Carbapenems belong to the β-lactam class of antibiotic drugs and their chemical structure differs from penicillin by possessing a carbon atom at position 1 in place of sulfur and a double bond between C2 and C3 in the five-membered fused ring [6]. Table 1 shows the clinically available carbapenems where their structure can also be visualized. The discovery of carbapenems was made while searching for β-lactamase inhibitors to preserve the use of penicillin [7]. The impressive chemical structure of carbapenems is key to their β-lactamase inhibitory activity. Previous β-lactams such as penicillin have a *cis* acylamino side chain that make them susceptible to β-lactamase inhibitors, while carbapenems possess a trans-α-1-hydroxyethyl in its place, giving them their broad-spectrum activity and resistance

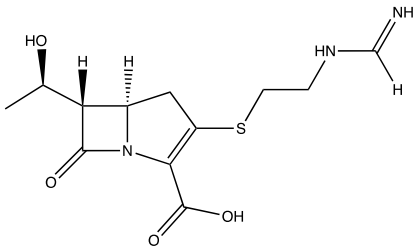
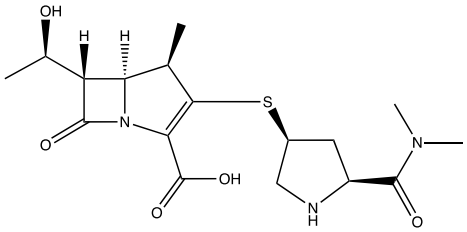
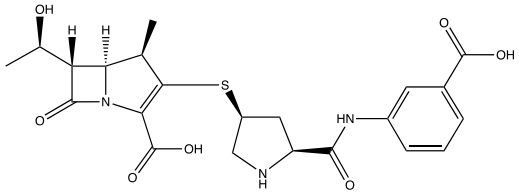
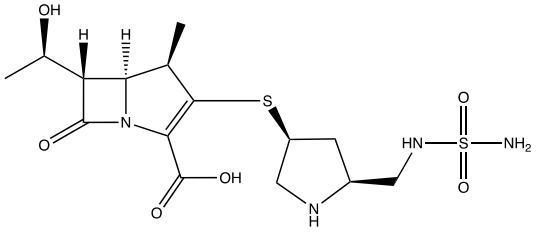
to hydrolysis by β-lactamases [7, 8]. The trans-α-1-hydroxyethyl substituent displaces the water necessary for β-lactamases for hydrolysis of the acylated enzyme and thus rendering it inactive [9].

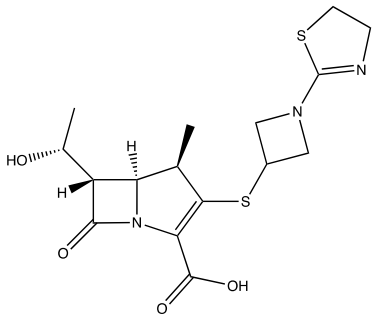
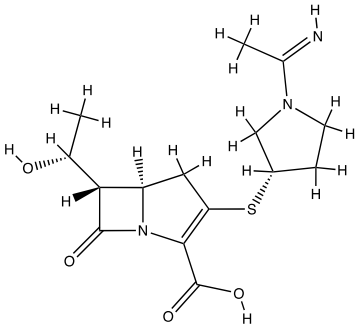
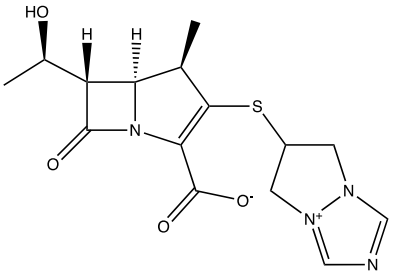
Despite their impressive resistance to β-lactamase activity, the earliest carbapenems, such as imipenem and panipenem, were susceptible to degradation by dehydropeptidase 1 (DHP-1) located in the renal brush border via hydrolysis, therefore, requiring the co-administration of DHP-1 inhibitors [8, 9]. The hydrolysis of imipenem by DHP-1 explained how in earlier studies, animals experienced proximal tubular necrosis which can be prevented by cilastatin, a DHP-1 inhibitor [6]. Additionally, this was overcome in more recent carbapenems such as meropenem, ertapenem, and doripenem, as they possess a 1-β methyl group which protects the carbonyl group of β-lactam against hydrolysis by renal DHP-1 [9]. Interestingly, the later carbapenems also have a pyrrolidine ring as a side chain which renders them more stable and broadens their activity spectrum [7].

Specific carbapenems also have specific features in their chemical structure that differentiates them from the rest. For example, ertapenem differs from other carbapenems by the presence of a meta-substituted benzoic acid at the 2 position which further stabilizes it against DHP-1, increases its half-life, and allows for stronger significantly stronger protein binding [10]. Additionally, its structural modification increases is activity against gram-negative bacteria as this enables ertapenem to penetrate their cells walls slower than other carbapenems [8]. The latest carbapenem to be approved clinically was doripenem because its unique structure shows it possesses a sulfamoxil-aminomethyl group in place of dimethyl-carboxyl chain at position 2, which is responsible for its increased activity against non-fermentative Gram-negative bacilli [11]. Finally, tebipenem pivoxil, a novel carbapenem

approved in Japan and in phase 3 clinical trials in both the United States and Europe, is the first orally available due to its structure which has a pivaloyloxymethyl ester added at position 2, that allows for rapid absorption and therefore conversion to its active form [12]. Tebipenem pivoxil's structure allows it to be more stable against DHP-1 than previous carbapenems [12].

Table 1. List of clinically available carbapenems, their current status, and chemical structure.

Compound Name	**Current Status**	**Chemical Structure**
Imipenem	FDA approved since 1985. Approved for use by EMA	
Meropenem	FDA approved since 1996. Approved for use by EMA	
Ertapenem	FDA approved since 2001. Approved for use by EMA	
Doripenem	FDA approved since 2007	

Tebipenem	Phase 3 clinical trial (USA; Europe) Approved since 2009 (Japan)	
Panipenem	Approved since 1993 (Japan, China, and Korea)	
Biapenem	Phase 1 clinical trial (USA) Approved since 2001 (Japan)	

FDA: The Food and Drug Administration

EMA: European Medicines Agency

2.2 Spectrum – Uses

Carbapenems are effective against a broad range of bacteria, including Gram-positive and Gram-negative, but do not work against *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Stenotrophomonas maltophilia*. Table 2 describes the specific bacteria each clinically available carbapenem covers. Meropenem, owing to its

varying affinities for different PBPs, has been demonstrated to be more potent than imipenem for gram-negative bacteria, such as *Klebsiella pneumoniae*, *Proteus mirabilis*, *Haemophilus influenzae*, and *Escherichia coli* [8]. Ertapenem has a narrower range of activity compared to imipenem, meropenem, and doripenem, because it is not effective against *Pseudomonas aeruginosa* and *Enterococcus* species [8]. Doripenem's antimicrobial spectrum is very similar to imipenem and meropenem, however, possesses greater activity against *P. aeruginosa* [13]. Imipenem and doripenem both have shown to be more potent than the other carbapenems against *S. pneumoniae*, *S. aureus*, and other Gram-positive aerobic bacteria [11].

Imipenem and meropenem are the carbapenems that are most established when used in cases of nosocomial infections and polymicrobial infections, particularly in patients who are severely ill [8]. Meropenem has also shown to be very effective and potent in treating cases of meningitis, especially those caused by Gram-negative bacteria [8]. Ertapenem has limited efficacy in treating nosocomial infections and is often reserved for treating community-acquired infections, intra-abdominal and pelvic infections [14]. Doripenem currently is only approved for intra-abdominal infections and urinary tract infections (UTIs) [13]. Recent studies have shown that doripenem is noninferior to imipenem for treating ventilator-associated pneumonia, and noninferior to meropenem for treatment of complicated intrabdominal infections [13]. A list of the specific indications of each drug is summarized in Table 2.

Table 2. The clinical indications and spectrum coverage of the carbapenems approved by the FDA and in Europe [13, 15].

Compound Name	**Spectrum coverage (bacteria)**	**Clinical Indications**
Imipenem	Gram-positive • methicillin-susceptible *Staphylococcus aureus* (MSSA) • *S. pneumoniae* & *S. pyogenes* • *E. faecalis*[1] Gram-negative: • *P. aeruginosa* • *Neisseria* species • *Enterobacteriaceae* • *Acinetobacter* species	• Intra-abdominal infections • Skin and soft tissue infections • UTIs • Lower respiratory tract infections (LRTIs) (including pneumonia[4]) • Osteoarticular infections • Endocarditis • Obstetric infections • Sepsis • Polymicrobial infections
Meropenem	Gram-positive • MSSA	• Intra-abdominal infections • Skin infections

	• *S. pneumoniae* & S. *pyogenes* • *E. faecalis*[1] Gram-negative: • *P. aeruginosa* • *Neisseria* species • *Enterobacteriaceae* • *Acinetobacter* species	• Meningitis
Ertapenem	Gram-positive • MSSA • *S. pneumoniae*[2] & *S. pyogenes* • *E. faecalis* Gram Negative: • *Neisseria* species • *Enterobacteriaceae*	• Intra-abdominal infections • Skin and soft tissue infections • UTIs • LRTIs (including pneumonia[4])
Doripenem[3]	Gram-positive • MSSA • *S. pneumoniae* & *S. pyogenes* • *E. faecalis*[1]	• Intra-abdominal infections • UTIs

	Gram-negative: • *P. aeruginosa* • *Enterobacteriaceae* • *Acinetobacter* species	

[1]Their activity does not cover vancomycin-resistant *E. faecalis*.

[2]Their activity does not cover penicillin-resistant *S. pneumoniae*.

[3]Not approved for use in Europe.

[4]Only approved for community-acquired pneumonia.

2.3 Side-effects induced by their use

2.3.1 Toxicities

The currently approved carbapenems are all considered safe, with mild and self-limited adverse effects similar to other β-lactam antibiotics. The most common side effects in all carbapenems are gastrointestinal side effects, such as vomiting (1.4% to 12%) and diarrhea (1.8% to 11%). The highest percentages of gastrointestinal side effects were reported with doripenem but this could be due to the lower amount of patients that the drug has been tested in trials as compared to other carbapenems [15]. Additionally, due to their route of administration, local injection site reactions and thrombophlebitis are common. These reactions range from 1.1% with meropenem to 3.2% with ertapenem [15].

Another important side effect common among all commercially available carbapenems is a transient and self-limiting increase in liver enzymes, that usually resolves

once the antibiotic is stopped [8, 16]. In the literature, there has been reported one case of severe liver injury following meropenem in a 63-year-old man that ceased once the drug was terminated [17]. No other cases of acute liver injury associated with carbapenem use were reported in the literature.

Finally, neurotoxic adverse reactions have been reported with the use of imipenem, meropenem and ertapenem, that include seizures and headaches [15]. Imipenem has the highest protentional to cause seizures, with a reported frequency of 1.5 – 2%, while ertapenem-inducted seizures were reported in 0.2% of those who received the drug [8]. Risk factors for carbapenem-induced seizures include older age, higher dose of the drug, renal impairment, underlying central nervous system disease, and concomitant use of anticonvulsant drugs [18].

Fortunately, allergies against carbapenems are rare and only occur in 0.3% – 3.7% in patients and consist of self-limiting rash, pruritus, and urticaria, with no reported cases of anaphylaxis in clinical trials and post-surveillance studies [19]. In the literature, there has been a report of a case of anaphylactic shock thought to be due to meropenem (following a positive allergy skin test), however, the patient was able to receive ertapenem without any allergic reactions [20]. It is important to note that a major limitation of current clinical trials is the exclusion of patients with a history of anaphylaxis to other beta-lactam antibiotics, since historically beta-lactam allergies are known to be cross reactive [19]. Studies have also shown that patients who developed mild allergic reactions, such as rash to carbapenems, were more likely to have a history of developing similar reactions to other carbapenems [19]

2.3.2 *Clostridioides difficile* infection (CDI)

CDI is a well-recognized adverse effect associated with many antimicrobial agents; however, studies have shown that specific antibiotics are more likely than others to result in infection. All commercially available carbapenems are thought to increase the risk of CDI [21].

A recent meta-analysis of multiple randomized controlled trials compared the risk of CDI among different antibiotics. Their results showed that compared to penicillin, the risk of CDI was comparable, however, it was higher with carbapenem use compared to fluoroquinolones [risk ratio (RR) = 2.44, 95% confidence interval (CI) 1.32–4.49] and cephalosporins (RR = 2.24, 95% CI 1.46–3.42) [22]. It is thought that this association occurs to the inherent resistance of *C. difficile* to some carbapenems. In-vitro studies have shown that meropenem and doripenem are active against all *C. difficile* strains, however, ertapenem had a lower activity [23]; therefore, it is likely that ertapenem could cause CDI through ertapenem-resistant *C. difficile.*

Other mechanisms such as disruption in colonic flora and suboptimal drug concentration in feces could also be responsible for the increased risk of CDI. Studies have shown that imipenem and meropenem result in colonic microflora disruption and reduce the number of *Clostridia* species, which is only restored after discontinuation [22]. This could lead to *C. difficile* colonization during the restoration period and explain the increased risk of CDI.

2.3.3 Carbapenem-resistant (CR) pathogens

There are three major CR pathogens that are of importance and currently constitute a public health threat: CR *Enterobacteriaceae*, CR *Acinetobacter* species, and CR *Pseudomonas* species. There are three common mechanisms in which these pathogens become resistant to carbapenems, and they include genetic mutations that alter the function of porins, production of enzymes such as carbapenemase, and activation of efflux pumps [24-26].

Enzyme production of carbapenemase is considered the most significant mechanism of resistance when discussing CR pathogens, thus it is common to group these pathogens into those that are carbapenemase producing and those which are not.

Carbapenemases are the most powerful β-lactamases, and their activity extends to all β-lactam antibiotics [27]. There exist hundreds of carbapenemases, with the most clinically significant and effective in hydrolyzing carbapenems being: KPC (*K. pneumoniae* carbapenemase), OXA (Oxacillin-hydrolyzing carbapenemases)-48, VIM (Verona integron-encoded metallo-β-lactamase), IMP (imipenemase), and NDM (New Delhi metallo-β-lactamase) [28]. However, many are still undiscovered, and it is very likely that newer and more powerful carbapenemases will continue to be acquired by Gram-negative pathogens. In general, the production of carbapenemases can either be chromosomally encoded which are usually induced in response to imipenem, plasmid-encoded, or a mixture of both [29].

As with all enzymes, their classification can either be functional or molecular. The functional classification, which was first proposed in 1989 with the latest update in 2010, attempts to classify the different carbapenemases based on their phenotype in clinical isolates (either those that utilize serine or require divalent zinc ions for β-lactam hydrolysis) [30]. The functional classification is divided into 3 major groups (1-3); groups 1 and 2 is for serine β-lactamases, while group 3 includes metallo-β-lactamases [30]. The functional groups/subgroups of interest are:

- Subgroup 2df β-lactamases, which include the OXA enzymes that are capable of inhibiting carbapenems and are most frequently found in *A. baumannii* [30].
- Subgroup 2f β-lactamases, which includes serine carbapenemases, such as the KPC carbapenemases found in *K. pneumoniae* and other *Enterobacteriaceae* [30].

- Subgroup 3a include the plasmid-encoded metallo-carbapenemases, such as IMP and VIM, which are found in *P. aeruginosa* and *Enterobacteriaceae* [30].

The more commonly and widely used classification is the Ambler classification which classifies β-lactamases into 4 main molecular classes (A-D) based on distinguishing amino acid configurations [31]. The serine carbapenemases are found in classes A and D while metallo-carbapenemases belong to class B [32]. Currently, there exists only one carbapenemase that belongs to class C known as CMY-10 which is capable of inactivating imipenem and is found in *Enterobacteriaceae* and *P. aeruginosa* [33]. Class B carbapenemases are of particular interest because all current existed β-lactamase inhibitors (clavulanate, sulbactam, tazobactam, avibactam, vaborbactam, and relebactam) are ineffective against them [29].

As mentioned above, all three major CR pathogens are capable of producing carbapenemases. Carbapenemase-producing CR *Enterobacteriaceae* (cpCRE) are of great concern and have been spreading rapidly worldwide. Numerous carbapenemases have been identified in cpCRE with KPC, NDM-1, IMP-type, VIM, and OXA-48 being the most clinically relevant. Interestingly, VIM and IMP-type carbapenemases produced by cpCRE were acquired through horizontal transfer via plasmid from *P. aeruginosa* [24]. NDM-1, produced by *K. pneumoniae* and *E. coli*, is the latest discovered carbapenemases and is encoded on plasmids containing the bla_{NDM} gene, which also encode for other β-lactamases and 16S rRNA methylases, making these bacteria resistant to virtually all β-lactams and aminoglycosides [24]. Different geographic locations harbour specific cpCRE organisms. In South Asia, NDM-1 producing *K. pneumoniae* and *E. coli* are a major source of CR infections, while in Turkey OXA-48 producing *K. pneumoniae* have been a major cause of hospital-acquired infections [34, 35]. Of interest, KPC, NDM, and VIM producing *Enterobacteriaceae* are currently endemic in

Greece [36]. The most alarming cpCRE is a specific clone of KPC producing *K. pneumoniae*, known as ST258, which through plasmid-mediated (specifically a IncF plasmid with FIIK replicons) spread has caused worldwide epidemics and has acquired specific resistance traits that can be spread to other *Enterobacteriaceae* [32]. For example, a case report from Israel documented the transfer of KPC-3 from *K. pneumoniae* ST258 *to E. coli* through horizontal transfer [37].

Carbapenemase-producing CR *Pseudomonas* (cpCRP) species produce all 3 classes of carbapenemases (A, B, and D) [32]. Among Class A carbapenemases, cpCRP produce GES carbapenemases which were identified in *P. aeruginosa* on genes encoded in transferrable plasmids (GES-1) and chromosomally encoded (GES-5 and GES-18) [32]. Interestingly, recent studies have also identified the presence of KPC in *P. aeruginosa* clinical isolates, suggesting horizontal transfer of plasmids encoding for KPC genes from *Enterobacteriaceae* [38, 39]. Class B carbapenemases (metallo-β-lactamases) are the primary carbapenemases produced by *P. aeruginosa* and are significant due to all being encoded on transferable plasmids that can easily spread to other bacteria [32]. Evidently, metallo-β-lactamases genes first appeared in *P. aeruginosa* and were later transferred to other bacteria, with new genes still being discovered to this day for metallo-β-lactamases such as bla_{CAM-1} identified in 2019 in Canada [40].

The final group of clinically significant carbapenemases-producing CR pathogens are carbapenemase-producing CR *Acinetobacter* species (cpCRA). Of the *Acinetobacter* species, *A. baumannii* is the most relevant and it is becoming a leading cause of nosocomial infections worldwide. The major carbapenemases produced by cpCRA belong to classes B and D. Of class B, NDM-1 producing *A. baumannii* is of great concern as since its identification in 2010 and it

has rapidly spready across the globe including several European countries, such as Greece [41]. Class D carbapenemases genes are naturally occurring in *A. baumannii* and their intrinsic activity against carbapenems is usually weak, however, overexpression of specific genes such as bla_{OXA-51}-like genes due to insertion of ISAba1 sequences can increase the expression of OXA-51 carbapenemases by eight-fold, leading to inactivity of carbapenems [32]. Additionally, cpCRA has acquired different class D carbapenemases with the most important being OXA-23, which unlike previous carbapenemases is encoded by multiple gene entities such as bla_{OXA-23} and the transposons *Tn2006*, *Tn2007*, and *Tn2008*, making it much more difficult to control and has been responsible for multiple hospital outbreaks [32]. Much like previous pathogens, novel variants of OXA producing *Acinetobacter* species continue to be discovered in clinical isolates with varying degrees of resistance to carbapenems and β-lactam antibiotics [42, 43].

Another important mechanism that Gram-negative bacteria acquired or inherently possessed resistance to carbapenems is overexpression or activation of efflux pumps. Overexpression of efflux pumps is a powerful way in which many pathogens can acquire resistance to multiple and different antimicrobials since efflux pumps can easily recognize numerous substrates of varying physiological and chemical features [44]. The overexpression of efflux pumps in *P. aeruginosa* is especially interesting as it occurs differently depending on which carbapenem is used. The most important pump sy*stem P. aeruginosa* possesses is MexAB-OprM (Multidrug efflux system AB-Outer membrane protein M) which makes it resistant to multiple antibiotics, including meropenem but not imipenem [45]. Evidence suggests that the use of meropenem could act as a catalyst to the overexpression of efflux pump systems in *P. aeruginosa* [46]. In contrast, imipenem has been associated with an increase of expression of genes responsible for efflux pump systems in *E. coli* [47]. As with *P.*

aeruginosa, *Enterobacteriaceae* and *Acinetobacter* species also possess various resistance-nodulation-division efflux pump systems that play an important role in their resistance to different antibiotics including carbapenems [24, 48].

The final significant mechanism of resistance among Gram-negative bacteria includes modifications to porins which alters their permeability to different antibiotics. Porins are important outer membrane proteins in Gram-negative bacteria that control membrane permeability which alters the diffusion of numerous substrates into the bacterium cell [49]. *P. aeruginosa* strains intrinsically have a reduced expression of their porins, which makes them resistant to several antibiotics. However, this intrinsic ability does not inhibit the diffusion of all carbapenems [29]. Specifically, meropenem and doripenem can easily diffuse through OprD porin in *P. aeruginosa* membrane [25]. Recent studies have identified clinical isolates of *P. aeruginosa* with low OprD porin expression, making them resistant against most carbapenems [50]. Similar mutations in porin proteins have also been identified in CR *Enterobacteriaceae*, specifically in cpCRE, such as AmpC- and carbapenemase-producing *K. pneumoniae* (loss of OmpK35 or OmpK36 porins) and in non-cpCRE, such as *Enterobacter aerogenes* (Omp35 and Omp36 porin genes downregulation) [51, 52]. Finally, numerous studies have also shown porin mutations in carbapenem resistant *A. baumannii*, such as mutations in the *carO* (carbapenem-associated OMP) porin genes that lead to its under-expression [26, 53].

3. Antimicrobial Resistance (AMR)

3.1 AMR delineation

The emergence of AMR is considered to be a highly significant public health issue with worldwide implications due to a substantial decrease in number of effective antibiotics against resistant bacteria [54]. AMR is defined as the resistance of microorganisms to an antimicrobial agent to which they were at first sensitive [54]. Subcategories of AMR include multi-drug resistance (MDR), extensively-drug resistant or extremely-drug resistance (XDR) and pan-drug resistance (PDR) [55]. MDR may be defined as "acquired non-susceptibility to at least one agent in three or more antimicrobial categories", while the epidemiological significance of bacteria categorized as XDR (non-susceptible to ≥1 agent in all but ≤2 categories of antimicrobials that normally are active) lies in their alarming propensity to be resistant to nearly all approved antimicrobial agents [55-57]. Several definitions exist for PDR, with "non-susceptibility to all agents in all antimicrobial categories" being a commonly used definition [55]. Many bacteria that cause common or severe infections have gradually, or in some cases rapidly, developed resistance to each newly introduced antibiotic [55]. In light of this reality, it is crucial to take action to prevent a growing global healthcare crisis.

A vast number of bacteria have developed resistance to numerous antimicrobials and the World Health Organization in 2017 created a category to focus on development of new antibiotics to certain bacteria and categorized them with a priority status, with bacteria being designated into "critical-priority", high-priority", or "medium-priority (5). Bacteria that are considered critical priority include ESKAPE (*E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* species) pathogens [58]. These pathogens are capable of causing severe and often fatal infectious diseases, as they are resistant to multiple antibiotics [58]. Meanwhile, bacteria like *S. pneumoniae* and *Shigella* fall under the medium-priority category, as they may exhibit some resistance, but can be combated with existent effective antibiotics [58, 59].

S. aureus is one of the most common pathogens that exhibit antimicrobial resistance [60]. Patients infected with *S. aureus* are susceptible to a wide range of infections, including severe skin infections, bacterial endocarditis, pulmonary abscesses, and device-related infections [60]. *P. aeruginosa* is another pathogen commonly implicated in the context of antimicrobial resistance, due to its contagiousness and multiple mechanisms for developing antimicrobial resistance [61]. *P. aeruginosa* infections commonly arise as nosocomial and may lead to pneumonia, bloodstream infections, skin infections - especially in patients with burns - and urinary tract infections [61]. In 2019, *E. coli*, followed by *K. pneumoniae* and *S. aureus*, were the pathogens responsible for the most deaths related to antimicrobial resistance, due to complications such as pneumonia, meningitis, and urinary tract infections [2]. Most common infections and deaths attributable to antimicrobial resistance are due to lower respiratory infections, bone infections, intra-abdominal infections, urinary tract infections and tuberculosis [2].

When discussing AMR, it is important to understand the different mechanisms in which different bacteria become resistant to antimicrobials. β-Lactam antibiotics inactivate penicillin-binding proteins (PBPs) by binding covalently to these enzymes, and alterations in PBPs with enzymatic degradation leads to resistance in Gram-positive bacteria [62]. For Gram-negative bacteria, several mechanisms could be involved to acquire resistance to β-Lactam antibiotics, such as alterations in PBPs, decreased access to bind to PBPs, and ability to produce β-lactamases [62]. Of interest, as it has been already mentioned, resistance to carbapenems could occur due to cytoplasmic membrane intrinsic differences, due to increased activity or expression of efflux pumps, which clear the antibiotic before it can access its target and perform its actions, or productions of enzymes [63]. Carbapenem resistance is discussed in more detail in previous sections.

Resistance to aminoglycosides is attributed to several mechanisms, mainly due to enzymatic modification and subsequent inactivation of the aminoglycosides, increased expression of efflux pumps, or modifications to the 30S ribosomal subunit which leads to decreased binding action of the antibiotic [64].

Alterations of the peptidoglycan synthesis pathway due to the substitution of D-Alanine-D-Alanine (D-Ala-D-Ala), to D-Alanine-D-Lactate (D-Ala-D-Lac) or D- Alanine-D-Serine (D-Ala-D-Ser) leads to vancomycin resistance due to decreased binding affinity to these substitutes in the peptidoglycan compared to the normal pathway consisting of D-Alanine-D-Alanine (D-Ala-D-Ala) [65].

Various mechanisms contribute to resistance to tetracyclines, most notably due to modifications of the 30S ribosomal subunit, acquisition of genetic elements containing resistance genes specific to tetracyclines, tetracycline-specific efflux pumps, and binding-site mutations mainly in 16S rRNA [66].

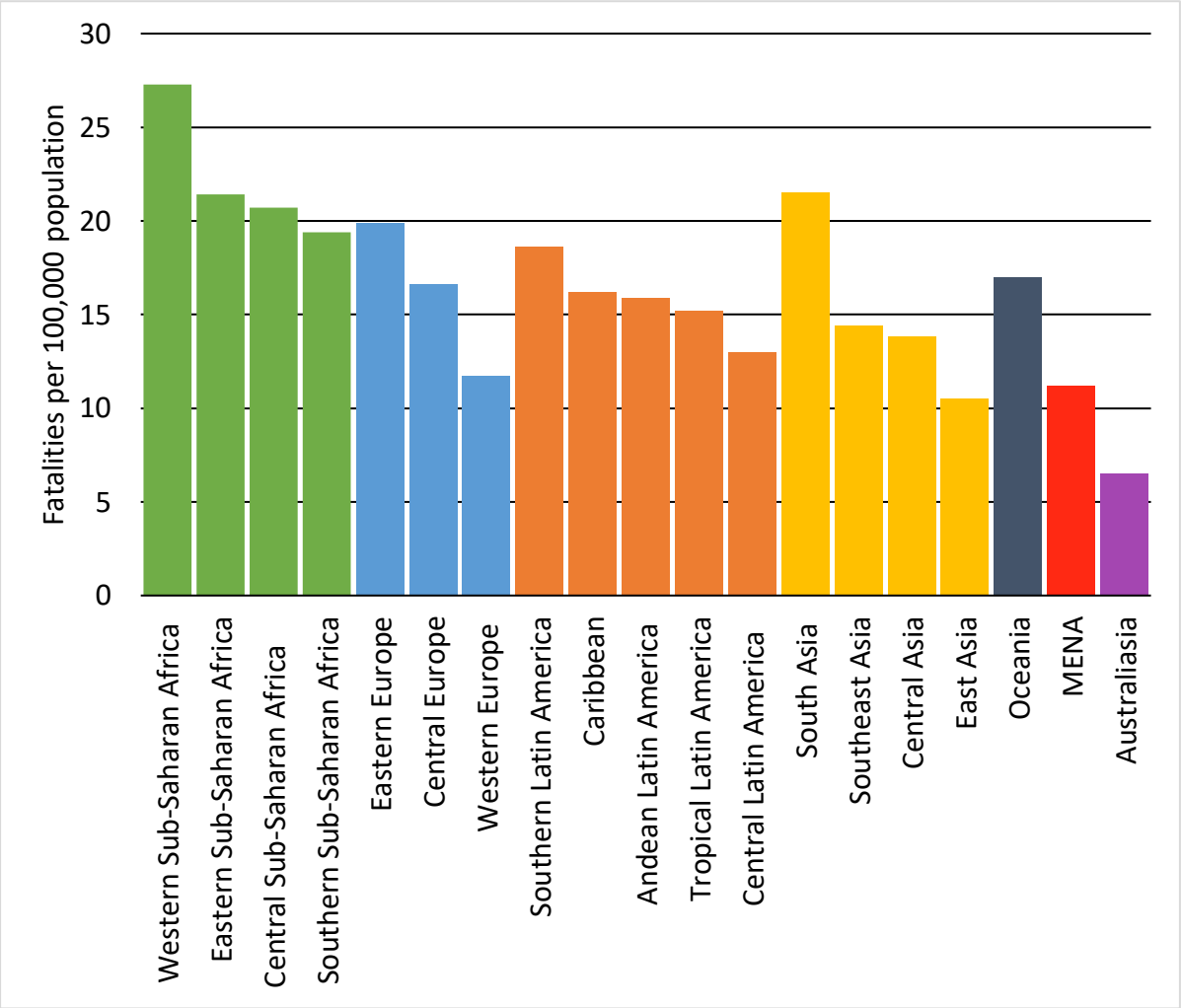
Macrolides are susceptible to resistance through three main mechanisms: bacterial ribosome undergoing modifications through methylation or mutations thereby interfering with binding of the antibiotic with the 50S ribosome, macrolide-specific efflux from the bacterial cell through ATP-binding cassette superfamily proteins and major facilitator superfamily, and drug inactivation due to the presence of esterases [67].

Finally, resistance to polymyxins may occur through modification of the lipopolysaccharide, mediated by two-component signal transduction system (TCS), to decrease the interaction with the polymyxin-outer membrane [59, 60]. Moreover, acquired resistance may be achieved through acquiring plasmids, such as mobile colistin resistance (*mcr*), that encode for polymyxin resistance [60, 62].

3.2 Burden of AMR

The burden of AMR infections can be studied by examining the overall fatalities and disability-adjusted life-years caused by resistant pathogens. A recent analysis from Global Research on Antimicrobial Resistance project aimed to estimate the 2019 fatalities and disability-adjusted life-years associated and attributed to AMR bacteria worldwide. They were able to include data from over 200 countries for over 20 pathogens and estimated a 1.27 million [95% (uncertainty interval (UI) 0.911–1.71] fatalities attributed to resistant bacteria worldwide in 2019 [2]. The highest burden was in Western sub-Saharan Africa which had an estimated 27.3 (95% UI 20.9–35.3) fatalities per 100,000 attributed to resistant bacteria and the lowest burden was in Australia which had an estimated 6.5 (95% UI 4.3–9.4) fatalities per 100,000 attributed to AMR (Figure 1) [2].

Figure 1. Estimates of fatalities attributable to AMR bacteria by region in 2019 [2].



When examining numbers concerning Europe, Eastern Europe number had a higher burden with an estimated 19.9 (95% UI 13.1–28.5) fatalities per 100,000 attributed to AMR than Central Europe [16.6 (95% UI 10.5–25.0) per 100,000 attributed to resistant bacteria] and Western Europe [11.7 (95% UI 8.0–16.6) per 100,000 attributed to AMR bacteria] [2]. AMR related infections with the highest burden worldwide were LRTIs, bacteremia, and intra-abdominal infections, which accounted for around 78% of all fatalities attributable to AMR in 2019 worldwide [2]. Of interest, carbapenem resistant pathogens accounted for over 240,000 fatalities attributable to resistance [2].

Another recent study aimed to estimate fatalities and disability-adjusted life-years associated and attributed to AMR by country level in the WHO European region in 2019. In 2019, 133,000 fatalities were attributable to resistant bacteria in the WHO European region with 80% of these fatalities attributable to bloodstream infections (47,200 fatalities), LRTIs (28,500 fatalities), and intra-abdominal infections (31,200 fatalities) [68]. Of interest, CR pathogens were the second most common cause (14%) of attributable fatalities [68]. In Greece, 11.9% of all-cause deaths that occurred in 2019 were attributable to AMR [68].

3.3 Causes of AMR

Many factors lead to antimicrobial resistance, with spread by horizontal gene transfer (HGT) through mobile genetic elements that exist in bacteria being one of the most influential and leading causes [69]. Several mechanisms are involved in HGT, notably conjugation, transformation, and transduction [70]. Conjugation refers to the process by which genetic material, such as plasmid DNA, is transmitted from one bacterium to another via direct physical contact between cells and occurs when two bacteria in close proximity come in contact, allowing mobile genetic elements like plasmids and integrating and conjugation elements to be transferred through a pilus or pore [70]. This mechanism of horizontal transfer is highly significant and is prevalent in various types of bacteria and enables resistance genes to be passed between bacteria of the same genus [70]. On the other hand, transformation refers to the process by which recipient bacteria take up extracellular DNA from donor bacteria that have been lysed and integrate this DNA into their own genomes, allowing several traits to be integrated into the recipient bacteria [71]. The extracellular DNA that is taken up during transformation is typically composed of plasmid DNA and fragmented DNA that has been released during bacterial lysis or active secretion [72]. This DNA often contains

antibiotic resistance genes [72]. Several bacteria have developed resistance through natural transformation, such as *S. pneumoniae* and *E. coli* [72]. Finally, transduction is a process in which a bacteriophage serves as a carrier to transfer non-viral DNA from one bacteria host cell to another, thereby allowing the recipient bacteria to obtain several new traits that lead to antibiotic resistance [73]. Phages have been found to coexist with antibiotic resistance genes in the same bacteria [69].

Inappropriate use and underuse and overuse of antibiotics may lead to development of resistance. Antibiotics are able to kill susceptible bacteria, but the resistant bacteria are able to survive and reproduce through natural selection [74]. Despite the fact that using antibiotics too often is strongly discouraged, there are still many cases of over-prescription in healthcare [73]. Studies have shown that in up to 50% of cases, the duration or choice of antibiotic prescribed may be inappropriate, inducing AMR [74, 75]. Prescribing antibiotics inappropriately can limit therapeutic benefits and may also lead to a wide array of complication [76]. When administered in subinhibitory and subtherapeutic concentrations, antibiotics elicit changes in gene expression, mutagenesis, and HGT, thus promoting the development of antibiotic resistance [77]. Changes in gene expression triggered by antibiotics may lead to an increase virulence, and the increased mutagenesis and HGT can facilitate the spread of antibiotic resistance [77]. In addition, antibiotics overuse is a quite strong factor implicated in antibiotic resistance worldwide. A major study has revealed that there are certain states in the United States where the total number of prescribed antibiotic treatments administered each year surpasses the population size, resulting in over one course of treatment per individual per year [78]. These prescribing trends are the same in many European countries. In Greece, an analysis showed that between 2010-2013, 768 antibiotics were prescribed per 1,000 people [79]. Excessive use of antibiotics leads to the development

of AMR through selection pressure. Resistance can be acquired through HGT between cells [80]. Evidence suggests that identical sequences of drug-resistance genes have been found in the DNA of both environmental and clinical bacterial strains, indicating that HGT plays a role in the spread of antibiotic resistance in antibiotic overuse [80].

Antibiotics are commonly utilized worldwide as growth enhancers in livestock. Over 73% of antibiotics sales globally are dedicated to livestock, mainly to encourage growth and to decrease the number of infections [80]. Administering antibiotics to animals is believed to enhance their general well-being, resulting in higher yields and better-quality products [72]. Through molecular detection techniques, it has been proven that antibiotic-resistant bacteria in livestock are transmitted to consumers through meat products consumed by the public [82]. Following administration of antibiotics to livestock, antibiotics are able to kill sensitive and vulnerable bacteria, however, creating a favourable environment for the growth of resistant bacteria and therefore lead to AMR spread to humans [83]. The vast majority of antibiotics administered to farm animals are excreted in urine or stool and therefore scattered into the soil or water sources [84].

Additionally, studies have indicated a potential correlation between pesticides and AMR. Certain strains of pesticide-degrading bacteria found in soils that have been exposed to pesticides have exhibited resistance to antibiotics such as tetracyclines [85]. This resistance may be linked to a plasmid causing cross resistance through an unspecific organophosphorus hydrolase, which can also break down antibiotic derivatives [86]. This scenario demonstrates cross-resistance, where the development of MDR may be influenced by the natural selection process that occurs during HGT [86]. In addition, another study evaluated the effect of biocidal agents for disinfection on cross-resistance to antibiotics and revealed that the use of

octenidine and didecyldimethylammonium chloride led to cross-resistance to antibiotics in some cases [87].

Another factor leading to antimicrobial resistance is the poor development of new antibiotics. Several major pharmaceutical companies have halted their antibiotic fields and henceforth no longer develop new antibiotics [82]. Furthermore, most of the pharmaceutical companies have started to focus on developing more profitable drugs, such as medications for chronic conditions, rather than antibiotics, which are not typically purchased by an individual for a prolonged duration of time [82]. In addition to that, antibiotics commonly are charged significantly less than medications for chronic conditions, such as chemotherapeutic drugs or medications for neuromuscular disorders [82]. In addition, due to the capability of the bacteria for rapid emergence of AMR, a new antibiotic may lose its efficacy within a short period of use, decreasing the need for prescribing, thus, decreasing the profit of the investment that has been made by the industry [3].

3.4 Consequences of the AMR

As it has been already mentioned, AMR is a public health concern due to its multiple negative impacts on population health, individual patient health, economy, and healthcare systems. Clinical consequences of AMR include an increase in all-cause mortality, increased hospital length of stay, increased need for intensive and invasive treatment, decline in patient functional parameters, and an excess need for surgery [88]. Specifically, multiple studies have demonstrated that MRSA bacteremia is associated with a higher mortality rate compared with MSSA, and the gap in mortality rate is more pronounced in low-income countries [89-91]. These trends continue to be true even in more recent studies conducted after 2011 with the new available treatments against MRSA [89]. This could be because even the alternative

antibiotics against MRSA are more expensive and toxic [92]. Moreover, these findings are not limited to bacteremia, as many studies have showed increased mortality rate (short-term and long-term), complications, risk of hospitalization, and intensive care unit (ICU) admission across many different infections such as pneumonia, endocarditis, and osteoarticular infections caused by MRSA compared to MSSA in adult and pediatric population across various countries [93-97].

Worsened clinical outcomes are also seen in other drug-resistant infections. A recent meta-analysis showed that bacteremia caused by extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* was associated with a 1.7 increased risk of all-cause mortality, a 1.75 increased risk of attributable mortality, increased admission to ICU (by 3 days), and longer hospitalisation (by around 4 days) [98]. Another recent retrospective cohort study in Ontario, Canada, with 15,843 infections of *E. coli* bacteremia, showed that for each case of resistant *E. coli* strains, the 90-day mortality was higher when compared to non-resistant *E. coli* strains. Their study showed the increased odds were highest among carbapenem resistant *E. coli* (aOR 2.06, 95% CI 0.91–4.66), and those resistant to multiple antimicrobials (aOR 2.58, 95% CI 0.87–7.66) [99].

Studies have also demonstrated the increased mortality by about 2 to 5-fold in patients with MDR *P. aeruginosa* compared to those with multidrug-susceptible *P. aeruginosa* [100]. There is also an additional increased risk in patient morbidity such as increased risk of hospitalization, invasive procedures, and length of hospital stay with MDR *P. aeruginosa* [100]. A recent prospective cohort study that included over 40 hospitals worldwide, further highlighted the worrisome clinical impact of cpCR *P. aeruginosa* on 30-day mortality, which was increased compared to non-cpCR *P. aeruginosa* [101].

Other than worsened clinical outcomes, AMR has also negative impacts on the economy and healthcare systems by increasing financial costs on a national and individual level and reducing hospital activities. The increased costs associated with AMR vary among different regions of the globe. However, it is difficult to calculate the exact economical costs associated with AMR pathogens, especially in low-income countries. It is now a priority of many countries and international institutions to quantify the costs associated with AMR pathogens [102].

The Centers for Disease Control and Prevention (CDC) tried to estimate the financial costs associated with AMR pathogens in the United States from 2005 to 2015. The direct costs were estimated to be over 4.6 billion (95% CI, 4.1–5.1) US dollars annually for the six most common MDR bacterial infections [MRSA, vancomycin-resistant enterococci (VREs), ESBL, CR *Enterobacteriaceae*, CR *Acinetobacter*, and MDR *Pseudomonas*] receiving treatment in community and hospital settings [103]. Interestingly, CR *Acinetobacter* accounted for the highest costs in community and hospital settings [102]. Another analysis by the CDC showed that the treatment of patients over 65 years with MDR bacteria accounted for 1.9 billion US dollars annually [104]. These analyses do not include indirect costs such as future patient disability from infection complications, missed days at work or costs from treating complications such as CDI, therefore, the financial costs are thought to be even higher.

Additionally, the World Bank ran a comprehensive economic simulation to predict the effect of AMR on the global gross domestic product by the year 2050. Their simulation predicted that AMR could result in a 3.8% loss of the annual global gross domestic product by 2050 with an annual loss equalling 3.4 trillion US dollars by 2030, which is comparatively worse than the loses caused by the 2008–2009 global financial crisis [105]. Their simulation

further demonstrated that these effects will be harder on low-income countries, further increasing the gaps in wealth inequality [105], thus, making AMR a very dangerous threat to the world's economy. The World Bank also noted that different aspects of economy will be affected and not just healthcare costs, including international trade and livestock production which could acquire a 11% loss by 2050 [105]. However, it is important to understand that these are just predications based on simulations and more accurate data analysis is required to understand the true economic impact of AMR. Finally, European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) have released a technical report in 2009 where the financial consequences of AMR were estimated. In 2007, it was estimated that 900 million euros were spent in the European Union in extra-hospital costs and 10 million euros in outpatient care due to treating AMR pathogens, with an estimated 150 million euros loss due to loss of workdays of infected people [106]. The overall cost of AMR in the European Union is estimated to be 1.5 billion euros annually [106].

4. Tackling AMR

4.1 Antimicrobial Stewardship programs

ASPs are among the most vital tools that can be used to battle AMR in both community and healthcare settings, however, their implementation has been quite challenging, especially in community settings. ASPs have not only been successful in tackling AMR, but they also improve patient outcomes, reduce healthcare costs, and reduce adverse effects association with antimicrobial use, such as CDI [107]. Their effectiveness in reducing antimicrobial use, improving patient outcomes, and decreasing the incidence of antibiotic

resistance is well established making them an essential component to tackle AMR in hospitals as recommended by the CDC and WHO [108, 109].

The core elements of successful ASPs whether in community or hospitals include committed leadership groups, healthcare providers and prescribers to be accountable, experienced staff (that should include infectious disease specialists, pharmacists and microbiologists) with antimicrobial agents, education of healthcare providers and patients, and appropriate resource allocation [110].

Hospital-sector ACPs prioritize interventions that can be implemented in hospital-like institution and target hospitalized patients and hospital-acquired infections that are largely caused by AMR pathogens. The two major ASP strategies used in hospitals are prospective auditing and feedback and pre-authorization, which will be discussed in detail in upcoming sections. It is important to understand the usefulness of such interventions before implementing them. A recent systematic review aimed to assess the value of hospital ASPs, in which 146 studies included that were conducted mainly in North America and Europe [110]. Their results revealed that hospital ASPs provide great value to healthcare systems by decreasing hospital stay, saving healthcare related costs (average of US$732 per patient), and reducing antibiotic expenditure [110]. To evaluate whether the reduction of the antibiotic expenditure results in reduction in resistant pathogens is quite complicated and difficult to measure. Eleven of the included studies did, however, reveal that after an average period of 2 years of implementing ASPs, there was a decrease in bacterial resistance to at least one antibiotic agent. However, two studies showed an increase in resistance in other agents due to selection pressure [110]. Therefore, it is important to address such challenges when implementing ASPs. Another review also revealed similar trends where hospital ASPs were

successful in reducing carbapenem resistance in *P. aeruginosa* and control of AMR related infections [111].

Community-sector ASPs include interventions that can be implemented in primary care settings to tackle antibiotic use and typically address community-acquired infections that are treated in outpatient services. ASPs in community sections are thought to be more difficult to implement due to limited resources and lack of skilled personnel [112]. However, there are examples of ASPs that have been implemented in community settings with favorable results. For example, in Australia, there are systems that offer feedback to primary care physicians about their antibiotic prescribing patterns which has resulted in 18% reduction in the amount of antibiotics prescribed by them [113]. Educational ASPs can also be easily implemented in community settings to educate primary care physicians about AMR and its relationship to antibiotic misuse. This proves that with proper coordination among healthcare leadership in countries and community doctors, ASPs can be successful and provide an important tool to tackle AMR.

4.2 Infection Prevention and Control interventions

An important element to combat AMR is IPC interventions. Logically, preventing infections from occurring would result in reduction of antibiotic use, which is one of the main drivers of antibiotic resistance. IPC interventions are now considered the norm in many healthcare settings and are including in any global policy that aims to reduce AMR. In healthcare settings, the major role of IPC is to prevent hospital-acquired infections (HAIs) such as hospital-acquired pneumonia (HAP), catheter-related blood stream infections (CRBSIs), and surgical site infections (SSIs), which can be caused by a vast number of resistant pathogens and are associated with high mortality and morbidity [114]. The basic IPC

interventions include hand hygiene, standard precautions, transmission precautions, and environmental precautions [114, 115]. When followed accurately, these preventions have demonstrated great success in reducing the transmission of AMR in healthcare settings [116].

Hand hygiene is an important strategy because evidence has shown that healthcare workers hands are colonized with numerous AMR pathogens such as MRSA, VRE and MDR-Gram-negative bacteria [115]. Additionally, hand carriage of AMR pathogens has been associated with an increase in hospital-acquired infections [115]. There have been numerous studies conducted that assessed the results of using hand hygiene protocols on reduction of AMR infections. Studies conducted in various hospital units, such as ICUs and pediatric units, showed that hand hygiene, using triclosan 1% or alcohol-based antiseptics, with hand hygiene observation and educational posters have resulted in significant reductions in MRSA and VRE infections and colonization rates [116]. The efficacy of specific products for hand hygiene over others for the control of AMR is not yet established, however, it is evident that even basic hand hygiene protocols can reduce the transmission and cross-contamination with resistant pathogens.

Other strategies in IPC protocols, such standard precautions and contact precautions, have mixed results in controlling resistant pathogens. The effectiveness of such precautions is difficult assess in the literature due to the variability of practices and high risk of bias in such studies [117]. A recent meta-analysis 14 studies assessed whether the discontinuation of contact precaution in patients colonized with MRSA and VRE increased the rate of infections. Interestingly, their results revealed no change in the amount of MRSA infections and a statistically significant reduction in VRE infections [118]. Taken into context with previous information, these results show that basic IPC strategies such as hand hygiene and standard

precautions could be more effective in controlling the spread and infection rate of AMR pathogens than more complicated strategies and should remain in the cornerstone of future policies.

Another critical strategy that could reduce the risk resistant pathogens in healthcare and clinical settings is environmental control of these pathogens. Studies have clearly demonstrated that patients that use hospital equipment or rooms that harbor AMR bacteria are at an increased risk of infection from these pathogens [119]. This means environmental cleaning plays a pivotal role in controlling these infections. Evidence also backs up these conclusions as numerous multicenter studies in various healthcare settings such as ICUs have concluded that enhanced environmental cleaning measures such as chemical disinfection with soap-based products or probiotic cleaning has resulted in reduction of colonization rates and infection rates with difficult-to-treat pathogens [119-121].

As for community-based IPC interventions, vaccination remains the most powerful tool to tackle the increasing rates of AMR. Vaccines can directly and indirectly prevent the emergence of AMR. Directly this occurs by preventing the infection from bacterial pathogens that can acquire resistance. An important example is *S. pneumoniae* which has acquired resistance to penicillin. Vaccination against was successful in reducing penicillin-resistant *S. pneumoniae* by 45% in adults above 65 years in the United Sates [122]. Similar trends were also observed in European countries such as Italy where there was a reduction by 12% [122]. The biggest hurdle remains that many of such pathogens such as *S. aureus*, *P. aeruginosa*, and *K. pneumoniae* still have no available vaccines, however, currently vaccination development against such pathogens is a priority [123]. Indirectly, vaccinations against viruses can also reduce the emergence of AMR as it results in a reduction of symptomatic viral infections and

therefore a reduction in antibiotic misuse and/or overuse which, as discussed previously, is a major cause of AMR [123].

4.3 Global Policies

Various organizations have created action plans and guidelines to tackle the AMR such as the WHO, CDC, and various European regulator bodies. There are plans that have been conducted at national levels in specific countries, especially those known to be endemic to AMR infections. For example, in Greece, the National Action Plan on Antimicrobial Resistance based on the WHO Global Action plan was launched and includes measures to improve surveillance and monitoring of AMR, promote the responsible use of antibiotics, and increase public awareness of the risks associated with AMR [124]. Additionally, the Ministry of Health in Greece has implemented multiple antimicrobial stewardship programs per hospitals to monitor the prescribing of antimicrobials and created the Agency for Quality Assurance in Health S.A. to implement of educational programs on hospital-acquired infection prevention and control [125].

On a global context, the WHO have developed several initiatives and policies to tackle the increase in AMR worldwide. The WHO released a policy package, which includes recommendations for countries to implement around the globe to combat AMR. The policy package included recommendations such as strengthening surveillance and laboratory capacity, optimizing and regulating rational use of antimicrobial medicines, enhance infection prevention and control, and promote development and research for new relative tools [126].

In the United States, the CDC has developed a range of policies and initiatives to combat AMR. These include the Antibiotic Resistance Solutions Initiative, which aims to coordinate efforts across the public health and healthcare sectors to address AMR, and the

National Healthcare Safety Network (NHSN), a secure online surveillance system that healthcare facilities can use to track HAIs and antimicrobial use [127, 128]. The CDC also provides guidelines for healthcare providers on the appropriate use of antibiotics in hospital and community settings that can help establish local antimicrobial stewardship initiatives.

In Europe, the European One Health Action Plan provides a comprehensive framework that seeks to prevent and control AMR across human health, animals, and the environment. The plan includes a range of measures, such as improving surveillance and monitoring of AMR in farm animals, food, and healthcare settings, promoting the responsible use of antibiotics, promoting infection prevention and control practices in hospital settings and the community, and increasing research and development into new treatments for infectious diseases [129]. The guidelines also emphasize measures to be undertaken in agriculture settings to reduce antimicrobial uptake in farm animals [129].

4.4 Public awareness

Public awareness strategies when used efficiently can aid in communicating with the general public about AMR and therefore help in reducing its transmission and spread. Efficient public awareness campaigns can positively influence the behavior of patients, healthcare providers, and policymakers towards the appropriate use of antimicrobial agents. This is important because studies have shown that there exists a correlation between lack of awareness of the risks associated with AMR among patients and healthcare providers and the overuse and/or misuse of antimicrobials and the emergence of AMR in most countries [130].

A systematic review assessed the results of public awareness campaigns on antibiotic use in the United States. The studies included were heterogenous and included different type of target population such as veterans, parents of sick children, and Spanish speaking patients.

Interestingly, the majority of the studies showed a reduction in prescribing antibiotics following such campaigns [131]. However, there remains a lack in evidence if these interventions would directly result in a reduction of AMR in the community or healthcare settings.

Similar trends were also observed in studies conducted in Europe. In Europe, a campaign known as the European Antibiotic Awareness Day was launched and received positive reception from the public and leaders from numerous European countries [132]. Studies in various European countries, such as France and Belgium, have demonstrated that this campaign resulted in a decrease in antibiotic use in the community [133, 134]. Also, a study in Slovenia showed aa reduction in the resistance of *S. pneumoniae* to penicillin and macrolides [133].

To create effective public awareness campaigns, several steps should be undertaken. It is vital to measure the level of awareness among the general population and specific target populations before such campaigns are used [76]. Additionally, leaders, such as health ministries and important figures in healthcare, should ensure that their message is unified and clear since conflicting messages or those filled with misinformation can have negative impacts [76]. However, it is imperative to remember that such campaigns without other methods to tackle AMR would seldom result in long-term reduction of the AMR rates.

5. Antimicrobial Stewardship

5.1 Definition

Antimicrobial stewardship is defined as a coordinated interventions by healthcare organizations to optimize and standardize antibiotic use and promote the selection of appropriate antibiotic regimens to treat infections [107]. It can take place in varying healthcare systems with the goals of its programs to improve patient outcomes, reduce healthcare associated costs, reduce adverse effects associated with antibiotic use, and tackle the negative impacts associated with AMR [106]. In the literature, many terminologies have been used interchangeably to refer to antimicrobial stewardship, which include antibiotic policies, antibiotic management programs, and antibiotic consumption control programs [112].

5.2 Strategies

The major strategies of hospital ASPs involve prospective audit and feedback, and pre-authorization and antibiotic restriction. Other ASP strategies involve educating healthcare providers, combining antimicrobial treatments, oral-to-parenteral switching, optimizing antimicrobial dosages, and developing guidelines or clinical pathways [135]. Table 3 describes the different ASP strategies that can be utilized in healthcare settings.

Table 3. Antimicrobial stewardship program strategies in healthcare settings [107, 136].

Program	**Description**	**Strength of recommendation and quality of evidence[1]**
Preauthorization	Designed to restrict antimicrobial agent use by requiring healthcare providers to request approval prior to	Strong recommendation and

	prescribing certain antimicrobial agents	moderate-quality evidence
Prospective Audit and Feedback	Designed to augment antimicrobial use by reviewing antimicrobial treatment strategies with healthcare providers and providing them feedback following initiation of treatment	Strong recommendation and moderate-quality evidence
Educational didactics	Designed to provide education to healthcare providers in healthcare institutions an interactive lecture format to expand their knowledge about antimicrobial agents and their clinical use. These sessions can also cover certain hospital guidelines and clinical pathways	Weak recommendation and low-quality evidence
Institution-specific treatment guidelines	Involves the creation of evidence-based clinical practice guidelines and algorithms to standardize the prescribing habits of healthcare providers in these institutions. They should be evidence-based and	Weak recommendation and low-quality evidence

	tailored towards the local epidemiology	
Clinical pathways	These are clinical pathways that are designed for specific infectious diseases syndromes to improve and standardize prescribing habits among healthcare providers. They can be institution-based or nationally/internationally based	Weak recommendation and low-quality evidence
a) Dose-optimization and, b) Duration-optimization strategies	a) Designed to create alternative dosing strategies based on antimicrobial agents pharmacokinetic and pharmacodynamic properties in hospitalised patients. b) Duration-optimization protocols aim to create guidelines that recommend a specific duration for therapy based on patient-specific factors and infection	a) Strong recommendation and moderate-quality evidence (for aminoglycosides) Weak recommendation and low-quality evidence (for broad-spectrum β-lactams and vancomycin) b) Strong recommendation and moderate-quality

		evidence (for shortest duration)
Intravenous (iv) to oral conversion	Designed to implement programs that prioritize the use of oral antibiotics when appropriate and timely transition IV to oral antimicrobials	Strong recommendation and moderate-quality evidence

[1]Following recommendation by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA).

Pre-authorization and prospective audit and feedback are the major and most efficient ASP strategies that can be utilized, and both can be comprehensive enough to include other ASP strategies. Pre-authorization requires healthcare providers to get prior authorization for certain antimicrobials before prescribing them, while prospective audit and feedback is an intervention that in which antimicrobial prescribing is assessed by direct interaction with healthcare providers and providing feedback to providers following prescription [107]. Among both strategies, there is limited evidence to recommend one over the other. When hospitals and healthcare facilities consider which strategies to adapt, they need to have a clear understanding of their needs and goals (such as cost-savings or healthcare providing prescribing patterns) and resources (such as available personnel and their skills and data resources) [136].

Pre-authorization strategies are restrictive in nature and aim to directly control the prescribing habits of healthcare providers. The most comprehensive pre-authorization

strategies would involve the healthcare prescribing requesting authorization from the ASP before an antimicrobial agent is dispensed from the pharmacy [135]. This allows the ASP to properly review the antimicrobial agent and ensure it is the appropriate choice for the specific patient.

As for prospective audit and feedback, it is a strategy that emphasizes a team-based approach to patient care while protecting healthcare providers autonomy. It works by having the ASP team have direct interaction with healthcare providers by reviewing the antimicrobial therapy after it administration [136]. Following the review, feedback is provided which could serve as an education opportunity for the prescribers.

5.*3 Advantages and Disadvantages of each strategy*

As with any strategy, different ASP strategies have different advantages and disadvantages, which are vital to understand to allow for proper implementation. It is important to note that no study has proven for any of the major interventions to be superior, however, certain interventions could be more difficult to implement at different institutions.

The major advantages of pre-authorization strategies include:

- Significant reduction in the inappropriate use of antimicrobial agents, leading to reduction in antibiotic resistance,
- Utilization of evidence-based indications and appropriate use of cultures prior to initiating antimicrobials,
- Optimization of empiric antimicrobial choice, and
- Significant reduction in antimicrobial associated costs by reduction of treating their side-effects (such as CDI) or reduction of using high-cost agents [107].

As for the disadvantages of pre-authorization strategies, they include:

- Effectiveness of strategy depends on the skills of the people providing approval,
- Downstream use of antibiotics in place of empiric options is not addressed,
- Healthcare providers could report a loss of autonomy,
- Requires the availability of real-time providers for quick approvals,
- May shift antimicrobial resistance patterns to more broad-spectrum agents, and
- May result in delay of therapy [107].

On the other hand, the advantages provided by prospective audit and feedback interventions are different and may also address many of the disadvantages of pre-authorization. These advantages include:

- Prescriber's autonomy is maintained,
- Requires less real-time resources as it does not need to be implemented daily,
- Aids in building collegial relationships which enhances multidisciplinary team function,
- Increases the amount of clinical evidence available leading to better perception by healthcare providers,
- Provides educational benefit to clinicians, and
- Addresses de-escalation and other ASPs strategies, such as antimicrobial dose optimization and duration of treatment [107].

Provided prospective audit and feedback intervention also have specific disadvantages that need to be taken into consideration before their implementation. These include:

- Requires specific resources, such as computerized systems,

- Effectiveness depends on the available infrastructure and methods of delivering feedback,
- Labor-intensive, and
- Persuading healthcare workers to change treatment could prove difficult, which could cause these programs to long before any outcomes are met [107].

5.4 Existing experience of already implemented hospital ASPs

Since the introduction of hospital ASPs and the strong recommendation by international and national organizations for their use, there has been numerous studies conducted to assess their effectiveness in varying parts of the globe. A recent systematic review and meta-analysis aimed to assess the results of published studies of hospital ASPs until 2016 and found that there were over 200 published papers [137]. The majority of published literature covers studies conducted in North America and Europe, which further highlights the gap and difficulties in implementing ASPs in low-income countries. It is important to note that, when discussing the findings of such studies, many of them have used varying strategies of ASPs that were explained above.

The main findings of the meta-analysis revealed that ASPs were strongly effective in increasing compliance with antibiotic guidelines (15% difference from non-ASP interventions), reducing the duration of antibiotic treatment by around 2 days, and reducing in hospital length of stay by 1.12 days, without an increase in patient mortality or adverse effects [137]. There was also a weak association between ASPs and reduction in the CDI rates and in the resistance rates of Gram-negative and Gram-positive bacteria [137].

Even though the authors found no difference in adverse effects between hospitalized patients receiving treatment following ASPs and those that did not, there were few studies

that reported on these effects [137]. Additionally, it is important to note that one randomized controlled trial that used automatic antibiotic stop orders had to be terminated early due to delay in antibiotic therapy [138]. Therefore, more studies are still required to fully understand the adverse outcomes associated with specific ASP strategies [137]. The authors of the meta-analysis further divided ASPs strategies into restrictive interventions, that included prior authorization, and enabling interventions, that included prospective audit and feedback and education. When comparing these interventions, it was showed that both were independently associated with the results described above, however, their combination enhanced the desired effects [137]. Interestingly, their findings also revealed that enabling ASPs that included feedback were more effective than other strategies, however, the number of studies used for comparison was too low to make a definitive conclusion [137].

5.5 Barriers and facilitators to implementation of ASPs

The barriers and facilitators to implementation of ASPs vary by the sector in which interventions are to be implemented and the economic situation of the institutions and countries. Evidence suggests that ASPs are more readily implemented in developed countries compared to low-to-middle income countries [112].

Barriers in low-income countries are broad and include lack of infrastructure and resources, lack of national initiatives and local guidelines, and difficulty in changing prescribing behaviors [139]. In these countries, involvement of local stakeholders, availability of evidence-based guidelines, and availability of readily adaptable resources were considered as facilitators [139].

In developed countries, the barriers to ASP implementation include lack of funding, lack of information systems availability, lack of technological resources such as data analysis

programs, lack of qualified personnel, lack of laboratories for antibiotic susceptibility testing, poor communication and leadership, lack of performance metrics (for feedback), gaps in microbiology and infectious disease knowledge, and lack of awareness about the value of ASPs among healthcare administrators [140]. Additionally, in countries with MDR bacteria epidemics, limited availability of antimicrobial options could be a perceived barrier to ASP implementation [141]. In contrast, facilitators reported in developed countries included securing of specialized funding to implement ASPs, availability of infectious disease specialists, pharmacist and microbiologists to lead these projects, existing of local guidelines on implementing ASPs, and availability of electronic prescribing systems [140].

6. References

1. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022;400(10369):2221-48.

2. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399(10325):629-55.

3. Holmes AH, Moore LS, Sundsfjord A, Steinbakk M, Regmi S, Karkey A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387(10014):176-87.

4. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis. 2014;14:13.

5. Wilson APR. Sparing carbapenem usage. J Antimicrob Chemother. 2017;72(9):2410-7.

6. Moellering RC, Jr., Eliopoulos GM, Sentochnik DE. The carbapenems: new broad spectrum beta-lactam antibiotics. J Antimicrob Chemother. 1989;24 Suppl A:1-7.

7. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrob Agents Chemother. 2011;55(11):4943-60.

8. Zhanel GG, Wiebe R, Dilay L, Thomson K, Rubinstein E, Hoban DJ, et al. Comparative review of the carbapenems. Drugs. 2007;67(7):1027-52.

9. El-Gamal MI, Brahim I, Hisham N, Aladdin R, Mohammed H, Bahaaeldin A. Recent updates of carbapenem antibiotics. Eur J Med Chem. 2017;131:185-95.

10. Abdel-Rahman SM, Kearns GL, Topelberg S, Jacobs RF, Mistry GC, Majumdar A, et al. Pharmacokinetics and tolerability of single-dose intravenous ertapenem in infants, children, and adolescents. Pediatr Infect Dis J. 2010;29(12):1072-6.

11. Alvarez-Lerma F, Grau S, Ferrández O. Characteristics of doripenem: a new broad-spectrum antibiotic. Drug Des Devel Ther. 2009;3:173-90.

12. Tang C, Cai L, Liu S, Zheng Z, Li G, Chen J, et al. Crystal structure of tebipenem pivoxil. Acta Crystallogr E Crystallogr Commun. 2018;74(Pt 9):1215-7.

13. Chahine EB, Ferrill MJ, Poulakos MN. Doripenem: a new carbapenem antibiotic. Am J Health Syst Pharm. 2010;67(23):2015-24.

14. Cada DJ, Levien T, Mistry B, Baker DE. Doripenem for Injection. Hospital Pharmacy. 2008;43(3):210-21.

15. Lo TS, Welch JM, Alonto AM, Vicaldo-Alonto EA. A review of the carbapenems in clinical use and clinical trials. Recent Pat Antiinfect Drug Discov. 2008;3(2):123-31.

16. Redman R, File TM, Jr. Safety of intravenous infusion of doripenem. Clin Infect Dis. 2009;49 Suppl 1:S28-35.

17. Tattersall T, Wright H, Redmond A. Meropenem-induced liver injury and beta-lactam cross-reactivity. BMJ Case Reports. 2018;11(1):e227124.

18. Vardakas KZ, Kalimeris GD, Triarides NA, Falagas ME. An update on adverse drug reactions related to β-lactam antibiotics. Expert Opin Drug Saf. 2018;17(5):499-508.

19. Lee Y, Bradley N. Overview and Insights into Carbapenem Allergy. Pharmacy (Basel). 2019;7(3).

20. Gil-Serrano J, Cardona V, Luengo O, Guilarte M, Sala-Cunill A, Galvan-Blasco P, et al. Anaphylactic shock to meropenem with ertapenem tolerance: A case report. J Allergy Clin Immunol Pract. 2019;7(6):2057-8.

21. Shiber S, Yahav D, Avni T, Leibovici L, Paul M. β-Lactam/β-lactamase inhibitors versus carbapenems for the treatment of sepsis: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2015;70(1):41-7.

22. Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. Clostridium difficile infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. International Journal of Antimicrobial Agents. 2016;48(1):1-10.

23. Hecht DW, Galang MA, Sambol SP, Osmolski JR, Johnson S, Gerding DN. In vitro activities of 15 antimicrobial agents against 110 toxigenic clostridium difficile clinical isolates collected from 1983 to 2004. Antimicrob Agents Chemother. 2007;51(8):2716-9.

24. Suay-García B, Pérez-Gracia MT. Present and Future of Carbapenem-resistant Enterobacteriaceae (CRE) Infections. Antibiotics (Basel). 2019;8(3).

25. Meletis G, Exindari M, Vavatsi N, Sofianou D, Diza E. Mechanisms responsible for the emergence of carbapenem resistance in Pseudomonas aeruginosa. Hippokratia. 2012;16(4):303-7.

26. Li S, Duan X, Peng Y, Rui Y. Molecular characteristics of carbapenem-resistant Acinetobacter spp. from clinical infection samples and fecal survey samples in Southern China. BMC Infectious Diseases. 2019;19(1):900.

27. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. Clin Microbiol Rev. 2007;20(3):440-58, table of contents.

28. Bonnin RA, Jousset AB, Emeraud C, Oueslati S, Dortet L, Naas T. Genetic Diversity, Biochemical Properties, and Detection Methods of Minor Carbapenemases in Enterobacterales. Front Med (Lausanne). 2020;7:616490.

29. Aurilio C, Sansone P, Barbarisi M, Pota V, Giaccari LG, Coppolino F, et al. Mechanisms of Action of Carbapenem Resistance. Antibiotics (Basel). 2022;11(3).

30. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother. 2010;54(3):969-76.

31. Hall BG, Barlow M. Revised Ambler classification of β-lactamases. Journal of Antimicrobial Chemotherapy. 2005;55(6):1050-1.

32. Hammoudi Halat D, Ayoub Moubareck C. The Current Burden of Carbapenemases: Review of Significant Properties and Dissemination among Gram-Negative Bacteria. Antibiotics (Basel). 2020;9(4).

33. Sawa T, Kooguchi K, Moriyama K. Molecular diversity of extended-spectrum β-lactamases and carbapenemases, and antimicrobial resistance. Journal of Intensive Care. 2020;8(1):13.

34. Walsh TR. New Delhi metallo-β-lactamase-1: detection and prevention. Cmaj. 2011;183(11):1240-1.

35. Carrër A, Poirel L, Yilmaz M, Akan OA, Feriha C, Cuzon G, et al. Spread of OXA-48-encoding plasmid in Turkey and beyond. Antimicrob Agents Chemother. 2010;54(3):1369-73.

36. Tängdén T, Giske CG. Global dissemination of extensively drug-resistant carbapenemase-producing Enterobacteriaceae: clinical perspectives on detection, treatment and infection control. J Intern Med. 2015;277(5):501-12.

37. Goren MG, Carmeli Y, Schwaber MJ, Chmelnitsky I, Schechner V, Navon-Venezia S. Transfer of carbapenem-resistant plasmid from Klebsiella pneumoniae ST258 to Escherichia coli in patient. Emerg Infect Dis. 2010;16(6):1014-7.

38. Falahat S, Shojapour M, Sadeghi A. Detection of KPC Carbapenemase in Pseudomonas aeruginosa Isolated From Clinical Samples Using Modified Hodge Test and Boronic Acid Phenotypic Methods and Their Comparison With the Polymerase Chain Reaction. Jundishapur J Microbiol. 2016;9(9):e27249.

39. Hagemann JB, Pfennigwerth N, Gatermann SG, von Baum H, Essig A. KPC-2 carbapenemase-producing Pseudomonas aeruginosa reaching Germany. J Antimicrob Chemother. 2018;73(7):1812-4.

40. Boyd DA, Lisboa LF, Rennie R, Zhanel GG, Dingle TC, Mulvey MR. Identification of a novel metallo-β-lactamase, CAM-1, in clinical Pseudomonas aeruginosa isolates from Canada. J Antimicrob Chemother. 2019;74(6):1563-7.

41. Voulgari E, Politi L, Pitiriga V, Dendrinos J, Poulou A, Georgiadis G, et al. First report of an NDM-1 metallo-β-lactamase-producing Acinetobacter baumannii clinical isolate in Greece. Int J Antimicrob Agents. 2016;48(6):761-2.

42. Tietgen M, Leukert L, Sommer J, Kramer JS, Brunst S, Wittig I, et al. Characterization of the novel OXA-213-like β-lactamase OXA-822 from Acinetobacter calcoaceticus. J Antimicrob Chemother. 2021;76(3):626-34.

43. Higgins PG, Pérez-Llarena FJ, Zander E, Fernández A, Bou G, Seifert H. OXA-235, a novel class D β-lactamase involved in resistance to carbapenems in Acinetobacter baumannii. Antimicrob Agents Chemother. 2013;57(5):2121-6.

44. Elshamy AA, Aboshanab KM. A review on bacterial resistance to carbapenems: epidemiology, detection and treatment options. Future Sci OA. 2020;6(3):Fso438.

45. Köhler T, Michea-Hamzehpour M, Epp SF, Pechere JC. Carbapenem activities against Pseudomonas aeruginosa: respective contributions of OprD and efflux systems. Antimicrob Agents Chemother. 1999;43(2):424-7.

46. Codjoe FS, Donkor ES. Carbapenem Resistance: A Review. Med Sci (Basel). 2017;6(1).

47. Chetri S, Bhowmik D, Paul D, Pandey P, Chanda DD, Chakravarty A, et al. AcrAB-TolC efflux pump system plays a role in carbapenem non-susceptibility in Escherichia coli. BMC Microbiology. 2019;19(1):210.

48. Kornelsen V, Kumar A. Update on Multidrug Resistance Efflux Pumps in Acinetobacter spp. Antimicrob Agents Chemother. 2021;65(7):e0051421.

49. Choi U, Lee CR. Distinct Roles of Outer Membrane Porins in Antibiotic Resistance and Membrane Integrity in Escherichia coli. Front Microbiol. 2019;10:953.

50. Richardot C, Plésiat P, Fournier D, Monlezun L, Broutin I, Llanes C. Carbapenem resistance in cystic fibrosis strains of Pseudomonas aeruginosa as a result of amino acid substitutions in porin OprD. International Journal of Antimicrobial Agents. 2015;45(5):529-32.

51. Hao M, Ye M, Shen Z, Hu F, Yang Y, Wu S, et al. Porin Deficiency in Carbapenem-Resistant Enterobacter aerogenes Strains. Microb Drug Resist. 2018;24(9):1277-83.

52. Lee YQ, Sri La Sri Ponnampalavanar S, Chong CW, Karunakaran R, Vellasamy KM, Abdul Jabar K, et al. Characterisation of Non-Carbapenemase-Producing Carbapenem-Resistant Klebsiella pneumoniae Based on Their Clinical and Molecular Profile in Malaysia. Antibiotics (Basel). 2022;11(11).

53. Nguyen M, Joshi SG. Carbapenem resistance in Acinetobacter baumannii, and their importance in hospital-acquired infections: a scientific review. J Appl Microbiol. 2021;131(6):2715-38.

54. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-18.

55. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.

56. Falagas ME, Koletsi PK, Bliziotis IA. The diversity of definitions of multidrug-resistant (MDR) and pandrug-resistant (PDR) Acinetobacter baumannii and Pseudomonas aeruginosa. Journal of Medical Microbiology. 2006;55(12):1619-29.

57. Falagas ME, Karageorgopoulos DE. Pandrug Resistance (PDR), Extensive Drug Resistance (XDR), and Multidrug Resistance (MDR) among Gram-Negative Bacilli: Need for International Harmonization in Terminology. Clinical Infectious Diseases. 2008;46(7):1121-2.

58. De Oliveira DMP, Forde BM, Kidd TJ, Harris PNA, Schembri MA, Beatson SA, et al. Antimicrobial Resistance in ESKAPE Pathogens. Clin Microbiol Rev. 2020;33(3).

59. Biondo C. Bacterial Antibiotic Resistance: The Most Critical Pathogens. Pathogens. 2023;12(1).

60. Gimza BD, Cassat JE. Mechanisms of Antibiotic Failure During Staphylococcus aureus Osteomyelitis. Front Immunol. 2021;12:638085.

61. Henrichfreise B, Wiegand I, Pfister W, Wiedemann B. Resistance mechanisms of multiresistant Pseudomonas aeruginosa strains from Germany and correlation with hypermutation. Antimicrob Agents Chemother. 2007;51(11):4062-70.

62. Tang SS, Apisarnthanarak A, Hsu LY. Mechanisms of β-lactam antimicrobial resistance and epidemiology of major community- and healthcare-associated multidrug-resistant bacteria. Adv Drug Deliv Rev. 2014;78:3-13.

63. Tran QT, Williams S, Farid R, Erdemli G, Pearlstein R. The translocation kinetics of antibiotics through porin OmpC: insights from structure-based solvation mapping using WaterMap. Proteins. 2013;81(2):291-9.

64. Cooksey RC, Morlock GP, McQueen A, Glickman SE, Crawford JT. Characterization of streptomycin resistance mechanisms among Mycobacterium tuberculosis isolates from patients in New York City. Antimicrob Agents Chemother. 1996;40(5):1186-8.

65. Ahmed MO, Baptiste KE. Vancomycin-Resistant Enterococci: A Review of Antimicrobial Resistance Mechanisms and Perspectives of Human and Animal Health. Microb Drug Resist. 2018;24(5):590-606.

66. Trieber CA, Taylor DE. Mutations in the 16S rRNA genes of Helicobacter pylori mediate resistance to tetracycline. J Bacteriol. 2002;184(8):2131-40.

67. Miklasińska-Majdanik M. Mechanisms of Resistance to Macrolide Antibiotics among Staphylococcus aureus. Antibiotics. 2021;10(11):1406.

68. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. Lancet Public Health. 2022;7(11):e897-e913.

69. Tao S, Chen H, Li N, Wang T, Liang W. The Spread of Antibiotic Resistance Genes In Vivo Model. Can J Infect Dis Med Microbiol. 2022;2022:3348695.

70. Partridge SR, Kwong SM, Firth N, Jensen SO. Mobile Genetic Elements Associated with Antimicrobial Resistance. Clin Microbiol Rev. 2018;31(4).

71. Yu Z, Wang Y, Henderson IR, Guo J. Artificial sweeteners stimulate horizontal transfer of extracellular antibiotic resistance genes through natural transformation. Isme j. 2022;16(2):543-54.

72. Overballe-Petersen S, Harms K, Orlando LA, Mayar JV, Rasmussen S, Dahl TW, et al. Bacterial natural transformation by highly fragmented and damaged DNA. Proc Natl Acad Sci U S A. 2013;110(49):19860-5.

73. Borodovich T, Shkoporov AN, Ross RP, Hill C. Phage-mediated horizontal gene transfer and its implications for the human gut microbiome. Gastroenterol Rep (Oxf). 2022;10:goac012.

74. Read AF, Woods RJ. Antibiotic resistance management. Evolution, Medicine, and Public Health. 2014;2014(1):147-.

75. Lushniak BD. Antibiotic Resistance: A Public Health Crisis. Public Health Reports. 2014;129(4):314-6.

76. Mathew P, Sivaraman S, Chandy S. Communication strategies for improving public awareness on appropriate antibiotic use: Bridging a vital gap for action on antibiotic resistance. J Family Med Prim Care. 2019;8(6):1867-71.

77. Viswanathan VK. Off-label abuse of antibiotics by bacteria. Gut Microbes. 2014;5(1):3-4.

78. Gross M. Antibiotics in crisis. Current Biology. 2013;23(24):R1063-R5.

79. Kourlaba G, Gkrania-Klotsas E, Kourkouni E, Mavrogeorgos G, Zaoutis TE. Antibiotic prescribing and expenditures in outpatient adults in Greece, 2010 to 2013: evidence from real-world practice. Euro Surveill. 2016;21(26).

80. Serwecińska L. Antimicrobials and Antibiotic-Resistant Bacteria: A Risk to the Environment and to Public Health. Water. 2020;12(12):3313.

81. Tiseo K, Huber L, Gilbert M, Robinson TP, Van Boeckel TP. Global Trends in Antimicrobial Use in Food Animals from 2017 to 2030. Antibiotics (Basel). 2020;9(12).

82. Bartlett JG, Gilbert DN, Spellberg B. Seven Ways to Preserve the Miracle of Antibiotics. Clinical Infectious Diseases. 2013;56(10):1445-50.

83. Wee BA, Muloi DM, van Bunnik BAD. Quantifying the transmission of antimicrobial resistance at the human and livestock interface with genomics. Clin Microbiol Infect. 2020;26(12):1612-6.

84. Armalytė J, Skerniškytė J, Bakienė E, Krasauskas R, Šiugždinienė R, Kareivienė V, et al. Microbial Diversity and Antimicrobial Resistance Profile in Microbiota From Soils of Conventional and Organic Farming Systems. Front Microbiol. 2019;10:892.

85. Golkar Z, Bagasra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. J Infect Dev Ctries. 2014;8(2):129-36.

86. Malagón-Rojas JN, Parra Barrera EL, Lagos L. From environment to clinic: the role of pesticides in antimicrobial resistance. Rev Panam Salud Publica. 2020;44:e44.

87. Kampf G. Biocidal Agents Used for Disinfection Can Enhance Antibiotic Resistance in Gram-Negative Species. Antibiotics. 2018;7(4):110.

88. Friedman ND, Temkin E, Carmeli Y. The negative impact of antibiotic resistance. Clin Microbiol Infect. 2016;22(5):416-22.

89. Bai AD, Lo CKL, Komorowski AS, Suresh M, Guo K, Garg A, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. Clin Microbiol Infect. 2022;28(8):1076-84.

90. Bai AD, Lo CK, Komorowski AS, Suresh M, Guo K, Garg A, et al. Staphylococcus aureus bacteremia mortality across country income groups: A secondary analysis of a systematic review. Int J Infect Dis. 2022;122:405-11.

91. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis. 2003;36(1):53-9.

92. French GL. Clinical impact and relevance of antibiotic resistance. Adv Drug Deliv Rev. 2005;57(10):1514-27.

93. Camacho-Cruz J, Gutiérrez IF, Brand-López K, Sosa-Rodríguez YA, Vásquez-Hoyos P, Gómez-Cortés LC, et al. Differences Between Methicillin-susceptible Versus Methicillin-resistant Staphylococcus aureus Infections in Pediatrics: Multicenter Cohort Study Conducted in Bogotá, Colombia, 2014-2018. Pediatr Infect Dis J. 2022;41(1):12-9.

94. Kanyo EC, Nowacki AS, Gordon SM, Shrestha NK. Comparison of mortality, stroke, and relapse for methicillin-resistant versus methicillin-susceptible Staphylococcus aureus

infective endocarditis: a retrospective cohort study. Diagn Microbiol Infect Dis. 2021;100(4):115395.

95. Chatterjee A, Rai S, Guddattu V, Mukhopadhyay C, Saravu K. Is methicillin-resistant Staphylococcus Aureus infection associated with higher mortality and morbidity in hospitalized patients? A cohort study of 551 patients from South Western India. Risk Manag Healthc Policy. 2018;11:243-50.

96. Katsarou I, Paraskevopoulou NM, Papadimitriou-Olivgeris M, Giormezis N, Militsopoulou M, Kolonitsiou F, et al. Fatality of Staphylococcus aureus infections in a Greek university hospital: role of inappropriate empiric treatment, methicillin resistance, and toxin genes' presence. Eur J Clin Microbiol Infect Dis. 2020;39(3):443-50.

97. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA. Outcome and attributable mortality in critically Ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant Staphylococcus aureus. Arch Intern Med. 2002;162(19):2229-35.

98. Shamsrizi P, Gladstone BP, Carrara E, Luise D, Cona A, Bovo C, et al. Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria-producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. BMJ Open. 2020;10(1):e030266.

99. Daneman N, Fridman D, Johnstone J, Langford BJ, Lee SM, MacFadden DM, et al. Antimicrobial resistance and mortality following E. coli bacteremia. EClinicalMedicine. 2023;56:101781.

100. Hirsch EB, Tam VH. Impact of multidrug-resistant Pseudomonas aeruginosa infection on patient outcomes. Expert Rev Pharmacoecon Outcomes Res. 2010;10(4):441-51.

101. Reyes J, Komarow L, Chen L, Ge L, Hanson BM, Cober E, et al. Global epidemiology and clinical outcomes of carbapenem-resistant Pseudomonas aeruginosa and associated carbapenemases (POP): a prospective cohort study. Lancet Microbe. 2023;4(3):e159-e70.

102. Morel CM, Alm RA, Årdal C, Bandera A, Bruno GM, Carrara E, et al. A one health framework to estimate the cost of antimicrobial resistance. Antimicrob Resist Infect Control. 2020;9(1):187.

103. Nelson RE, Hatfield KM, Wolford H, Samore MH, Scott RD, Reddy SC, et al. National Estimates of Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Hospitalized Patients in the United States. Clin Infect Dis. 2021;72(Suppl 1):S17-s26.

104. Nelson RE, Hyun D, Jezek A, Samore MH. Mortality, Length of Stay, and Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Elderly Hospitalized Patients in the United States. Clin Infect Dis. 2022;74(6):1070-80.

105. Jonas OB, Irwin A, Berthe FCJ, Le Gall FG, Marquez PV. Drug-resistant infections: a threat to our economic future. 2017 01/03/2019. Report No.: 114679.

106. The bacterial challenge: time to react. Technical Report. Stockholm; 2009. Contract No.: EMEA/576176/2009.

107. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51-77.

108. Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. Clin Infect Dis. 2014;59 Suppl 3(Suppl 3):S97-100.

109. Antimicrobial stewardship programmes in health-care facilities in low- and middle-income countries. A practical toolkit. Geneva; 2019.

110. Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. Antimicrobial Resistance & Infection Control. 2019;8(1):35.

111. Shirazi OU, Ab Rahman NS, Zin CS. A Narrative Review of Antimicrobial Stewardship Interventions within In-patient Settings and Resultant Patient Outcomes. J Pharm Bioallied Sci. 2020;12(4):369-80.

112. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev. 2005;18(4):638-56.

113. Glasziou P, Dartnell J, Biezen R, Morgan M, Manski-Nankervis JA. Antibiotic stewardship: A review of successful, evidence-based primary care strategies. Aust J Gen Pract. 2022;51(1-2):15-20.

114. Daniels TL, Talbot TR. Infection control and prevention considerations. Cancer Treat Res. 2014;161:463-83.

115. Mathur P. Hand hygiene: back to the basics of infection control. Indian J Med Res. 2011;134(5):611-20.

116. Allegranzi B, Pittet D. Role of hand hygiene in healthcare-associated infection prevention. J Hosp Infect. 2009;73(4):305-15.

117. Moralejo D, El Dib R, Prata RA, Barretti P, Corrêa I. Improving adherence to Standard Precautions for the control of health care-associated infections. Cochrane Database Syst Rev. 2018;2(2):Cd010768.

118. Marra AR, Edmond MB, Schweizer ML, Ryan GW, Diekema DJ. Discontinuing contact precautions for multidrug-resistant organisms: A systematic literature review and meta-analysis. Am J Infect Control. 2018;46(3):333-40.

119. Kernéis S, Lucet JC. Controlling the Diffusion of Multidrug-Resistant Organisms in Intensive Care Units. Semin Respir Crit Care Med. 2019;40(4):558-68.

120. Huang J, Cui C, Zhou S, Chen M, Wu H, Jin R, et al. Impact of multicenter unified enhanced environmental cleaning and disinfection measures on nosocomial infections among patients in intensive care units. J Int Med Res. 2020;48(8):300060520949766.

121. Leistner R, Kohlmorgen B, Brodzinski A, Schwab F, Lemke E, Zakonsky G, et al. Environmental cleaning to prevent hospital-acquired infections on non-intensive care units: a pragmatic, single-centre, cluster randomized controlled, crossover trial comparing soap-based, disinfection and probiotic cleaning. EClinicalMedicine. 2023;59:101958.

122. Buchy P, Ascioglu S, Buisson Y, Datta S, Nissen M, Tambyah PA, et al. Impact of vaccines on antimicrobial resistance. Int J Infect Dis. 2020;90:188-96.

123. Micoli F, Bagnoli F, Rappuoli R, Serruto D. The role of vaccines in combatting antimicrobial resistance. Nature Reviews Microbiology. 2021;19(5):287-302.

124. Greece: National action plan on antimicrobial resistance. 2009.

125. Barmpouni M, Gordon JP, Miller RL, Pritchard CRJ, Dennis JW, Grammelis V, et al. Estimating the Clinical and Economic Impact of Introducing a New Antibacterial into Greek

Clinical Practice for the Management of Hospital-Acquired Infections with Limited Treatment Options. Infect Dis Ther. 2023;12(2):527-43.

126. Leung E, Weil DE, Raviglione M, Nakatani H. The WHO policy package to combat antimicrobial resistance. Bull World Health Organ. 2011;89(5):390-2.

127. National Academies of Sciences E, Medicine, Health, Medicine D, Board on Population H, Public Health P, et al. The National Academies Collection: Reports funded by National Institutes of Health. In: Palmer GH, Buckley GJ, editors. Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine. Washington (DC): National Academies Press (US)

Copyright 2022 by the National Academy of Sciences. All rights reserved.; 2021.

128. Kuehn BM. CDC Establishes Global Networks to Combat Antimicrobial Resistance. JAMA. 2022;327(4):315-.

129. A European One Health Action Plan against Antimicrobial Resistance (AMR). 2017.

130. Huttner B, Saam M, Moja L, Mah K, Sprenger M, Harbarth S, et al. How to improve antibiotic awareness campaigns: findings of a WHO global survey. BMJ Glob Health. 2019;4(3):e001239.

131. Burstein VR, Trajano RP, Kravitz RL, Bell RA, Vora D, May LS. Communication interventions to promote the public's awareness of antibiotics: a systematic review. BMC Public Health. 2019;19(1):899.

132. Earnshaw S, Monnet DL, Duncan B, O'Toole J, Ekdahl K, Goossens H. European Antibiotic Awareness Day, 2008 - the first Europe-wide public information campaign on

prudent antibiotic use: methods and survey of activities in participating countries. Euro Surveill. 2009;14(30):19280.

133. Cizman M, Plankar Srovin T, Beović B, Vrdelja M, Bajec T, Blagus R. European Antibiotic Awareness Day (EAAD): any impact on antibiotic consumption and public awareness in Slovenia? Journal of Antimicrobial Chemotherapy. 2018;73(9):2567-72.

134. Sabuncu E, David J, Bernède-Bauduin C, Pépin S, Leroy M, Boëlle PY, et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. PLoS Med. 2009;6(6):e1000084.

135. Ababneh MA, Nasser SA, Rababa'h AM. A systematic review of Antimicrobial Stewardship Program implementation in Middle Eastern countries. International Journal of Infectious Diseases. 2021;105:746-52.

136. Practical Implementation of an Antibiotic Stewardship Program. Cambridge: Cambridge University Press; 2018.

137. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2(2):Cd003543.

138. Strom BL, Schinnar R, Aberra F, Bilker W, Hennessy S, Leonard CE, et al. Unintended Effects of a Computerized Physician Order Entry Nearly Hard-Stop Alert to Prevent a Drug Interaction: A Randomized Controlled Trial. Archives of Internal Medicine. 2010;170(17):1578-83.

139. Wu S, Tannous E, Haldane V, Ellen ME, Wei X. Barriers and facilitators of implementing interventions to improve appropriate antibiotic use in low- and middle-income countries: a

systematic review based on the Consolidated Framework for Implementation Research. Implementation Science. 2022;17(1):30.

140. Rzewuska M, Duncan EM, Francis JJ, Morris AM, Suh KN, Davey PG, et al. Barriers and Facilitators to Implementation of Antibiotic Stewardship Programmes in Hospitals in Developed Countries: Insights From Transnational Studies. Front Sociol. 2020;5:41.

141. Pulcini C, Tebano G, Mutters NT, Tacconelli E, Cambau E, Kahlmeter G, et al. Selective reporting of antibiotic susceptibility test results in European countries: an ESCMID cross-sectional survey. Int J Antimicrob Agents. 2017;49(2):162-6.

CHAPTER II

Antimicrobial Prescribing before and after the Implementation of a Carbapenem-Focused Antimicrobial Stewardship Program in a Greek Tertiary Hospital during the COVID-19 Pandemic

Nikolaos Spernovasilis [1,2,3], Evangelos I. Kritsotakis [1,4] , Anna Mathioudaki [2], Alexandra Vouidaski [2], Ioulia Markaki [2], Despoina Psaroudaki [2], Petros Ioannou [1,2] and Diamantis P. Kofteridis [1,2]

[1] School of Medicine, University of Crete, 71500 Heraklion, Greece

[2] Department of Internal Medicine and Infectious Diseases, University Hospital of Heraklion, 71500 Heraklion, Greece

[3] Department of Infectious Diseases, German Oncology Center, 4108 Limassol, Cyprus

[4] Laboratory of Biostatistics, School of Medicine, 71500 Heraklion, University of Crete

Published in: ***Antibiotics (Basel). 2022 Dec 27;12(1):39.***

1. Abstract

Background: Irrational use of antimicrobials poses a significant risk for public health by aggravating antimicrobial resistance. The aim of this repeated point prevalence survey (PPS) was to evaluate the impact of a carbapenem-focused antimicrobial stewardship program (ASP) on overall antimicrobial use and quality of antimicrobial prescribing during the COVID-19 pandemic.

Methods: All adult inpatients in the University Hospital of Heraklion in Greece were audited twice, before and after the implementation of the ASP, in October 2019 and October 2020, respectively. Patient characteristics, indications and diagnoses for antimicrobial administration, antimicrobials prescribed, and compliance with treatment guidelines were recorded.

Results: Of 743 adult inpatients on the days of the two surveys, 398 (53.6%) were on antimicrobials for 437 diagnoses. Following implementation of the ASP, there was substantial decrease in the utilization of carbapenems (4.9% of all antibacterials prescribed in the second PPS compared to 10.3% in the first PPS). A significant improvement was observed for all indicators of the quality of antimicrobial prescribing.

Conclusions: Our study demonstrated a positive impact of an ASP implementation during the first stages of the COVID-19 pandemic on reducing the use of last-line antimicrobials and improving overall quality of antimicrobial prescribing.

2. Introduction

Antimicrobial overuse and misuse represent major public health problems worldwide and are tightly linked with negative patient outcomes, emergence and spread of antimicrobial resistance (AMR), increased risk of side effects, and higher healthcare cost [1,2]. The COVID-19 pandemic aggravated the issue of inappropriate antimicrobial use in several ways. Specifically, in many cases antibiotics were used irrationally to treat COVID-19 patients without proof or suspicion of bacterial co- or superinfection, and antiparasitics were often used as repurposed drugs against SARS-CoV-2 in the absence of scientific evidence [3–5].

For many years now, Greece ranks among the European countries with the highest rates of antibiotic consumption and AMR, both in community and hospital settings, and is one of the largest consumers of last-line antibiotics, such as carbapenems and polymyxins [6,7]. Implementation of targeted efforts, based on local data, is imperative for improvement of antimicrobial use. These efforts should aim to various levels of the antimicrobial prescription chain, including prescriber education, prescription practices, patient monitoring and feedback, and communication [8]. Relatively little investment per capita in infection prevention and control (IPC) strategies and antimicrobial stewardship programs (ASPs) could pay itself back in a very short time by reducing the burden of disability and death due to infections caused by multidrug-resistant bacteria [9]. Currently, a national action plan on AMR is under development, while few Greek hospitals have already attempted to optimize IPC practices and to implement ASPs [10–13].

On the 1 January 2020, a carbapenem-focused ASP was implemented in all adult clinics of our hospital in Greece. The program was based on the prospective audit and feedback strategy, along with case-based education and meetings on proper use of antimicrobials. The

ASP team was alerted by the hospital pharmacy upon prescription order of a carbapenem and, within 72 h, provided unsolicited in-person consultation.

In parallel to the carbapenem-focused ASP in our hospital, repeated point prevalence surveys (PPS) were performed among all adult inpatients, aiming to identify risk factors associated with inappropriate antimicrobial use in our hospital and to evaluate the impact of the ASP on overall antimicrobial utilization and quality of antimicrobial prescribing.

3. Results

In all, 743 patients were hospitalized on the days of the two surveys, of whom 398 patients (53.6%) were receiving antimicrobials for 437 diagnoses. Of the 398 inpatients surveyed in the 2019 PPS, 203 (51.0%) were on antimicrobials, while in the 2020 PPS, 195 (56.5%) of the 345 inpatients were receiving antimicrobials. Baseline characteristics of patients on antimicrobials are presented in Table 1.

The majority of antimicrobial prescriptions was for therapeutic reasons. The most common indication for antimicrobial treatment was community-acquired infection (CAI) followed by hospital-acquired infection (HAI), while between the two surveys there was a statistically significant difference regarding indications for antimicrobial administration. The top three diagnoses for antimicrobial prescription in both PPSs were respiratory infections, followed by skin, soft tissue, bone and joint infections, and gastrointestinal infections (including intra-abdominal and *Clostridioides difficile* infections) (Table 2).

Table 1. Patients' characteristics, 2019 vs 2020.

	Total (n=398)	**2019 (n=203)**	**2020 (n=195)**	**p-value**
Female	164 (41.2%)	95 (46.8%)	69 (35.4%)	0.021
Age (years)	65.5 (49.0-78.0)	66.0 (50.0-78.0)	65.0 (48.0-78.0)	0.59
BMI (kg/m^2)	26.0 (23.0-29.0)	25.0 (23.0-29.0)	27.0 (24.0-30.0)	0.30
McCabe score				0.006
Non-fatal	233 (58.5%)	133 (65.5%)	100 (51.3%)	
Ultimately fatal	127 (31.9%)	52 (25.6%)	75 (38.5%)	
Rapidly fatal	33 (8.3%)	13 (6.4%)	20 (10.3%)	
Missing	5 (1.3%)	5 (2.5%)	0 (0.0%)	
Treatment setting				0.19
Medical	191 (48.0%)	106 (52.2%)	85 (43.6%)	
Surgical	176 (44.2%)	81 (39.9%)	95 (48.7%)	
Intensive care	31 (7.8%)	16 (7.9%)	15 (7.7%)	
Inserted invasive devices (total)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	0.20
Indwelling urinary catheter	164 (41.2%)	81 (39.9%)	83 (42.6%)	0.59
Peripheral vascular catheter	349 (87.7%)	182 (89.7%)	167 (85.6%)	0.22
Central vascular catheter	59 (14.8%)	29 (14.3%)	30 (15.4%)	0.76

Invasive respiratory endotracheal intubation	34 (8.5%)	15 (7.4%)	19 (9.7%)	0.40
Inserted tubes and drains	50 (12.6%)	16 (7.9%)	34 (17.4%)	0.004

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

Table 2. Indications and diagnoses for antimicrobial use, 2019 vs. 2020.

Indicator	**2019**	**2020**	**P-value**
Hospitalized patients	398 (100.0%)	345 (100.0%)	-
Patients on antimicrobials [(1)]	203 (51.0%)	195 (56.5%)	0.133
Total number of diagnoses [(2)]	217 (54.5%)	220 (63.8%)	0.102
Indication [(3)]			0.021
CAI	83 (38.2%)	94 (42.7%)	
SP1	1 (0.5%)	0 (0.0%)	
SP2	0 (0.0%)	10 (4.5%)	
SP3	42 (19.4%)	34 (15.5%)	
HAI	68 (31.3%)	64 (29.1%)	
MP	15 (6.9%)	15 (6.8%)	
UNK	8 (3.7%)	3 (1.4%)	
Diagnosis [(2)]			0.142
UNK	9 (4.1%)	2 (0.9%)	
CNS	6 (2.8%)	4 (1.8%)	
EYE	0 (0.0%)	2 (0.9%)	

ENT	6 (2.8%)	6 (2.7%)	
RESP	46 (21.2%)	41 (18.6%)	
CVS	9 (4.1%)	4 (1.8%)	
GI	35 (16.1%)	37 (16.8%)	
SSTBJ	36 (16.6%)	43 (19.5%)	
UTI	30 (13.8%)	27 (12.3%)	
GUOB	12 (5.5%)	17 (7.7%)	
BAC	4 (1.8%)	13 (5.9%)	
SEPSIS	9 (4.1%)	4 (1.8%)	
FN	5 (2.3%)	5 (2.3%)	
OTHER/NDS	10 (4.6%)	15 (6.8%)	
Treatment for HAI or CAI [4]			0.310
Empirical	102 (67.5%)	98 (62.0%)	
Targeted	49 (32.5%)	60 (38.0%)	

Notes: [1] percentages calculated over the total number of hospitalized patients; [2] each patient could have more than one diagnosis; [3] percentages calculated over the total number of diagnoses; [4] percentages calculated over the sum of CAIs and HAIs. Abbreviations: CAI = community acquired infection, SP1 = surgical prophylaxis 1 dose, SP2 = surgical prophylaxis for 1 day, SP3 = surgical prophylaxis > 1 day, HAI = hospital acquired infection, MP = medical prophylaxis, UNK = unknown, CNS = central nervous system infection, EYE = eye infection, ENT = ear, nose, throat infection, RESP = respiratory infection, CVS = cardiovascular system infection, GI = gastrointestinal infection, SSTBJI = skin and soft tissue and bone/joint infection, UTI = urinary tract infection, GUOB = genitourinary and obstetric/gynecological infection, BAC = bacteremia or fungemia with no clear anatomic site and no shock, SEPSIS = sepsis of any

origin, sepsis syndrome or septic shock with no clear anatomic site, FN = fever in neutropenic patient, NDS = no defined site.

No statistically significant differences were observed between the two survey periods regarding the frequency of use of different antimicrobial types (Table 3). Antibacterials were the most common antimicrobials prescribed, followed by antifungals. In both PPSs, cephalosporins were the most commonly prescribed antibacterials, while fluoroquinolones and penicillins ± β-lactamase inhibitors alternated in the second and third position of the most commonly prescribed antibacterials (Table 4). Importantly, after the implementation of the carbapenem-focused ASP, there was substantial decrease in the utilization of carbapenems (4.9% of all antibacterials prescribed in the second PPS compared with 10.3% in the first PPS). Apart from McCabe score, no significant differences were observed regarding the characteristics of the patients receiving carbapenems in the two surveys (Table 5). This decrease in carbapenem use after the ASP implementation was also accompanied by a decrease in colistin use and an increase in piperacillin/tazobactam and tigecycline utilization, while the use of cephalosporins ± β-lactamase inhibitors (i.e., ceftolozane/tazobactam and ceftazidime/avibactam) remained largely unchanged (Table 4).

Table 3. Frequencies of antimicrobials prescribed by type, 2019 vs 2020.

Antimicrobial type	**2019 (n=343)**	**2020 (n=348)**	**P-value**
Antibacterial	310 (90.4%)	307 (88.2%)	0.358
Antimycobacterial	0 (0.0%)	3 (0.9%)	0.085
Antifungal	25 (7.3%)	30 (8.6%)	0.518

Antiviral	7 (2.0%)	8 (2.3%)	0.816
Antiparasitic	1 (0.3%)	0 (0.0%)	0.313

Data are presented as n (%) of total number of antimicrobials.

Table 4. Type of antibacterials, 2019 vs 2020.

	Total (n=617)	**2019 (n=310)**	**2020 (n=307)**	**p-value**
Antibacterial group				0.094
Penicillin ± β-lactamase inhibitor	89 (14.4%)	38 (12.3%)	51 (16.6%)	
Cephalosporin	130 (21.1%)	67 (21.6%)	63 (20.5%)	
Cephalosporin ± β-lactamase inhibitor	11 (1.8%)	5 (1.6%)	6 (2.0%)	
Carbapenem	47 (7.6%)	32 (10.3%)	15 (4.9%)	
Aminoglycoside	9 (1.5%)	5 (1.6%)	4 (1.3%)	
Tetracycline	1 (0.2%)	1 (0.3%)	0 (0.0%)	
Macrolide	7 (1.1%)	5 (1.6%)	2 (0.7%)	
Lincosamide	11 (1.8%)	5 (1.6%)	6 (2.0%)	
Fluoroquinolone	78 (12.6%)	40 (12.9%)	38 (12.4%)	
Trimethoprim/Sulfamethoxazole	10 (1.6%)	3 (1.0%)	7 (2.3%)	
Metronidazole	49 (7.9%)	20 (6.5%)	29 (9.4%)	
Oxazolidinone	19 (3.1%)	13 (4.2%)	6 (2.0%)	
Glycopeptide	42 (6.8%)	19 (6.1%)	23 (7.5%)	
Daptomycin	37 (6.0%)	20 (6.5%)	17 (5.5%)	
Tigecycline	25 (4.1%)	7 (2.3%)	18 (5.9%)	

Colistin	29 (4.7%)	18 (5.8%)	11 (3.6%)	
Other antibacterial	23 (3.7%)	12 (3.9%)	11 (3.6%)	

Data are presented as n (%) of total number of antibacterials.

Table 5. Characteristics of patients receiving carbapenems, 2019 vs 2020.

	Total (n=44)	**2019 (n=31)**	**2020 (n=13)**	**p-value**
Female	17 (38.6%)	13 (41.9%)	4 (30.8%)	0.49
Age (years)	68.0 (55.5-79.0)	68.0 (53.0-79.0)	68.0 (59.0-79.0)	0.85
BMI (kg/m^2)	25.0 (22.0-30.0)	24.0 (21.0-30.0)	27.0 (22.0-30.0)	0.40
McCabe				0.004
Non-fatal	17 (38.6%)	16 (51.6%)	1 (7.7%)	
Ultimately fatal	18 (40.9%)	11 (35.5%)	7 (53.8%)	
Rapidly fatal	7 (15.9%)	2 (6.5%)	5 (38.5%)	
Missing	2 (4.5%)	2 (6.5%)	0 (0.0%)	
Treatment unit				0.92
Medical	29 (65.9%)	21 (67.7%)	8 (61.5%)	
Surgical	9 (20.5%)	6 (19.4%)	3 (23.1%)	
Intensive care	6 (13.6%)	4 (12.9%)	2 (15.4%)	
Inserted invasive devices (total)	2.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (2.0-2.0)	0.14

Indwelling urinary catheter	24 (54.5%)	15 (48.4%)	9 (69.2%)	0.21
Peripheral vascular catheter	35 (79.5%)	26 (83.9%)	9 (69.2%)	0.27
Central vascular catheter	12 (27.3%)	8 (25.8%)	4 (30.8%)	0.74
Invasive respiratory endotracheal intubation	5 (11.4%)	3 (9.7%)	2 (15.4%)	0.59
Inserted tubes and drains	5 (11.4%)	1 (3.2%)	4 (30.8%)	0.009

Data are presented as median (IQR) for continuous measures and n (%) for categorical measures.

Regarding the quality of antimicrobial prescribing, a statistically significant improvement was observed in all relative indicators after the implementation of the carbapenem-focused ASP in our hospital (Table 6). The rate of documentation of reason and of stop/review date of antimicrobial administration was significantly higher ($p<0.001$) in the second PPS, while full compliance to national or international treatment guidelines was also significantly increased from 61.8% to 73.6% ($p=0.003$) after ASP implementation.

Table 6. Therapy quality indicators by diagnoses, 2019 vs 2020.

	Total (n=437)	**2019 (n=217)**	**2020 (n=220)**	**p-value**
Reason in notes	331 (75.7%)	130 (59.9%)	201 (91.4%)	<0.001
Stop/Review Date Documented	204 (46.7%)	49 (22.6%)	155 (70.5%)	<0.001
Guidelines Compliance				0.003
No	93 (21.3%)	47 (21.7%)	46 (20.9%)	

Yes	296 (67.7%)	134 (61.8%)	162 (73.6%)
Not assessable	9 (2.1%)	8 (3.7%)	1 (0.5%)
No information	11 (2.5%)	9 (4.1%)	2 (0.9%)
Partially	28 (6.4%)	19 (8.8%)	9 (4.1%)

Data are presented as n (%) of the total number of diagnoses for which an antimicrobial was prescribed.

4. Materials and Methods

4.1. Study Design and Study Site

The first and second PPSs were conducted in October 2019 and October 2020, respectively. All adult wards of the University Hospital of Heraklion in Greece, a 770-bed hospital that covers all medical and surgical specialties, were audited. The study was approved by the hospital review board.

4.2. Study Population

All adult inpatients who were in the ward at 08:00 a.m. were audited for receipt of antimicrobials, including antibacterials, antifungals, antivirals, and antiparasitics. The routes of antimicrobial administration were parenteral (i.e., intravenous, subcutaneous, intramuscular, intraventricular, and intraperitoneal), inhalation, oral, and rectal. Outpatients, patients in the emergency department, and day hospitalizations were excluded. The number of eligible patients on the day of each survey determined the study size and no a priori calculation of sample size was performed.

4.3. Data Collection

Each survey was conducted on a single day by the infection control team, which constituted by infectious disease fellows and internal medicine residents. Both surveys were

conducted by the same infection control team members. The Global Point Prevalence Survey (Global PPS) 2019 methodology was used with adaptations for data collection on ward and patient level [14]. The required patient data were collected by reviewing patients' case notes and prescribing charts.

Wards were grouped by type as follows: medicine, surgery, and intensive care unit (ICU). Antimicrobial utilization data is presented in terms of proportions. Numerator data included patients on at least one antimicrobial, while denominator data involved all hospitalized patients included in the surveys. For each patient receiving antimicrobials, information was collected about sex, age, body mass index (BMI), McCabe score, presence of invasive devices, therapeutic indication, diagnosis, microbiological data, antimicrobial agents, route of administration, dosage, and a set of quality indicators: documentation of reason for antimicrobial administration in notes and of stop/review date, and compliance with national or international treatment guidelines. Each patient could have more than one diagnoses for antimicrobial treatment. Treatment guidelines compliance per diagnosis was considered as partial if the choice of antimicrobial agent(s) was following existing guidelines but dosage, route of administration or duration of treatment were inappropriate, while compliance was considered as full if all of the aforementioned treatment parameters were according to relative national or international guidelines. Of note, treatment guidelines focus on diagnosis and a patient might have more than one infection diagnosed, while each infection might be treated with more than one antimicrobial. Therefore, and in contrast to most previous studies, we selected number of diagnoses as numerator and denominator (not antimicrobials or number of patients) for the above quality indicators.

4.4. Statistical Analysis

Categorical data were presented as frequencies and proportions (%) and were compared between the two independent surveys (2019 vs. 2020) by means of Pearson's chi square test. Continuous data were summarized as mean with standard deviation or median with interquartile range (IQR) depending on the degree of skewness in the distributions and were compared between 2019 and 2020 using the t-test and the Wilcoxon–Mann–Whitney U test, respectively. Statistical significance was considered at the $p < 0.05$ threshold. All analyses were performed using Stata version 17 (Stata Corp., College Station, TX, USA).

5. Discussion

This is the first study in the current literature examining the impact of a hospital-wide carbapenem-focused ASP that was implemented during the initial stages of the COVID-19 pandemic on antimicrobial utilization and quality of antimicrobial prescribing. The results of this study confirm the feasibility and effectiveness of a hospital ASP even under the difficult circumstances of a pandemic.

Among the main findings of our study is that the implementation of the carbapenem-focused ASP in our hospital led to a decrease of carbapenem use without increasing the utilization of newer antibiotics that can be used as alternatives to carbapenems, specifically ceftolozane/tazobactam and ceftazidime/avibactam, thus preserving their efficacy through prudent use. Furthermore, the ASP caused a statistically significant improvement in quality indicators of antimicrobial prescribing, specifically in indication/diagnosis and stop/review date documentation, and adherence to treatment guidelines.

The prevalence of antimicrobial use in both our surveys (51% and 56.5%) was higher than the overall prevalence rate reported for southern Europe (39%) and the weighted prevalence in the European Union/European Economic Area (30.5%) in the pre-COVID-19 era

[15,16], and also higher than the prevalence reported in multicenter studies in Japan (33.5%) and Canada (33.5%) [17,18]. However, the rates of antimicrobial use in our study were similar to those previously reported for Greece (55.6%) in the most recent (2016–2017) European Centre for Disease Prevention and Control PPS [16]. Prevalence of antimicrobial use over 50% in hospitalized patients has also been reported in studies from countries outside Europe, such as Brazil (52.2%) and Nigeria (59.6%) [19,20], and in a multinational study in Latin America that examined only the use of antibiotics (54.6%) [21]. In a multicenter PPS conducted in 2015 in the United States, almost half of inpatients surveyed were on antimicrobials [22]. Interestingly, in the above study, there was no significant reduction in the prevalence of antimicrobial use from 2011, even though the majority (79.4%) of participating hospitals reported having an ASP following the Centers for Disease Control and Prevention recommendation made in 2014 that all hospitals in the USA have an ASP [22,23]. However, compared with the 2011 survey, some positive, though unrelated to the overall prevalence of antimicrobial use, changes were observed, such as a smaller percentage of patients on fluoroquinolones and a lower prevalence of antimicrobial use in neonatal critical care settings [22]. Accordingly, in our study, although there was no significant change in the prevalence of antimicrobial use between the two surveys, ASP implementation had a positive impact on utilization of last-line antibiotics and on prescribing quality.

During the first waves of the COVID-19 pandemic, increased and often inappropriate use of antimicrobials was observed in patients with COVID-19 [24]. The reported pro portion of COVID-19 inpatients receiving antibiotics ranged between 6% and 58% and in most cases, treatment was empirical [25–27]. In a recent multinational European PPS, 52.7% of hospitalized COVID-19 patients were receiving antibiotics and/or antifungals (range, 32.9–85.6%), pneumonia was the most common diagnosis, and treatment was mostly empirical

[28]. Due to the low number of hospitalized COVID-19 patients on the day of the second survey of our study (data not shown), we did not perform separate analysis for these patients, although the majority (>50%) of them were on antibiotics and/or antifungals as empirical treatment for respiratory infections.

The most common indication of antimicrobial treatment was CAI, as has been observed in similar studies from all over the world, even during the pre-COVID-19 era [15,16,18–21,29,30]. Approximately 30% of total indications for antimicrobial treatment in both our surveys were HAIs, a proportion that is considered high compared to data reported from other countries [21]. There was a slight decrease in the rate of antimicrobial administration for HAIs in the second PPS of our study compared to the first (29.1% versus 31.3%); however, taking into account the strengthening of the infection control measures in our hospital due to the COVID-19 pandemic during the second survey, this only slight decrease cannot be considered as promising. Importantly, there was a decrease in the prevalence of surgical prophylaxis for more than one day among patients on antimicrobials in the second PPS, probably due to the implementation of the ASP.

In both surveys of this study, cephalosporins were the most common antibiotics prescribed, which has also been reported in Africa, Latin America, the United States, Middle East, India, and in other studies from Greece [20–22,30–32]. This is mostly due to the wide utilization of third generation cephalosporins, which are considered safe antibiotics that can be used as empirical treatment against many common bacteria in different infection sites, such as the abdomen, and the respiratory and urinary tract. The second most commonly prescribed group of antibacterials were penicillins ± β-lactamase inhibitors, while in other similar studies, particularly from northern/western Europe and Canada, these antibacterials were the most commonly used [15,29]. The third most common group were

fluoroquinolones, with an unchanged percentage of utilization between the two surveys (12.9% of all antibacterials in 2019 versus 12.4% in 2020), which is higher compared to that reported in studies derived from several other countries worldwide [21,29,30]. Taking into account the association of fluoroquinolone use with adverse drug reactions and risk of *C. difficile* infection, this class of antibacterials should be included among the primary targets of stewardship efforts.

An important outcome of our study was the decrease of carbapenem use between the two surveys after the implementation of the carbapenem-focused ASP, without concomitant increase in the utilization of most of the other antibiotics for multidrug-resistant Gram-negative bacteria, such as colistin and, most importantly, ceftolozane/tazobactam and ceftazidime/avibactam. Before the COVID-19 pandemic and the ASP implementation in our hospital, carbapenem use represented 10.3% of all antibacterials, which, even similar to that reported in a recent multinational study from Latin America [21], was considered as high and, therefore, was set as the main target of our antimicrobial stewardship intervention. In the second survey, post-ASP implementation, the respective percentage fell to 4.9%. Considering that our study was conducted in a setting of high endemicity for resistant Gram-negative microorganisms, while there was healthcare personnel shortage for stewardship activities due to the COVID-19 pandemic, this is an encouraging finding towards the feasibility of implementing an effective hospital ASP in countries with high AMR rates and limited staff resources.

The implementation of the ASP in our hospital took into account selected problems regarding antimicrobial prescribing quality that were detected during the first PPS. These problems were related to compliance to treatment guidelines and indication/diagnosis and stop/review date documentation in patient files. Even though guidelines cannot always

account for individual variations among patients, adherence is associated with favorable patient outcomes. In addition, reporting the reason for antimicrobial administration and of administration stop/review date in patient charts ensures communication of diagnosis and treatment among healthcare providers and allows for appropriate follow-up plans and interventions, such as antimicrobial de-escalation [15]. Before ASP implementation, the rates of full compliance to guidelines and documentation of the reason for treatment and stop/review date of treatment were considered low compared to most of other analogous studies, which, however, used a similar but not exactly the same approach for calculating these indicators [18,20,29,33]. In the second PPS, these rates were significantly improved, which indirectly reflects the effectiveness of our antimicrobial stewardship intervention. Of note, the majority (98.5%) of the doctors in our hospital were in favor of continuing and further developing the ASP during the COVID-19 pandemic [34].

The current study has several strengths and limitations. Apart from the fact that it is the first of its kind, both surveys were conducted by the same members of the infection control team, which was composed by doctors of the Internal Medicine and Infectious Diseases department of our hospital, thus minimizing bias in collecting and interpreting data. In addition, each PPS was conducted in the same season of the year, out of summer holiday, when hospital stuffing is usually low, and winter, when antimicrobial use is the highest, in order to reduce potential confounders. On the other hand, the main limitation of our study is inherent to the method used for the two cross-sectional surveys, namely the interpretation of single point data. Furthermore, this is a single center study, in a hospital whose capacity was not exceeded due to the COVID-19 pandemic, therefore the results should be generalized with caution. Finally, our intention in this repeated PPS was to detect changes in antibiotic prescribing indicators following the implementation of the carbapenem-focused ASP, but

should note that prevalence percentages presented in this study may be imprecise due to the small sample sizes available per year.

6. Conclusions

Our study demonstrated a positive impact of an ASP implementation on the utilization of last-line antimicrobials during the first stages of the COVID-19 pandemic in a healthcare setting with high AMR rates. Even under the pressure of the pandemic, the relation between stewardship efforts and improved quality of antimicrobial prescribing was confirmed. The findings of this study provide infectious disease doctors with useful insights into the design, implementation and further development of hospital ASPs.

7. References

1. Roberts SC, Zembower TR. Global increases in antibiotic consumption: a concerning trend for WHO targets. Lancet Infect Dis 2021, 21, 10-11.

2. Dik JW, Hendrix R, Poelman R, Niesters HG, Postma MJ, Sinha B, Friedrich AW. Measuring the impact of antimicrobial stewardship programs. Expert Rev Anti Infect Ther 2016, 14, 569-575.

3. Spernovasilis NA, Kofteridis DP. COVID-19 and antimicrobial stewardship: What is the interplay? Infect Control Hosp Epidemiol 2021, 42, 378-379.

4. Naggie S, Boulware DR, Lindsell CJ, Stewart TG, Gentile N, Collins S, McCarthy MW, Jayaweera D, Castro M, Sulkowski M, et al. Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA 2022, 328, 1595-1603.

5. Reis G, Silva E, Silva DCM, Thabane L, Milagres AC, Ferreira TS, Dos Santos CVQ, Campos VHS, Nogueira AMR, de Almeida A, et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. N Engl J Med 2022, 386, 1721-1731.

6. European Centre for Disease Prevention and Control (ECDC). Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report for 2020. Available online: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-consumption-europe-2020.

7. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe - 2020 data. Available online: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2020.

8. Dyar OJ, Huttner B, Schouten J, Pulcini C. What is antimicrobial stewardship? Clin Microbiol Infect 2017, 23, 793-798.

9. European Centre for Disease Prevention and Control (ECDC). Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020. Available online: https://www.ecdc.europa.eu/en/publications-data/health-burden-infections-antibiotic-resistant-bacteria-2016-2020.

10. Chrysou K, Zarkotou O, Kalofolia S, Papagiannakopoulou P, Mamali V, Chrysos G, Themeli-Digalaki K, Sypsas N, Tsakris A, Pournaras S. Impact of a 4-year antimicrobial stewardship program implemented in a Greek tertiary hospital. Eur J Clin Microbiol Infect Dis 2022, 41, 127-132.

11. Makina A-A, Poulakou G, Sympardi S, Souli M, Liakopoulou E, Matthaiou D, Karaiskou A, Arvaniti A, Alexiou N, Charalabaki N. Safety of a carbapenem-sparing approach as part of an antibiotic stewardship program, in a setting with increased carbapenem resistance. Infect Dis Clin Microbiol 2019, 1, 14-25.

12. Pitiriga V, Kanellopoulos P, Kampos E, Panagiotakopoulos G, Tsakris A, Saroglou G. Antimicrobial stewardship program in a Greek hospital: implementing a mandatory prescription form and prospective audits. Future Microbiol 2018, 13, 889-896.

13. Samarkos M, Skouloudi M, Anastasopoulou A, Markogiannakis A. Restricted antimicrobial prescribing in an area of highly prevalent antimicrobial resistance. Infect Dis Now 2021, 51, 526-531.

14. Global Point Prevalence Survey of Antimicrobial Consumption and Resistance. Global Point Prevalence Survey (PPS) – Year 2019 (GLOBAL PPS). Available online: https://www.global-pps.com/wp-content/uploads/2019/01/Data-collection-form-Global-PPS-2019.pdf.

15. Versporten A, Zarb P, Caniaux I, Gros M-F, Drapier N, Miller M, Jarlier V, Nathwani D, Goossens H, Koraqi A, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. The Lancet Global Health 2018, 6, e619-e629.

16. Plachouras D, Kärki T, Hansen S, Hopkins S, Lyytikäinen O, Moro ML, Reilly J, Zarb P, Zingg W, Kinross P, et al. Antimicrobial use in European acute care hospitals: results from the second point prevalence survey (PPS) of healthcare-associated infections and antimicrobial use, 2016 to 2017. Euro Surveill 2018, 23.

17. Komagamine J, Yabuki T, Kobayashi M, Okabe T. Prevalence of antimicrobial use and active healthcare-associated infections in acute care hospitals: a multicentre prevalence survey in Japan. BMJ Open 2019, 9, e027604.

18. German GJ, Frenette C, Caissy JA, Grant J, Lefebvre MA, Mertz D, Lutes S, McGeer A, Roberts J, Afra K, et al. The 2018 Global Point Prevalence Survey of antimicrobial consumption and resistance in 47 Canadian hospitals: a cross-sectional survey. CMAJ Open 2021, 9, E1242-E1251.

19. Porto APM, Goossens H, Versporten A, Costa SF. Global point prevalence survey of antimicrobial consumption in Brazilian hospitals. J Hosp Infect 2020, 104, 165-171.

20. Fowotade A, Fasuyi T, Aigbovo O, Versporten A, Adekanmbi O, Akinyemi O, Goossens H, Kehinde A, Oduyebo O. Point Prevalence Survey of Antimicrobial Prescribing in a Nigerian Hospital: Findings and Implications on Antimicrobial Resistance. West Afr J Med 2020, 37, 216-220.

21. Levy Hara G, Rojas-Cortés R, Molina León HF, Dreser Mansilla A, Alfonso Orta I, Rizo-Amezquita JN, Santos Herrera RG, Mendoza de Ayala S, Arce Villalobos M, Mantilla Ponte H,

et al. Point prevalence survey of antibiotic use in hospitals in Latin American countries. J Antimicrob Chemother 2022, 77, 807-815.

22. Magill SS, O'Leary E, Ray SM, Kainer MA, Evans C, Bamberg WM, Johnston H, Janelle SJ, Oyewumi T, Lynfield R, et al. Antimicrobial Use in US Hospitals: Comparison of Results From Emerging Infections Program Prevalence Surveys, 2015 and 2011. Clinical Infectious Diseases 2020, 72, 1784-1792.

23. Centers for Disease Control and Prevention (CDC). Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA: US Department of Health and Human Services, CDC; 2014. Available online: https://www.cdc.gov/antibiotic-use/healthcare/pdfs/core-elements.pdf.

24. Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, Daneman N, MacFadden DR. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect 2021, 27, 520-531.

25. Tan SH, Ng TM, Tay HL, Yap MY, Heng ST, Loo AYX, Teng CB, Lee TH. A point prevalence survey to assess antibiotic prescribing in patients hospitalized with confirmed and suspected coronavirus disease 2019 (COVID-19). J Glob Antimicrob Resist 2021, 24, 45-47.

26. Avdeev S, Rachina S, Belkova Y, Kozlov R, Versporten A, Pauwels I, Goossens H, Bochanova E, Elokhina E, Portnjagina U, et al. Antimicrobial Prescribing Patterns in Patients with COVID-19 in Russian Multi-Field Hospitals in 2021: Results of the Global-PPS Project. Trop Med Infect Dis 2022, 7.

27. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, Liu L, Shan H, Lei C-l, Hui DSC, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine 2020, 382, 1708-1720.

28. Papst L, Luzzati R, Carević B, Tascini C, Gorišek Miksić N, Vlahović Palčevski V, Djordjevic ZM, Simonetti O, Sozio E, Lukić M, et al. Antimicrobial Use in Hospitalised Patients with COVID-19: An International Multicentre Point-Prevalence Study. Antibiotics 2022, 11, 176.

29. Frenette C, Sperlea D, German GJ, Afra K, Boswell J, Chang S, Goossens H, Grant J, Lefebvre MA, McGeer A, et al. The 2017 global point prevalence survey of antimicrobial consumption and resistance in Canadian hospitals. Antimicrob Resist Infect Control 2020, 9, 104.

30. Al Matar M, Enani M, Binsaleh G, Roushdy H, Alokaili D, Al Bannai A, Khidir Y, Al-Abdely H. Point prevalence survey of antibiotic use in 26 Saudi hospitals in 2016. J Infect Public Health 2019, 12, 77-82.

31. Panditrao AM, Shafiq N, Chatterjee S, Pathak A, Trivedi N, Sadasivam B, Kshirsagar N, Kaul R, Biswal M, Kakkar A, et al. A multicentre point prevalence survey (PPS) of antimicrobial use amongst admitted patients in tertiary care centres in India. J Antimicrob Chemother 2021, 76, 1094-1101.

32. Ioannou P, Astrinaki E, Vitsaxaki E, Bolikas E, Christofaki D, Salvaraki A, Lagoudaki E, Ioannidou E, Karakonstantis S, Saplamidou S, et al. A Point Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use in Public Acute Care Hospitals in Crete, Greece. Antibiotics (Basel) 2022, 11.

33. Gürtler N, Erba A, Giehl C, Tschudin-Sutter S, Bassetti S, Osthoff M. Appropriateness of antimicrobial prescribing in a Swiss tertiary care hospital: a repeated point prevalence survey. Swiss Med Wkly 2019, 149, w20135.

34. Spernovasilis N, Ierodiakonou D, Spanias C, Mathioudaki A, Ioannou P, Petrakis EC, Kofteridis DP. Doctors' Perceptions, Attitudes and Practices towards the Management of

Multidrug-Resistant Organism Infections after the Implementation of an Antimicrobial Stewardship Programme during the COVID-19 Pandemic. Trop Med Infect Dis 2021, 6.

CHAPTER III

A carbapenem-focused antimicrobial stewardship programme implemented during the COVID-19 pandemic in a setting of high endemicity for multidrug-resistant Gram-negative bacteria

Nikolaos Spernovasilis [1,2], Evangelos I. Kritsotakis [1,3], Anna Mathioudaki [2], Alexandra Vouidaski [2], Christos Spanias [4], Maria Petrodaskalaki [5], Petros Ioannou [1,2], Georgios Chamilos [1,6] and Diamantis P. Kofteridis [1,2]

[1] School of Medicine, University of Crete, Heraklion, Greece

[2] Department of Internal Medicine and Infectious Diseases, University Hospital of Heraklion, Heraklion, Greece

[3] Laboratory of Biostatistics, School of Medicine, University of Crete, Heraklion, Greece

[4] Department of Pharmacy, University Hospital of Heraklion, Heraklion, Greece

[5] Department of Quality & Research, University Hospital of Heraklion, Heraklion, Greece

[6] Department of Clinical Microbiology, University Hospital of Heraklion, Heraklion, Greece

Published in: ***J Antimicrob Chemother . 2023 Apr 3;78(4):1000-1008***.

1. Abstract

Background: Greece is among the countries characterized by high rates of antimicrobial resistance and high consumption of antibiotics, including carbapenems.

Objectives: To measure the impact of a carbapenem-focused antimicrobial stewardship programme (ASP) on the antibiotic consumption and patient outcomes in a Greek tertiary hospital during the COVID-19 pandemic.

Methods: A quasi-experimental, before–after study, comparing a 12 month pre-intervention period with a 12 month intervention period in which a carbapenem-focused ASP was implemented.

Results: A total of 1268 patients were enrolled. The proportion of admitted patients who received carbapenems decreased from 4.1% (842 of 20 629) to 2.3% (426 of 18 245) (−1.8%; $P < 0.001$). A decrease of −4.9 DDD/100 patient-days (PD) (95% CI −7.3 to −2.6; $P = 0.007$) in carbapenem use and an increase in the use of piperacillin/tazobactam [+2.1 DDD/100 PD (95% CI 1.0–3.3; $P = 0.010$)] were observed. Thirty-day mortality following initiation of carbapenem treatment and all-cause in-hospital mortality remained unaltered after ASP implementation. In contrast, length of hospital stay increased (median 17.0 versus 19.0 days; $P < 0.001$), while the risk of infection-related readmission within 30 days of hospital discharge decreased (24.6% versus 16.8%; $P = 0.007$). In the post-implementation period, acceptance of the ASP intervention was associated with lower daily hazard of in-hospital death [cause-specific HR (csHR) 0.49; 95% CI 0.30–0.80], lower odds of 30 day mortality (OR 0.36; 95% CI 0.18–0.70) and higher rate of treatment success (csHR 2.45; 95% CI 1.59–3.77).

Conclusions: Implementing and maintaining a carbapenem-focused ASP is feasible, effective and safe in settings with high rates of antimicrobial resistance, even during the COVID-19 pandemic.

2. Introduction

Carbapenems are important elements of the antibiotic armamentarium, with established efficacy against most infections caused by MDR Gram-negative bacteria (GNB). Their efficacy is mainly due to (i) their stability against most β-lactamases, including the AmpCs and the ESBLs, and (ii) the broad spectrum of their activity [1]. In addition, carbapenems have a better safety profile compared with other last-line antibiotics, such as polymyxins [1]. However, inappropriate use of these broad-spectrum β-lactam antibiotics aggravates the problem of antimicrobial resistance (AMR) by promoting the emergence of XDR and pandrug-resistant Gram-negative nosocomial pathogens through the induction of selective pressure [2,3].

Over the last decade, Greece has ranked among the countries with the highest consumption of antibiotics in Europe, including carbapenems and other broad-spectrum antibiotics, both in community and hospital settings [4]. In parallel, the country's AMR rates, including carbapenem-resistant GNB, have been extremely high, and this is also the case in some other European countries [5]. The observed infections due to MDR-GNB in these countries pose a significant challenge for clinicians and a major threat for healthcare systems due to their high attributable mortality and hospital costs [6].

The threat of AMR may become more evident in the years to come, in part due to the high and often inappropriate use of antimicrobials during the coronavirus disease 2019 (COVID-19) pandemic [7]. Especially in the early phases of the pandemic, antimicrobials were widely used as repurposed drugs and as empirical coverage of coinfections and superinfections in COVID-19 patients [8]. However, no reliable scientific evidence supports the use of antibiotics, antiretrovirals and antiparasitics as repurposed drugs against severe

acute respiratory syndrome coronavirus 2 [9]. In addition, almost three-quarters of COVID-19 patients received antibiotics during the first months of the pandemic, but only a minority of them had documented bacterial coinfection or superinfection [10]. This observed overprescription included carbapenems in several studies of hospitalized patients, especially in ICU [11–14].

Accordingly, a pivotal target of antimicrobial stewardship programmes (ASPs) is to decrease unnecessary administration of carbapenems. To optimize carbapenem prescription in our hospital, a setting with high rates of MDR-GNB, a carbapenem-focused ASP was implemented during the first year of the COVID-19 pandemic. The aim of our study was to examine the impact of this ASP on the consumption of antibiotics used to treat MDR-GNB and on patient safety and outcomes.

3. Materials and methods

3.1 Study design, setting and population

This retrospective-prospective, before–after, quasi-experimental study was conducted at a 770-bed tertiary university hospital that covers all surgical and medical specialties, including cardiac surgery, neurosurgery, surgical oncology, rheumatology, oncology, haematology and ICU. Before January 2020 there was no formal ASP implemented in the study site. The pre-implementation period from January 2019 to December 2019 was retrospectively evaluated and was compared with the intervention period of January 2020 to December 2020.

The study enrolled all patients ≥16 years of age who received carbapenems (i.e., meropenem, imipenem or ertapenem) for at least 24 h during the 24-month study period. Those who received more than one course of carbapenems during each of the study

subperiods were only included once in the corresponding subperiod analysis, the first time they received the carbapenem antibiotic. Patients who died within 24 h of carbapenem administration or had been transferred from another hospital and had received carbapenem therapy during their hospitalization at that hospital were excluded.

The study was approved by the hospital's Review Board. The need for the patient's informed consent was waived because the study represented customary medical practice and the ASP complied with national medical guidelines and legislation for the control of AMR in Greece.

3.2 Intervention

Starting 1 January 2020, a multifaceted ASP was implemented to optimize the prescription of carbapenems with regard to indication, dosage and duration of administration. Whenever appropriate, the intervention promoted recommendation for judicious use of carbapenem-sparing antibiotics. The ASP team comprised of an infectious disease (ID) specialist, an ID fellow, a microbiologist and a pharmacist. The programme was based on the strategy of prospective audit and feedback to prescribers and was supplemented by parallel case-based educational sessions, meetings and presentations on proper use of antibiotics.

The ID specialist and the ID fellow were alerted by the pharmacy upon prescription order for a carbapenem and provided unsolicited in-person ('handshake') consultation within 72 h for all adult patients receiving a carbapenem antibiotic. Further ID consultation service was available 24/7 through telephone or in person upon request by the treating doctors. Unsolicited follow-up bedside ID consultation was provided daily or every other day for patients whose treating physicians had accepted the intervention. After examining each eligible patient and reviewing their medical record, the ID specialist or the ID fellow discussed

with the prescribers whether continuing carbapenems or using non-carbapenem antibiotics for empirical treatment would be appropriate. Whenever relevant microbiological data were available, the options of targeted de-escalation to narrow-spectrum antibiotics or targeted escalation to ceftazidime/avibactam, tigecycline or colistin were considered. Of note, and only when susceptibility data were available, ceftolozane/tazobactam was used as a carbapenem-sparing treatment option while ceftazidime/avibactam was used only for the targeted treatment of carbapenem-resistant GNB. Treating physicians were not obligated to comply with ASP team's recommendations.

3.3. Variables

Antibiotic consumption data per calendar quarter for carbapenems, piperacillin/tazobactam, ceftolozane/tazobactam, ceftazidime/avibactam, tigecycline and colistin were retrieved from the hospital pharmacy records and were expressed as DDD per 100 patient-days (PD).

Patient demographics, clinical characteristics, length of hospital stay, and outcomes were retrospectively reviewed during the pre-intervention period and prospectively collected during the intervention period. Outcome endpoints included inpatient death, death within 30 days of carbapenem initiation (including post-discharge cases) and infection-related readmission within 30 days of hospital discharge. Outcome during or at the end of the antibiotic treatment could be assessed only for the post-implementation cohort and was classified as death, new/recurrent infection or favourable outcome. For every patient in the post-implementation cohort, it was recorded whether the treating physician accepted the ASP recommendation or not.

3.4. Statistical analysis

The effect of the ASP implementation on hospital antibiotic use was assessed using interrupted time series analyses. A segmented Poisson regression model was employed to examine the extent to which the ASP was associated with an immediate level change and/or a gradual trend change of the monthly numbers of carbapenem-treated patients. In this model, the series of monthly counts of carbapenem-treated patients formed the dependent variable. Independent variables were the time elapsed since the start of the study, the ASP implementation indicator (post- versus pre-ASP) and the time after the intervention. The monthly series of hospital admissions (log transformed) was used as an offset variable to convert the outcome into a rate that accounts for variation in the hospital population size over time. Two pairs of sine–cosine Fourier functions of time were included to capture seasonality. The model coefficients were estimated using the maximum-likelihood method. Residual autocorrelation was ruled out by examining autocorrelation graphs. Sensitivity analyses were conducted by using the monthly numbers of hospitalized patients and PD as alternative denominators for the treatment rate, and by inflating the standard errors by the scaled Pearson chi-squared statistics to adjust for the possibility of overdispersion.

In addition, we examined the temporal trends in the consumption of carbapenems and other selected antibiotics with activity against MDR-GNB by using quarterly hospital data. A level-change linear regression model for interrupted time series was used for this purpose. Stratification per quarter was employed to adjust for seasonality. The model was estimated using the ordinary least squares method, and Newey–West standard errors were used to account for autocorrelation.

The impact on patient outcomes was assessed on an ITT principle by comparing all carbapenem-treated patients between the pre- implementation period and the ASP intervention period. Pearson’s chi-squared test was used to assess between-group

differences in overall proportions of in-hospital mortality, total mortality within 30 days of initiation of carbapenem treatment, and infection-related readmission within 30 days of hospital discharge. The Wilcoxon rank-sum test was used to assess between-group differences in length of hospital stay. Multivariable Cox regression was employed to obtain cause-specific HRs (csHRs) for in-hospital death and discharge alive, adjusting for differences in baseline covariates. The time origin was set to hospital admission. Discharge alive from the hospital was treated as a competing event to in-hospital death. In this analysis, a low csHR for discharge alive reflects a low daily rate of discharge resulting in prolonged hospital stay. Multivariable logistic regression was employed to estimate OR for total mortality within 30 days of initiation of carbapenem treatment and OR for infection-related readmission within 30 days of hospital discharge, correcting for differences in baseline covariates. All models adjusted for patient sex, age, ward of hospitalization, and history of previous hospitalization.

A series of sensitivity analyses were performed to assess the likely clinical impact of the ASP intervention under different conditions. On a modified ITT analysis, we compared the pre-implementation cohort to the post-implementation cohort, excluding patients for whom the intervention was not accepted. On per-protocol analysis, we compared patients who did not receive the intervention in either the pre- or the post-implementation period with those who received the intervention. Finally, restricting the analysis within the post-implementation period, we compared patients for whom the intervention was accepted with patients for whom the intervention was not. In the latter analysis, we additionally compared the clinical outcome at the end of therapy.

None of the study variables had missing data. Statistical significance was considered at the usual $P < 0.05$ threshold. Data processing and statistical modelling were performed using Stata version 17 (Stata Corp., College Station, TX, USA).

4. Results

4.1 Antibiotic consumption

In all, 1329 carbapenem courses were administered to 1268 patients during the 2 year study period, 55 of whom received more than one course of carbapenems in any of the two study subperiods. After the ASP implementation, the proportion of admitted patients who received carbapenem treatment decreased significantly, from 4.1% (842 of 20 629) to 2.3% (426 of 18 245) (−1.8%; $P < 0.001$). The interrupted time series analysis confirmed that the implementation of the carbapenem-focused ASP was associated with an overall level reduction in the rate of carbapenem treatments per 100 hospital admissions [incidence rate ratio (IRR) 0.63; 95% CI 0.50–0.80; $P < 0.001$], while no substantial trend change occurred after the ASP implementation (IRR 1.02; 95% CI 1.00–1.04; $P = 0.117$) (Figure 1). Sensitivity analyses confirmed that the estimated level change in the rate of carbapenem-treated patients was robust against different statistical modelling specifications and rate denominators (Table 1).

Analysis of quarterly data on hospital consumption of carbapenems showed that the ASP was associated with a decrease of −4.9 DDD/100 PD (95%CI −7.3 to −2.6; $P = 0.007$). A concurrent increase in the consumption of piperacillin/tazobactam was noted [+2.1 DDD/100 PD (95% CI 1.0–3.3; $P = 0.010$)]. There was also a non-statistically significant increase of tigecycline consumption and decrease of colistin consumption. The consumption of ceftolozane/tazobactam and ceftazidime/avibactam remained largely unaffected (Table 2 and Figure 2).

Figure 1. Monthly rates of carbapenem (CR)-treated patients per 100 hospital admissions, pre- and post-implementation of the ASP. Dots show observed rates, the solid line shows predicted rates from Poisson regression model adjusted for seasonality and overdispersion, the dashed line shows the deseasonalized trend, the dotted line shows the counterfactual scenario assuming the intervention was not implemented, and the vertical dashed line shows the time of the beginning of the intervention.

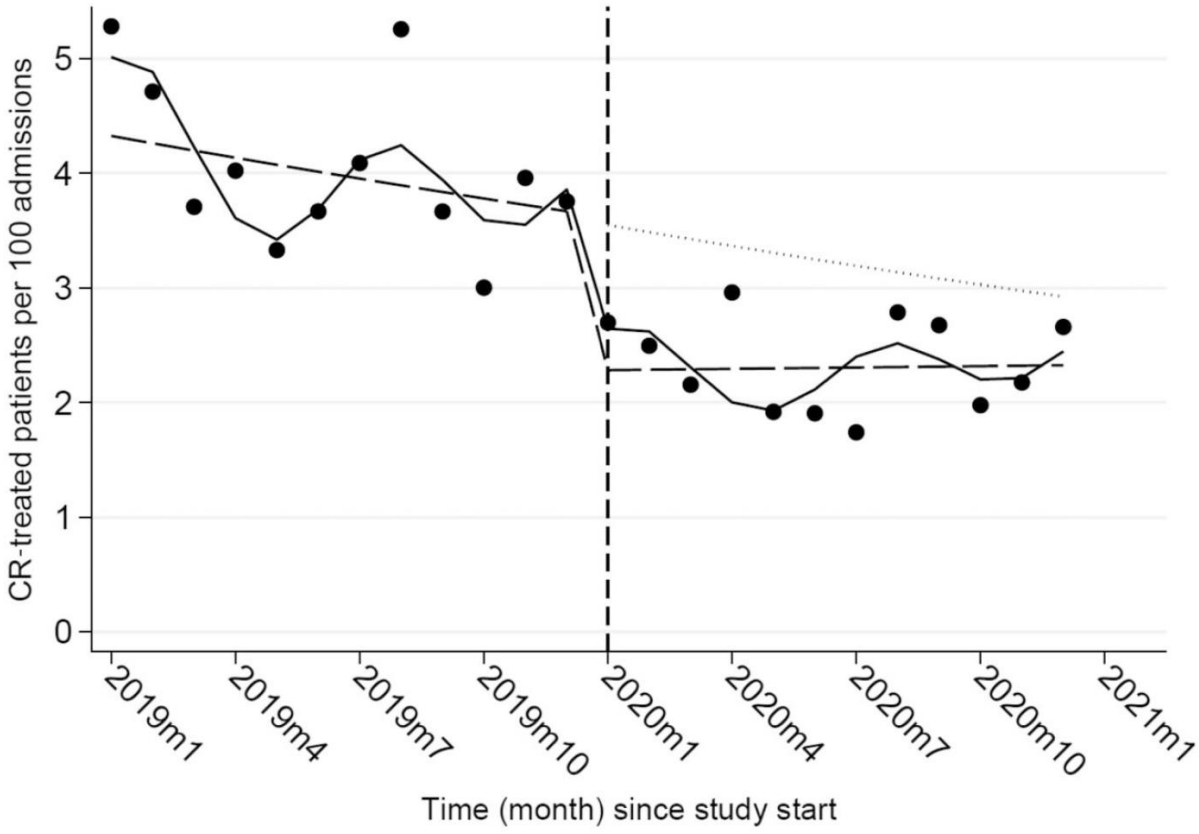


Table 1. Sensitivity analyses of estimating the effect of the antimicrobial stewardship programme implementation on the rate of carbapenem prescription for various types of model specifications.

Outcome being modelled	Poisson model specifications	IRR	95% CI	p-value
Monthly rate of carbapenem treated patients, per 100 hospital admissions	Unadjusted	0.70	0.56 - 0.87	0.002
	Adjusted for seasonality	0.63	0.50 - 0.80	<0.001
	Adjusted for seasonality, overdispersion	0.63	0.39 - 1.01	0.056
Monthly rate of carbapenem treated patients, per 100 in-patients	Unadjusted	0.71	0.57 - 0.88	0.002
	Adjusted for seasonality	0.69	0.55 - 0.86	0.001
	Adjusted for seasonality, overdispersion	0.69	0.44 - 1.08	0.103
Monthly rate of carbapenem treated patients, per 1000 patient-days	Unadjusted	0.68	0.55 - 0.85	0.001
	Adjusted for seasonality	0.71	0.57 - 0.88	0.002
	Adjusted for seasonality, overdispersion	0.71	0.46 - 1.08	0.107

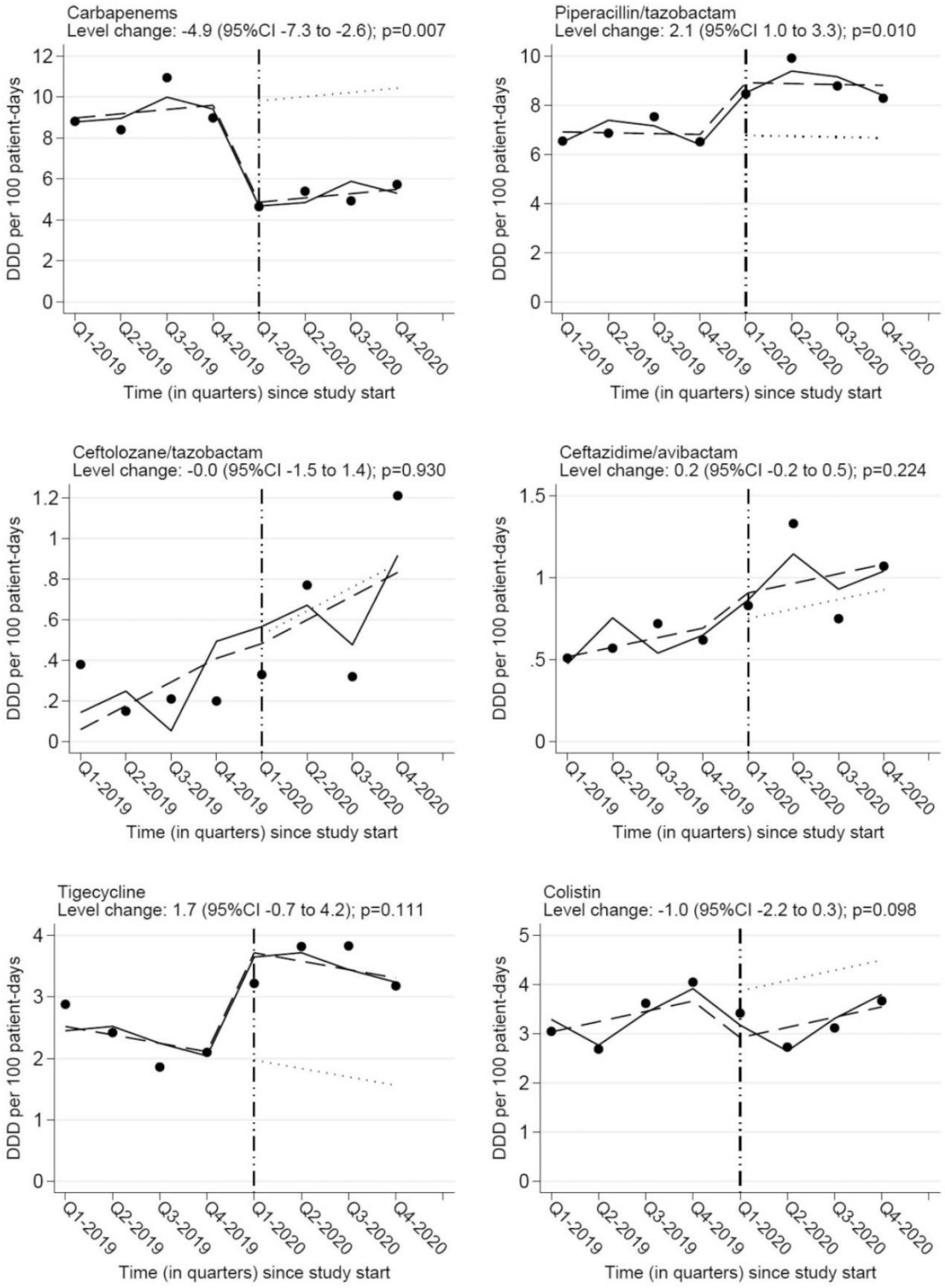
IRR, incidence rate ratio

Table 2. Quarterly hospital consumption of carbapenems and other selected antibiotics with activity against Gram-negative bacteria and level changes due to the antimicrobial stewardship programme implementation (measured in DDD per 100 patient-days). Level changes were estimated by segmented linear regression adjusting for seasonality and autocorrelation.

Antibiotic group or agent	2019 (pre-intervention year)				2020 (intervention year)				After-before level change		
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Estimate	95% CI	p-value
Carbapenems	8.81	8.40	10.94	8.98	4.65	5.40	4.93	5.73	-4.9	-7.3 to -2.6	0.007
Meropenem	8.67	8.33	10.80	8.91	4.56	5.20	4.65	5.44	-5.0	-7.3 to -2.6	0.007
Imipenem	0.02	0.00	0.02	0.01	0.02	0.00	0.04	0.00	0.0	-0.0 to 0.1	0.145
Ertapenem	0.12	0.07	0.12	0.06	0.07	0.20	0.24	0.29	0.0	-0.4 to 0.4	0.995
Piperacillin/tazobactam	6.54	6.86	7.53	6.51	8.46	9.91	8.78	8.28	2.1	1.0 to 3.3	0.010
Ceftolozane/tazobactam	0.38	0.15	0.21	0.20	0.33	0.77	0.32	1.21	0.0	-1.5 to 1.4	0.930
Ceftazidime/avibactam	0.51	0.57	0.72	0.62	0.83	1.33	0.75	1.07	0.2	-0.2 to 0.5	0.224
Tigecycline	2.88	2.42	1.86	2.10	3.22	3.82	3.83	3.18	1.7	-0.7 to 4.2	0.111
Colistin	3.05	2.69	3.62	4.05	3.42	2.73	3.12	3.67	-1.0	-2.2 to 0.3	0.098

Q, quarter

Figure 2. Interrupted time series graphs showing level changes in the consumption of carbapenems and other selected antibiotics with activity against MDR-GNB following the ASP implementation. The dots correspond to quarterly antibiotic consumption rates.



4.2. Clinical outcomes

Demographic and clinical characteristics of the patients before and after ASP implementation did not differ significantly, as summarized in Table 3. Mortality within 30 days of initiation of carbapenem treatment (22.4% versus 23.1%; *P* = 0.798) and all-cause in-hospital mortality (23.6% versus 28.4%; *P* = 0.065) remained unaltered after ASP implementation. In contrast, length of hospital stay increased (median 17.0 versus 19.0 days; *P* < 0.001), while the risk of infection-related readmission within 30 days of hospital discharge decreased (24.6% versus 16.8%; *P* = 0.007). Multivariable regression analyses showed similar effect sizes after adjustment for baseline differences in patient sex, age, ward of hospitalization, and history of previous hospitalization (Tables S1–S19, available as **Supplementary I** data). The results of sensitivity analyses in Table 4 confirmed that the effects of the ASP on patient outcomes were consistent under different assumed conditions.

Apart from age, demographic and clinical characteristics did not differ substantially between patients with and without acceptance of ASP recommendations during the post-implementation period, but patient outcomes were worse for the latter (Table 3). Multivariable analysis confirmed that patients for whom ASP recommendations were accepted had lower daily hazard of in-hospital death (csHR 0.49; 95% CI 0.30–0.80), lower odds of 30 day mortality (OR 0.36; 95% CI 0.18–0.70) and, albeit not statistically significant, lower odds of infection-related readmission (OR 0.57; 95% CI 0.20–1.61) compared with patients for whom the intervention was not accepted. Moreover, acceptance of the ASP intervention was associated with a higher rate of treatment success (csHR 2.45; 95% CI 1.59–3.77) (Table 4).

Table 3. Comparison of patient characteristics and outcomes on an ITT principle (pre- versus post-implementation of the antimicrobial stewardship programme) and per acceptance of the antimicrobial stewardship intervention.

	ITT analysis			Acceptance analysis (post-implementation cohort)		
Variables	Pre-implementation cohort (n=842)	Post-implementation cohort (n=426)	p-value	Intervention non-accepted (n=46)	Intervention accepted (n=380)	p-value
Male sex, n (%)	540 (64.1)	266 (62.4)	0.554	33 (71.7)	233 (61.3)	0.168
Age, median (IQR)	68.0 (56.0-78.0)	69.0 (58.0-79.0)	0.422	73.0 (64.0-84.0)	69.0 (56.0-78.0)	0.048
Ward of hospitalisation			0.591			0.200
Intensive care, n (%)	92 (10.9)	54 (12.7)		2 (4.4)	52 (13.7)	
Medicine, n (%)	529 (62.8)	263 (61.7)		29 (63.0)	234 (61.5)	
Surgery, n (%)	217 (25.8)	105 (24.6)		15 (32.6)	90 (23.7)	
Other, n (%)	4 (0.5)	4 (0.9)		0 (0.0)	4 (1.1)	
Previous hospitalisation, n (%)	493 (58.6)	236 (55.4)	0.284	20 (43.5)	216 (56.8)	0.085

CCI, median (IQR)	na	2.0 (1.0-4.0)	na	3.0 (2.0-6.0)	2.0 (1.0-4.0)	0.104
Length of hospital stay (days) before carbapenem therapy, median (IQR)	5.0 (1.0-11.0)	5.0 (1.0-12.0)	0.272	6.0 (3.0-14.0)	4.5 (1.0-12.0)	0.279
Length of hospital stay (days), median (IQR)	17.0 (9.0-31.0)	19.0 (12.0-37.0)	<0.001	17.0 (10.0-33.0)	20.0 (12.0-38.0)	0.497
In-hospital any-cause death	199 (23.6)	121 (28.4)	0.065	21 (45.7)	100 (26.3)	0.006
Death within 30 days of carbapenem initiation, n (%)	187 (22.4)	98 (23.1)	0.798	18 (39.1)	80 (21.1)	0.006
Infection-related readmission within 30 days of discharge alive, n (%)	153 (24.6)	51 (16.8)	0.007	6 (24.0)	45 (16.1)	0.313
Treatment outcome						<0.001
Death, n (%)				15 (32.6)	62 (16.3)	
New or recurrent infection, n (%)				8 (17.4)	9 (2.4)	
Success, n (%)				23 (50.0)	309 (81.3)	

na, not available; CCI, Charlson comorbidity index; IQR, interquartile range

Table 4. Results of multivariable Cox proportional hazards regression and logistic regression quantifying the effects of the antimicrobial stewardship programme on patient outcomes under different conditions (sensitivity analyses). All effects are corrected for baseline differences in patient sex, age, ward of hospitalisation, and history of previous hospitalisation.

	ITT analysis [a]			Modified ITT analysis [b]			Per protocol analysis [c]			Per acceptance analysis [d]		
Clinical outcomes and effect measure	ES (95%CI)		p-value	ES (95%CI)		p-value	ES (95%CI)		p-value	ES (95%CI)		p-value
In-hospital death, csHR	0.99	(0.79-1.24)	0.922	0.91	(0.71-1.16)	0.450	0.87	(0.69-1.11)	0.256	0.49	(0.30-0.80)	0.004
Discharge alive, csHR	0.80	(0.70-0.92)	0.002	0.83	(0.72-0.95)	0.009	0.85	(0.74-0.98)	0.022	1.32	(0.87-2.00)	0.187

30-day death, OR [e]	1.26	(0.95-	0.10	1.10	(0.82-	0.513	1.03	(0.77-	0.852	0.36	(0.18-	0.003
	1.67)		7	1.49)			1.38)			0.70)		
30-day infection-related	0.60	(0.42-	0.00	0.57	(0.39-	0.003	0.57	(0.39-	0.003	0.57	(0.20-	0.290
readmission, OR [f]	0.86)		6	0.83)			0.83)			1.61)		
Treatment outcome [g]												
Death, csHR										0.74	(0.40-	0.337
										1.37)		
Re-infection, csHR										0.26	(0.09-	0.011
										0.74)		
Success, csHR										2.45	(1.59-	<0.00
										3.77)		1

ES, effect size attributed to the intervention; csHR, cause-specific hazard ratio.

Notes:

[a] Compares the pre-implementation cohort (n=842) to the post-implementation cohort (n=426).

[b] Compares the pre-implementation cohort (n=842) to the post-implementation cohort excluding patients for whom the intervention was not accepted (n=380).

[c] Compares patients who did not receive the intervention in either the pre- or the post-implementation period (n=888) with those who received the intervention (n=380).

[d] Compares patients for whom the intervention was accepted (n=380) to patients for whom the intervention was not accepted (n=46) in the post-implementation period.

[e] Includes death from any cause within 30 days of initiation of carbapenem therapy.

[f] Assessed within 30 days of hospital discharge alive.

[g] Assessed during or at the end of treatment with carbapenems.

5. Discussion

This study describes the implementation of a carbapenem-focused ASP during the first year of the COVID-19 pandemic and its impact on the consumption of several broad-spectrum antibiotics with activity against MDR-GNB and on patient outcomes. It is one of the few studies to assess a hospital ASP for carbapenems in Greece, a country with high rates of antibiotic consumption and AMR. The results demonstrate that judicious use of carbapenems in a setting with high rates of MDR-GNB was feasible and led to a significant decrease of their consumption and, importantly, improvement of patient outcomes.

The implementation and maintenance of the ASP in our hospital during the first phases of the COVID-19 pandemic was a challenging and laborious process. At its beginning, the pandemic caused a tremendous depletion of human and structural resources in many hospitals worldwide, compromising their antimicrobial stewardship activities [15]. This resulted in increased consumption of antimicrobials in hospitals, including carbapenems [16], even though medical guidelines regarding the administration of this class of antibiotics had not changed during the COVID-19 pandemic. In some cases, the increased antimicrobial consumption was mitigated by reinstating stewardship activities [17] or by intensifying ongoing ASPs [14]. These observations are in accordance with the findings of our study regarding the feasibility of an effective ASP during the COVID-19 period.

The two core strategies of an ASP for inpatient populations include formulary restriction and pre-authorization, and prospective audit and feedback to prescribers. These strategies can be applied separately or in combination. In the pre-pandemic era, both strategies have been shown to effectively and safely reduce unnecessary in-hospital antibiotic use [18]. However, few

relevant data exist during the COVID-19 pandemic. The initial lack of evidence on optimal management of COVID-19 and the accompanying fear of it, the overwhelmed hospitals amid COVID-19 surges, the shortage of available skilled doctors for the implementation or maintenance of ASPs, and medication supply problems, had created an entirely new situation in the hospital sector that may have affected the performance of ASPs. In a recent study from an academic medical centre in the USA, introduction of restriction criteria regarding meropenem use for 2 months during the third year of the pandemic successfully reduced inappropriate meropenem utilization and hospital length of stay, contributing to significant cost savings for the institution [19]. On the other hand, the results of the present study confirm the preservation of the efficiency of an ASP based on a prospective audit and feedback strategy. Recently, another study showed that the strengthening of an ASP that was already in place, by using a combination of restrictive policies and persuasive techniques, was successful in safely controlling the observed increase of carbapenem consumption during the first wave of COVID-19 pandemic [14]. Thus, there is evidence to suggest that both core antimicrobial stewardship strategies continue to be safe and effective during the COVID-19 era.

Several reports before the COVID-19 pandemic described reduced carbapenem use without negatively affecting patient outcomes through the implementation of carbapenem-focused ASPs [20–25]. However, few studies on antimicrobial stewardship were performed in Greece [26–28], and only one study examined a carbapenem-focused intervention [27]. None of these studies addressed the impact of the intervention on the consumption of newer non-carbapenem antibiotics with activity against MDR-GNB. Our study adds new evidence as the sharp and sustained decrease in carbapenem use achieved by the ASP was associated with an

increase only in the consumption of piperacillin/ tazobactam, which has a lower ecological impact than carbapenems. Moreover, the carbapenem-focused ASP in this study did not significantly affect the consumption of tigecycline and colistin, which are associated with several toxicities and adverse effects, or the consumption of ceftolozane/tazobactam and ceftazidime/avibactam. The latter is important, considering the need to preserve the efficacy of new antibiotics through their judicious use.

Following the ASP implementation in this study, there were no significant changes in all-cause in-hospital mortality and 30 day mortality after carbapenem initiation. On the contrary, the infection-related readmission rate was lower over the post- implementation period. In addition, when the analysis was restricted to the post-implementation cohort, acceptance of the intervention was associated with reduced in-hospital and 30 day mortality after carbapenem initiation, as well as better treatment outcome. These findings are in accordance with the results of the great majority of hospital ASP studies that measured patient outcomes and reported statistically significant reductions or at least non-significant changes in patient mortality and infection-related readmissions [29–31].

The difference in treatment outcome between cases with accepted and non-accepted intervention in the post-implementation subgroup was probably due to the optimization of diagnostic work-up and antimicrobial treatment through the acceptance of the intervention, reflecting the benefits of ID consultation on this parameter [32–34]. However, other factors might have acted as potential sources of bias on the estimation of treatment outcome. First, contrary to cases where ASP team recommendation was declined and further consultation was provided only upon request, unsolicited follow-up consultation was given regularly until

completion of antimicrobial treatment when the intervention was accepted, thus enhancing the prompt, continuous and efficient handling of possible new-onset complications in these patients. Furthermore, the intervention was not accepted for a number of patients with terminal illness and without proof of concurrent infection for whom the treating physician hesitated to withdraw antibiotics, thus defying the ASP team recommendation.

Previous studies have reported reductions in length of hospital stay after implementing ASPs [18,30]. However, we found that patients in the post-implementation group experienced longer length of hospital stay, on average, compared with the pre-implementation group. This finding cannot be fully explained. A possible reason could be found in the decreased proportion of admitted patients that received carbapenems during the intervention period, indicating that treating physicians used carbapenems more judiciously then, reserving them only for severe cases, which, however, required longer hospitalization compared with the cases in the pre-intervention period. Unfortunately, we were unable to retrieve more data on the severity of patients' illness during the pre-implementation period to test this hypothesis.

A key strength of our study is the use of a multidimensional methodology to assess the impact of a carbapenem-focused ASP on antibiotic use and clinical outcomes. Another important feature is the high rate (89%) of acceptance of the intervention by treating physicians. Furthermore, a cross-sectional survey in our hospital near the end of the post-implementation period showed that the ASP described here had positive impact on doctors' perceptions, attitudes and practices regarding the management of infections due to MDR microorganisms, and 98.5% of respondents wanted the ASP to continue during the COVID-19 pandemic [35].

Finally, our study can be easily replicated in settings where targeting a specific antibiotic class is needed and ID physicians are available for this purpose.

The present study is not exempt from limitations. Although our segmental regression analysis of interrupted time series is recommended as a powerful tool to assess temporal trends following an intervention [36,37], it shares the same limitations as any analysis of observational data. Our analysis examined level and slope changes in the rates of use of carbapenems and other antibiotics following ASP implementation, by accounting for potential confounding effects by seasonality and varying inpatient population size over time. The absence of differences in demographic and clinical characteristics of the patients before and after ASP implementation provides some assurance that our results are unlikely to have been confounded by differences in local epidemiology between the pre-intervention and intervention periods. However, we cannot completely exclude the possibility of residual confounding by unmeasured factors, such as varying frequency and severity of infections with highly resistant bacteria that would require carbapenems. Our sensitivity analyses produced consistent estimates of the relative reduction in the number of patients treated with carbapenems following the ASP under different statistical modelling specifications, but we must note that adjustment for overdispersion resulted in less precise estimates and higher *P* values. We do not view the latter as a major concern as the *P* values remained relatively low (ranging from 0.056 to 0.107) after we inflated the standard errors for overdispersion, and because a separate analysis of hospital volume data of carbapenem consumption confirmed a significant reduction following the ASP implementation. Furthermore, we did not evaluate the impact of the ASP on AMR or the incidence of *Clostridioides difficile* infection, because we considered that the strengthening of infection prevention and control

measures due to COVID-19 in the post-implementation period would be an important confounder. In addition, the retrospective nature of the study in the pre-intervention period did not allow the retrieval of reliable data on patient comorbidities during that period. Moreover, paediatric patients were not included in our study. Lastly, this was a single-centre study in a large academic hospital whose capacity was not exceeded during the study period because of the COVID-19 pandemic, thus limiting the generalizability of our results to hospitals of different size and characteristics.

In conclusion, this study demonstrates that implementing and maintaining a carbapenem-focused ASP is feasible, effective and safe in settings with high rates of MDR-GNB, even during the COVID-19 pandemic. The ASP not only effectively reduced the use of carbapenems, but also led to improved patient outcomes, without increasing the consumption of newer antibiotics.

6. References

1. Meletis G. Carbapenem resistance: overview of the problem and future perspectives. Ther Adv Infect Dis 2016,3,15-21.

2. Pavez M, Vieira C, de Araujo MR, Cerda A, de Almeida LM, Lincopan N, Mamizuka EM. Molecular mechanisms of membrane impermeability in clinical isolates of Enterobacteriaceae exposed to imipenem selective pressure. Int J Antimicrob Agents 2016,48,78-85.

3. Simner PJ, Antar AAR, Hao S, Gurtowski J, Tamma PD, Rock C, Opene BNA, Tekle T, Carroll KC, Schatz MC, et al. Antibiotic pressure on the acquisition and loss of antibiotic resistance genes in Klebsiella pneumoniae. J Antimicrob Chemother 2018,73,1796-1803.

4. European Centre for Disease Prevention and Control (ECDC). Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report for 2020. Available online: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-consumption-europe-2020.

5. European Centre for Disease Prevention and Control (ECDC). Antimicrobial resistance surveillance in Europe - 2020 data. Available online: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2020.

6. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, Colomb-Cotinat M, Kretzschmar ME, Devleesschauwer B, Cecchini M, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019,19,56-66.

7. Lai CC, Chen SY, Ko WC, Hsueh PR. Increased antimicrobial resistance during the COVID-19 pandemic. Int J Antimicrob Agents 2021,57,106324.

8. Spernovasilis NA, Kofteridis DP. COVID-19 and antimicrobial stewardship: What is the interplay? Infect Control Hosp Epidemiol 2021,42,378-379.

9. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available online: https://www.covid19treatmentguidelines.nih.gov/.

10. Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, Daneman N, MacFadden DR. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. Clin Microbiol Infect 2021,27,520-531.

11. Liew Y, Lee WHL, Tan L, Kwa ALH, Thien SY, Cherng BPZ, Chung SJ. Antimicrobial stewardship programme: a vital resource for hospitals during the global outbreak of coronavirus disease 2019 (COVID-19). Int J Antimicrob Agents 2020,56,106145.

12. Castro-Lopes A, Correia S, Leal C, Resende I, Soares P, Azevedo A, Paiva JA. Increase of Antimicrobial Consumption in a Tertiary Care Hospital during the First Phase of the COVID-19 Pandemic. Antibiotics (Basel) 2021,10,778.

13. Grau S, Echeverria-Esnal D, Gómez-Zorrilla S, Navarrete-Rouco ME, Masclans JR, Espona M, Gracia-Arnillas MP, Duran X, Comas M, Horcajada JP, et al. Evolution of Antimicrobial Consumption During the First Wave of COVID-19 Pandemic. Antibiotics (Basel) 2021,10,132.

14. AlBahrani S, Almogbel F, Alanazi W, Almutairi SH, Alanazi M, Maximos S, Azaiez F, Osman A, Almuthen S, Jebakumar AZ, et al. Carbapenem use correlates with percentage of patients with COVID-19 in intensive care units. Infection 2022,1-6.

15. Tomczyk S, Taylor A, Brown A, de Kraker MEA, El-Saed A, Alshamrani M, Hendriksen RS, Jacob M, Löfmark S, Perovic O, et al. Impact of the COVID-19 pandemic on the surveillance, prevention and control of antimicrobial resistance: a global survey. J Antimicrob Chemother 2021,76,3045-3058.

16. Macera M, Onorato L, Calò F, Monari C, Annibale R, Signoriello G, Donnarumma G, Montemurro MV, Galdiero M, Coppola N. The Impact of the SARS-Cov2 Pandemic on a Persuasive Educational Antimicrobial Stewardship Program in a University Hospital in Southern Italy: A Pre-Post Study. Antibiotics (Basel) 2021,10,1405.

17. Meschiari M, Onorato L, Bacca E, Orlando G, Menozzi M, Franceschini E, Bedini A, Cervo A, Santoro A, Sarti M, et al. Long-Term Impact of the COVID-19 Pandemic on In-Hospital Antibiotic Consumption and Antibiotic Resistance: A Time Series Analysis (2015-2021). Antibiotics (Basel) 2022,11,826.

18. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2017,2,CD003543.

19. Wells DA, Johnson AJ, Lukas JG, Mason D, Cleveland KO, Bissell A, Hobbs ALV. Criteria Restricting Inappropriate Meropenem Empiricism (CRIME): a quasi-experimental carbapenem restriction pilot at a large academic medical centre. Int J Antimicrob Agents 2022,106661.

20. García-Rodríguez JF, Bardán-García B, Peña-Rodríguez MF, Álvarez-Díaz H, Mariño-Callejo A. Meropenem antimicrobial stewardship program: clinical, economic, and antibiotic resistance impact. Eur J Clin Microbiol Infect Dis 2019,38,161-170.

21. Faraone A, Poggi A, Cappugi C, Tofani L, Riccobono E, Giani T, Fortini A. Inappropriate use of carbapenems in an internal medicine ward: Impact of a carbapenem-focused antimicrobial stewardship program. Eur J Intern Med 2020,78,50-57.

22. García-Rodríguez JF, Bardán-García B, Juiz-González PM, Vilariño-Maneiro L, Álvarez-Díaz H, Mariño-Callejo A. Long-Term Carbapenems Antimicrobial Stewardship Program. Antibiotics (Basel) 2020,10,15.

23. López-Viñau T, Peñalva G, García-Martínez L, Castón JJ, Muñoz-Rosa M, Cano Á, Recio M, Cisneros JM, Pérez-Nadales E, Rumbao Aguirre J, et al. Impact of an Antimicrobial Stewardship Program on the Incidence of Carbapenem Resistant Gram-Negative Bacilli: An Interrupted Time-Series Analysis. Antibiotics (Basel) 2021,10,586.

24. Rungsitsathian K, Wacharachaisurapol N, Nakaranurack C, Usayaporn S, Sakares W, Kawichai S, Jantarabenjakul W, Puthanakit T, Anugulruengkitt S. Acceptance and outcome of interventions in a meropenem de-escalation antimicrobial stewardship program in pediatrics. Pediatr Int 2021,63,1458-1465.

25. Kit-Anan W, Boonsathorn S, Anantasit N, Techasaensiri C, Chaisavaneeyakorn S, Apiwattanakul N. Handshake stewardship reduces carbapenem prescription in a pediatric critical care setting. Pediatr Int 2022,64,e15227.

26. Pitiriga V, Kanellopoulos P, Kampos E, Panagiotakopoulos G, Tsakris A, Saroglou G. Antimicrobial stewardship program in a Greek hospital: implementing a mandatory prescription form and prospective audits. Future Microbiol 2018,13,889-896.

27. Makina A-A, Poulakou G, Sympardi S, Souli M, Liakopoulou E, Matthaiou D, Karaiskou A, Arvaniti A, Alexiou N, Charalabaki N. Safety of a carbapenem-sparing approach as part of an

antibiotic stewardship program, in a setting with increased carbapenem resistance. Infect Dis Clin Microbiol 2019,1,14-25.

28. Chrysou K, Zarkotou O, Kalofolia S, Papagiannakopoulou P, Mamali V, Chrysos G, Themeli-Digalaki K, Sypsas N, Tsakris A, Pournaras S. Impact of a 4-year antimicrobial stewardship program implemented in a Greek tertiary hospital. Eur J Clin Microbiol Infect Dis 2022,41,127-132.

29. Schuts EC, Hulscher M, Mouton JW, Verduin CM, Stuart J, Overdiek H, van der Linden PD, Natsch S, Hertogh C, Wolfs TFW, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis 2016,16,847-856.

30. Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. Antimicrob Resist Infect Control 2019,8,35.

31. Carrara E, Sibani M, Barbato L, Mazzaferri F, Salerno ND, Conti M, Azzini AM, Dalbeni A, Pellizzari L, Fontana G, et al. How to 'SAVE' antibiotics: effectiveness and sustainability of a new model of antibiotic stewardship intervention in the internal medicine area. Int J Antimicrob Agents 2022,60,106672.

32. Kim SH, Huh K, Cho SY, Kang CI, Chung DR, Peck KR. Factors associated with the recurrence of acute pyelonephritis caused by extended-spectrum β-lactamase-producing Escherichia coli: the importance of infectious disease consultation. Diagn Microbiol Infect Dis 2019,94,55-59.

33. Whittington KJ, Ma Y, Butler AM, Hogan PG, Ahmed F, Flowers J, Milburn G, Morelli JJ, Newland JG, Fritz SA. The impact of infectious diseases consultation for children with Staphylococcus aureus bacteremia. Pediatr Res 2022,92,1598-1605.

34. Mejia-Chew C, O'Halloran JA, Olsen MA, Stwalley D, Kronen R, Lin C, Salazar AS, Larson L, Hsueh K, Powderly WG, et al. Effect of infectious disease consultation on mortality and treatment of patients with candida bloodstream infections: a retrospective, cohort study. Lancet Infect Dis 2019,19,1336-1344.

35. Spernovasilis N, Ierodiakonou D, Spanias C, Mathioudaki A, Ioannou P, Petrakis EC, Kofteridis DP. Doctors' Perceptions, Attitudes and Practices towards the Management of Multidrug-Resistant Organism Infections after the Implementation of an Antimicrobial Stewardship Programme during the COVID-19 Pandemic. Tropical Medicine and Infectious Disease 2021,6,20.

36. Stone SP, Cooper BS, Kibbler CC, Cookson BD, Roberts JA, Medley GF, Duckworth G, Lai R, Ebrahim S, Brown EM, et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. J Antimicrob Chemother 2007,59,833-840.

37. Schweizer ML, Braun BI, Milstone AM. Research Methods in Healthcare Epidemiology and Antimicrobial Stewardship-Quasi-Experimental Designs. Infect Control Hosp Epidemiol 2016,37,1135-1140.

CHAPTER IV

Doctors' Perceptions, Attitudes and Practices towards the Management of Multidrug-Resistant Organism Infections after the Implementation of an Antimicrobial Stewardship Programme during the COVID-19 Pandemic

Nikolaos Spernovasilis [1], Despo Ierodiakonou [2,3], Christos Spanias [4], Anna Mathioudaki [5], Petros Ioannou [5], Emmanouil C. Petrakis [5] and Diamantis P. Kofteridis [1,5]

[1] School of Medicine, University of Crete, Heraklion, Greece

[2] Department of Social Medicine, School of Medicine, University of Crete, Heraklion, Greece

[3] Department of Primary Care and Population Health, University of Nicosia Medical School, Nicosia, Cyprus

[4] Department of Pharmacy, University Hospital of Heraklion, Heraklion, Greece

[5] Department of Internal Medicine, University Hospital of Heraklion, Heraklion, Greece

Published in: ***Trop Med Infect Dis. 2021; 6 (1): 20***

1. Abstract

Background: Greece is among the European countries with the highest consumption of antibiotics, both in community and hospital settings, including last-line antibiotics, such as carbapenems. We sought to explore doctors' perceptions, attitudes and practices towards the management of patients with multidrug-resistant organism (MDRO) infections after the implementation of an antimicrobial stewardship programme (ASP) in a tertiary academic hospital during the COVID-19 pandemic.

Methods: A self-administered, internet-based questionnaire survey was completed by doctors of the University Hospital of Heraklion in Crete, Greece.

Results: In total, 202 (59.1%) hospital doctors fully completed the questionnaire. Most of them agreed that the prospective audit and feedback ASP strategy is more effective and educational than the preauthorization ASP strategy. ASP implementation prompted most respondents to monitor the continuously evolving microbiological data of their patients more closely and affected them towards a multidisciplinary and personalised care of patients with infections caused by MDROs and towards a more rigorous implementation of infection prevention and control measures. The vast majority of participants (98.5%) stated that ASP must be continued and further developed during the COVID-19 pandemic.

Conclusion: The ASP implementation in our hospital had a beneficial impact on doctors' perceptions, attitudes and practices with regard to the management of infections due to MDROs.

2. Introduction

Excessive antimicrobial consumption and misuse are major problems worldwide and significantly contribute to antimicrobial resistance [1]. The emergence and spread of antimicrobial resistance negatively affect patient outcomes, healthcare costs and the enduring efficacy of antimicrobial agents [2,3]. Antibiotic consumption in Greece ranks among the highest in Europe, both in the community and the hospital sector [4], whereas recent data for other categories of antimicrobials do not exist. In parallel, antimicrobial resistance (AMR) rates in Greece are extremely high during this decade [5]. Therefore, a national action plan on AMR is currently under development [6], while many Greek hospitals have already optimised infection prevention and control (IPC) practices and implemented antimicrobial stewardship programmes (ASPs).

Since the beginning of 2020, an ASP has been implemented for a first time in the adult clinics of the University Hospital of Heraklion in Greece. This ASP is focused on the prescription of carbapenems with regard to the indication, dosage and duration of treatment, combined with the judicious use of carbapenem-sparing antibiotics whenever appropriate. The programme is based on the prospective audit and feedback strategy, along with a case-based education of treating doctors. An infectious diseases (ID) specialist and an ID fellow are being alerted by the hospital pharmacy upon prescription request for carbapenem and provide unsolicited in-person ("handshake") consultation within 72 h for all patients for whom the treating doctors have prescribed carbapenem. This approach includes a lack of prior authorization by the ASP members for carbapenem administration (i.e., treating doctors can prescribe a carbapenem for their patients without previous approval and even continue carbapenem administration despite a

potentially opposite recommendation by the ASP members), the patient's clinical examination by the ID specialist or ID fellow, review of the patient's laboratory data and of all prescribed antimicrobials, and a subsequent daily, rounding-based, in-person approach to feedback by the ID doctors. Further ID consultation service upon request is available 7 days a week, 24 h a day, through telephone or in-person. The execution of the ASP has not been affected by the COVID-19 pandemic, since our hospital's capacity has not been exceeded during the care of COVID-19 patients. In this context, and after eleven months of ASP implementation, we sought to examine doctors' perceptions, attitudes and practices towards the management of patients with multidrug-resistant organism (MDRO) infections. To the best of our knowledge, this was the first study of its kind conducted during the COVID-19 pandemic.

3. Materials and Methods

3.1. Study Design, Setting, Duration and Participants

A cross-sectional web-based survey was conducted from 21 November to 4 December 2020 at the 760-bed University Hospital of Heraklion in Greece. All resident and specialist doctors of hospital adult clinics were eligible to participate.

3.2. Survey Instrument

A self-administered questionnaire was developed on the SurveyMonkey platform (SurveyMonkey Inc., San Mateo, CA, USA) by a multidisciplinary team of infectious diseases specialists and fellows, clinical pharmacists and hospital epidemiologists. It was partially based on previously validated questionnaires in the published literature [7,8]. It consisted of 15 items, including close-ended, multiple choice and Likert-scale questions (with sub-questions), divided

as follows: 5 on demographics and practice-related information; 4 on previous and current experience with ASP; 4 on perceptions related to the management of patients with MDRO infections after ASP implementation; and 2 on attitudes and practices towards the management of patients' MDRO infections after ASP implementation. The questionnaire is available as **Supplementary II** material. Prior to dissemination, the questionnaire was piloted among 10 resident and specialist doctors to assess length and readability.

3.3. Participation and Ethical Approval

Participation was voluntary, anonymous and without compensation. The invitation to participate was sent via email through the SurveyMonkey platform. Questionnaires not completely answered within 10 days generated a single reminder email. Informed consent for the questionnaire's completion was declared on its first page. This study was approved by the hospital's Ethics Committee.

3.4. Statistical Analysis

Data coding and descriptive statistical analyses were performed in R version 3.6.2 (12 December 2019) (R Foundation for Statistical Computing, Vienna, Austria). Qualitative data are presented as counts and percentages. Continuous variables were assessed for normality and due to not normal distributions are presented as median and interquartile range. In addition, we used chi-square, Fisher's exact and Mann–Whitney U tests for assessing the differences according to the level of practice (resident versus specialist doctor) and to specialty (medical versus surgical). Significance level was set at 5%.

4. Results

4.1. Participants

Three hundred and forty-two hospital doctors were eligible to participate in this study. A total of 202 (59.1%) responded with the full completion of the questionnaire and were included in the analysis. Among them, 105 (52%) were residents and 97 (48%) were specialists. There was representation from all hospital adult specialties. Table 1 shows the basic characteristics of the respondents and their experience with previous and current ASPs.

Table 1. Characteristics of survey respondents and their experience with ASPs.

Characteristic	**Total (n=202)**	**Residents (n=105)**	**Specialists (n=97)**
Age, median (IQR)	37 (30-46)	30 (27-33)	46 (40-53)
Gender			
Male	114 (56.4)	50 (47.6)	64 (66)
Female	88 (43.6)	55 (52.4)	33 (34)
Specialty			
Medical	124 (61.4)	76 (72.4)	48 (49.5)
Surgical	65 (32.2)	29 (27.6)	36 (37.1)
ICU	13 (6.4)	0 (0)	13 (13.4)
Years of experience, median (IQR)			
In residency	n/a	4 (2-5)	n/a
Post-residency	n/a	n/a	11 (5-19)

Previous experience with ASPs			
Yes	29 (14.4)	9 (8.6)	20 (20.6)
No	173 (85.6)	96 (91.4)	77 (79.4)
Rate of patients with MDR gram-negative infection under respondents' care			
Zero	23 (11.4)	14 (13.3)	9 (9.3)
1-4 cases/month	120 (59.4)	72 (68.6)	48 (49.5)
5-10 cases/month	34 (16.8)	13 (12.4)	21 (21.6)
>10 cases/month	25 (12.4)	6 (5.7)	19 (19.6)
Rate of ASP consultation for patients with MDR Gram-negative infection under respondents' care			
Zero	29 (14.3)	20 (19)	9 (9.3)
1-4 times/month	125 (61.9)	70 (66.7)	55 (56.7)
5-10 times/month	40 (19.8)	13 (12.4)	27 (27.8)
>10 times/month	8 (4)	2 (1.9)	6 (6.2)

Respondents' adherence to ASP team recommendations			
Never	5 (2.5)	5 (4.8)	0 (0)
Rarely	5 (2.5)	1 (0.9)	4 (4.1)
Sometimes	32 (15.8)	14 (13.3)	18 (18.6)
Often	67 (33.2)	34 (32.4)	33 (34)
Always	93 (46)	51 (48.6)	42 (43.3)

All data in n (%), unless otherwise indicated.

ASPs: antimicrobial stewardship programmes; IQR: interquartile range; ICU: intensive care unit; n/a: not available; MDR: multidrug-resistant.

4.2. Perceptions

Respondents' perceptions in relation to the ASP strategy pursued are presented in Figure 1. The great majority of doctors believed that prospective audit and feedback ASP strategy is more effective and educational than preauthorization ASP strategy (90.6% and 77.7%, respectively). Most of respondents (90.6%) agreed that the implementation of an ASP improves patients' outcome compared to the absence of such a programme regardless of the strategy pursued, even though a third of participants considered that preauthorization strategy suits a Greek hospital better; yet less than 10% of participants agreed that prospective audit and feedback strategy of the current ASP should change.

More than 80% of respondents agreed that in-person consultation is the preferred practice for the ASP, welcome as often as possible, constituting at the same time an educational process for the treating doctors (Figure 2). Only 5% of respondents thought that in-person consultation disrupts their daily clinical practice, while approximately one-fourth of participants reported that it can be largely replaced by telephone or electronic communication.

Figure 1. Respondents' perceptions regarding the strategy pursued in our hospital's ASP.

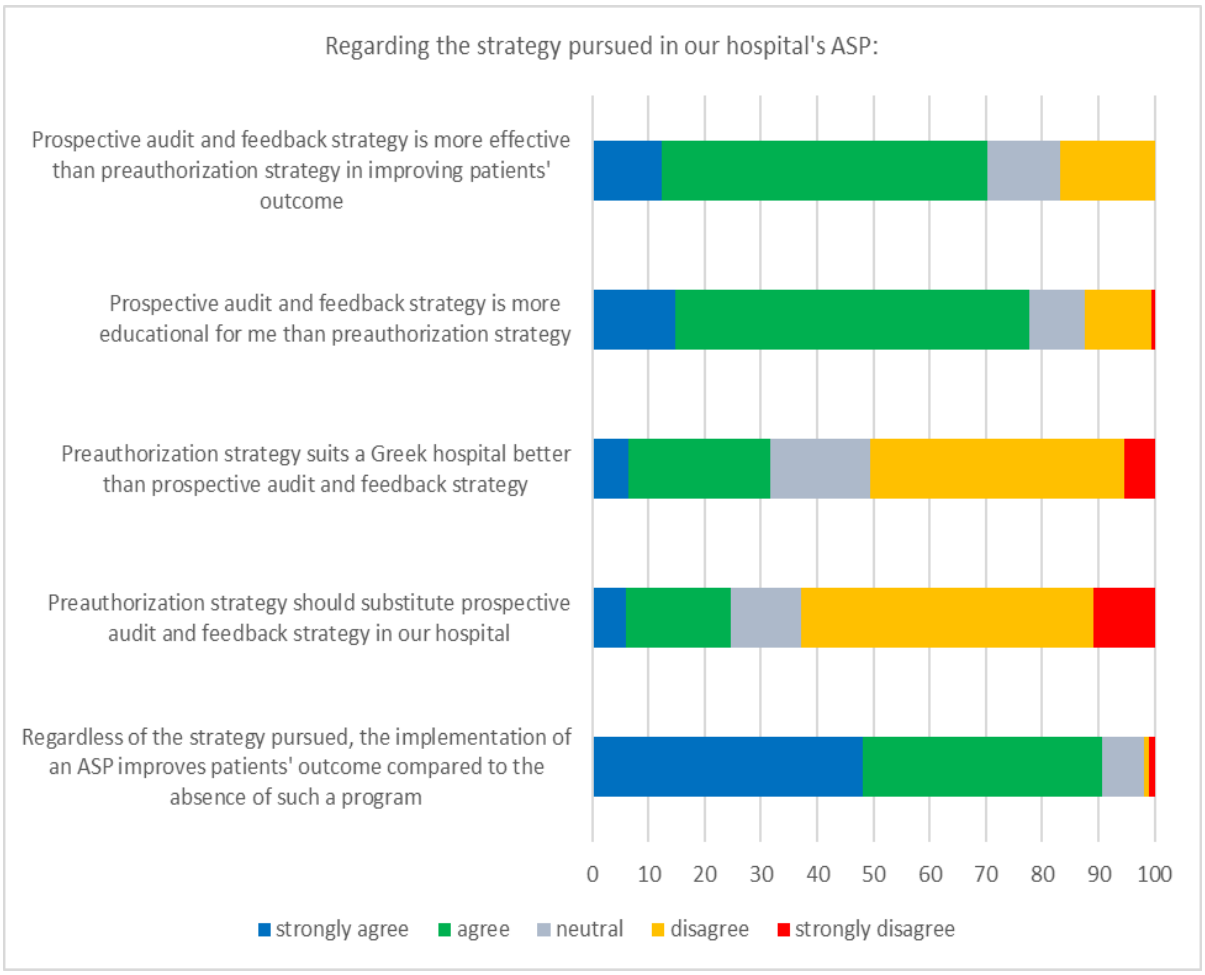
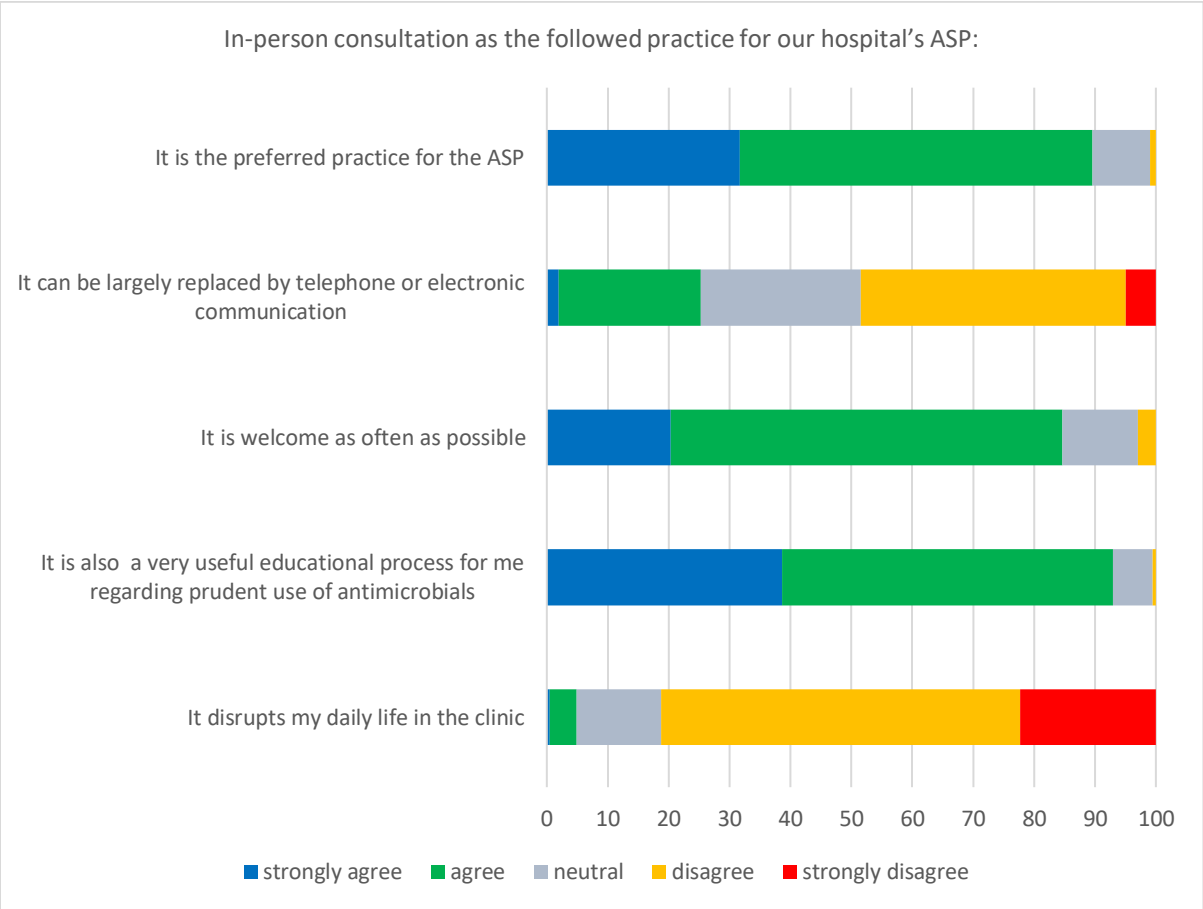
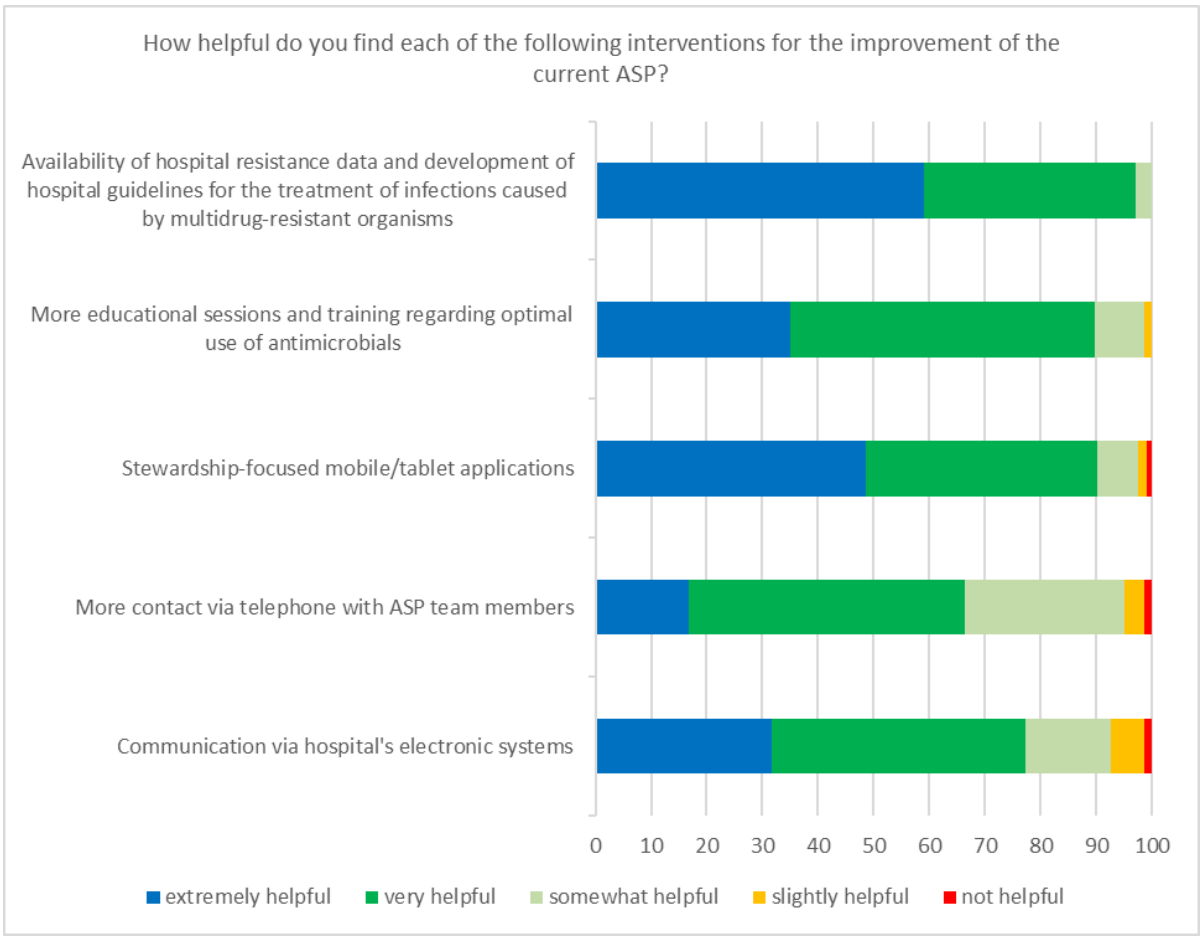


Figure 2. Respondents' perceptions regarding in-person consultation as the followed practice for our hospital's ASP.



Regarding the proposed measures for the improvement of the current ASP (Figure 3), the majority of participants agreed that these could be helpful, with the most popular preferences in the following order: availability of hospital resistance data and the development of hospital guidelines for the treatment of infections caused by MDROs, more educational sessions and training regarding the optimal use of antimicrobials, and the availability of stewardship-focused mobile/tablet applications. Noteworthy, in a subsequent question regarding the future of the ASP in our hospital during the COVID-19 pandemic, 98.5% of respondents stated that ASP must be continued and further developed, and only 1.5% that it must be postponed.

Figure 3. Respondents' perceptions regarding potential interventions to improve our hospital's ASP.



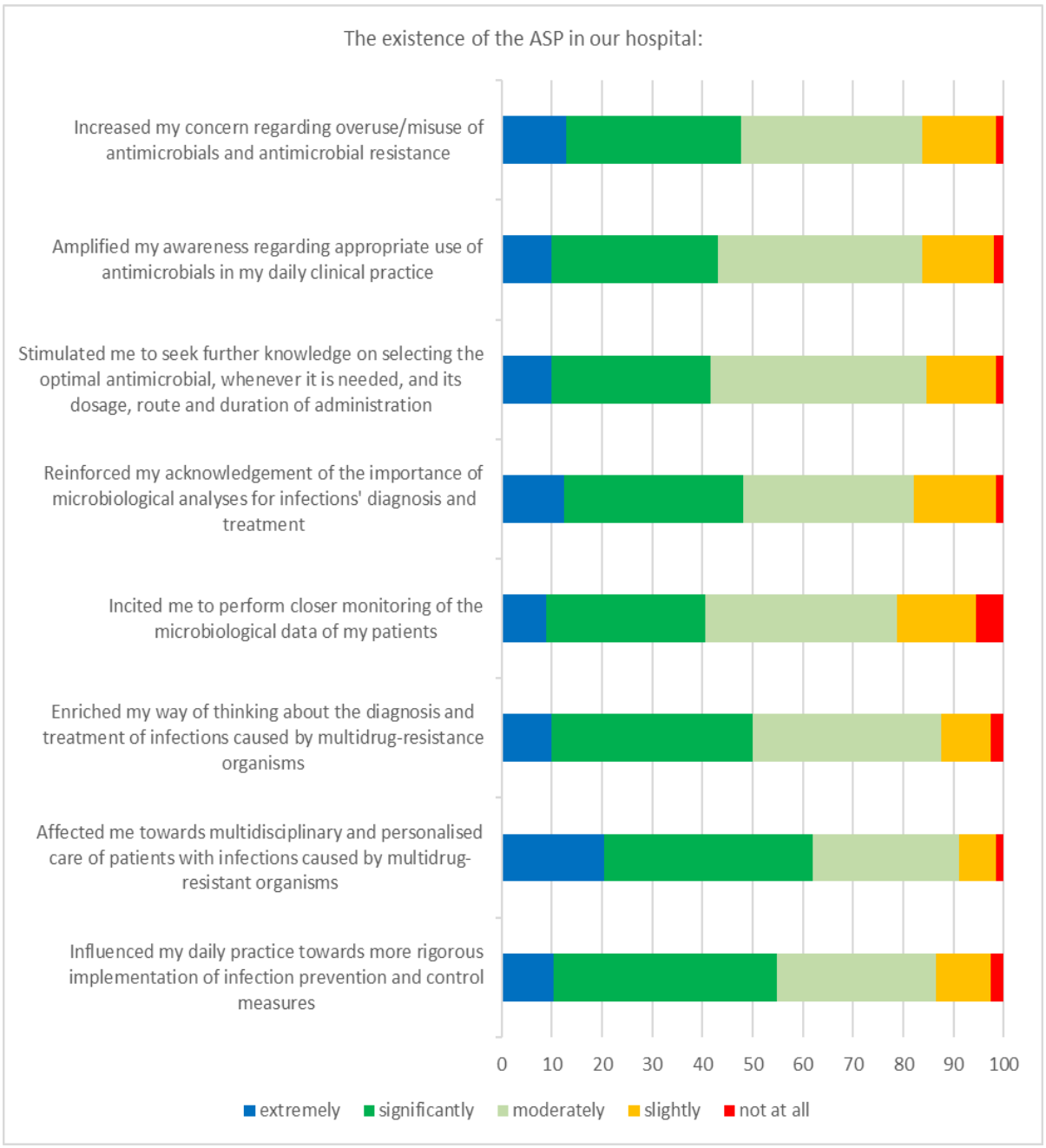
4.3. Attitudes

The impact of the ASP implementation on respondents' attitudes regarding management of patients with MDRO infections seemed to be quite positive (Figure 4). Specifically, ASP existence increased, at least moderately, most doctors' (>80%) concern regarding overuse/misuse of antimicrobials and antimicrobial resistance, and amplified their awareness regarding appropriate use of antimicrobials in their daily clinical practice. Similarly, ASP reinforced their acknowledgement of the importance of microbiological analyses, and enriched their way of thinking about the diagnosis and treatment of infections caused by MDROs. In a separate question regarding respondents' willingness to participate more actively in the ASP in the future, 67.3% responded positively and 33.7% negatively.

4.4. Practices

ASP incited the majority of respondents (>80%) to perform closer monitoring of the microbiological data of their patients, and stimulated them to seek further knowledge on selecting the optimal antimicrobial treatment for patients with infections caused by MDROs (Figure 4). In addition, ASP had a beneficial impact on most respondents (>85%) towards multidisciplinary and personalised care of patients with more rigorous implementation of IPC measures. Notably, with regard to respondents' perceptions, attitudes and practices, no statistically significant differences were identified between residents and specialists, and between medical and surgical specialties (data not shown).

Figure 4. Respondents' attitudes and practices towards management of patients with MDROs infections



5. Discussion

This study was the first to examine the perceptions, attitudes and practices of hospital doctors towards the management of hospitalised patients with infections caused by MDROs after the implementation of an ASP during the COVID-19 pandemic. The study's significance lies not only on its actual findings, but also in the fact that it was conducted under the pressure that COVID-19 put on health systems and healthcare workers worldwide.

The response rate of invited doctors in the current survey (59.1%) was comparable to or higher than most similar studies [7–11]. Both genders were represented almost equally in the study sample, as was also the case regarding the professional status, i.e., resident or specialist. About half of respondents reported that they always accept ASP team recommendations and about a third reported that they often do, in line with the adherence rates of 68–81% that have been reported in the literature [12].

The majority of participants in this study perceived the prospective audit and feedback strategy as more educational for the prescribers and more effective for patients' favourable outcome compared with the preauthorization strategy. Furthermore, the existence of an ASP was perceived as a contributing factor for improved patients' outcome compared with its absence. Indeed, the prospective audit and feedback strategy represents a more educational process for the prescribers through evidence-based discussions between them and the ASP team members [13]. However, no rigorously designed studies directly compare prospective audit and feedback to preauthorization with respect to patient outcomes [14]. In addition, current literature data show that ASPs, regardless of the strategy pursued, reduce patients' duration of treatment and hospital stay, but they do not affect mortality [15]. Thus, some of the

aforementioned perceptions may simply reflect the fact that doctors do not favour interventions that limit their prescribing autonomy.

Most respondents agreed that in-person consultation is the preferred practice for our hospital's ASP, however, the majority of respondents did not have previous experience with ASPs, making this positive perception of in-person consultation less objective. Regardless of that, in-person consultation was perceived as an educational interaction which is desirable as often as possible. The latter, in combination with what was mentioned in the preceding paragraph, further highlights doctors' tendency for additional education on antimicrobial prescribing in a country characterised by inappropriate use of antimicrobials and high resistance rates [16]. This tendency is confirmed by the fact that the demand for more educational sessions and training regarding the optimal use of antimicrobials was among the most popular interventions that participants want to be included or enhanced in the current ASP, along with the availability of hospital resistance data and guidelines.

A notable finding of the present study is that the vast majority of respondents wanted the ASP to be continued and further developed despite the fact that their workload had already been increased due to the COVID-19 pandemic [17]. This is quite encouraging, since high and inappropriate antimicrobial use has been observed during this pandemic [18,19]. Many studies revealed heavy use of empirical broad-spectrum antimicrobials in hospitals while evidence so far suggests that the rates of bacterial and fungal infection in COVID-19 patients are rather low [20,21]. Therefore, the integration of an ASP in every hospital's COVID-19 response effort is imperative.

The ASP implementation in our hospital had a beneficial impact on doctors' attitudes regarding the management of infections due to MDROs. Most of the participants reported an increase in their concern about the imprudent use of antimicrobials and in their awareness on this issue. They also reported a greater recognition of the importance of microbiological analyses, including Gram stain, cultures, molecular techniques and serology, which is a prerequisite for a successful ASP [22], and enrichment of their approach to managing MDRO infections. Interestingly, about two-thirds of respondents would be willing to participate in ASP activities to improve the quality of antimicrobial use in the hospital, a proportion similar to or even higher than that observed in other studies [7,8,23].

One of the most important findings of this study was the observed change in doctors' practices in their daily clinical activity, eleven months after ASP implementation. In particular, ASP implementation prompted most respondents to more closely monitor the continuously evolving microbiological data of their patients. Furthermore, respondents were affected towards a multidisciplinary and personalised care of patients with infections caused by MDROs, which is essential for a favourable outcome in many cases, especially during the COVID-19 pandemic [24,25]. In addition, a more rigorous implementation of IPC measures after the ASP initiation was reported by the majority of respondents, an encouraging finding considering that a successful ASP concurrently requires well-performing IPC practices [26].

The ASP of our hospital will incorporate the potential interventions that the participants of this study found most helpful, such as the development of hospital guidelines for the treatment of MDRO infections, more educational sessions regarding the prudent administration of antimicrobials, and the use of stewardship-focused mobile or tablet applications. Moreover,

in the near future, we will examine the impact of the ASP on patients' outcomes, on hospital antibiotic consumption and on hospital AMR, by comparing pre- and post-ASP implementation periods. Finally, the ASP will be expanded in order to monitor and direct the appropriate use of additional antimicrobials.

This study has certain limitations that should be mentioned. The survey was conducted at a single site, a well-resourced academic hospital whose capacity has not been exceeded during COVID-19 pandemic, therefore the results should be generalised with caution. In addition, as a survey, responses are prone to social desirability bias; confidentiality minimised this as much as possible. Furthermore, participation was voluntary, and volunteer bias is possible; however, the response rate was relatively high and all targeted departments were represented, therefore, there is confidence that the results are representative of the study population.

6. Conclusions

This study demonstrates a positive impact of ASP implementation on hospital doctors' perceptions, attitudes and practices towards the management of patients with MDRO infections. The study also confirms that doctors find the continuation of ASPs during the COVID-19 pandemic supportive and beneficial. The findings of this study will be useful for the design, implementation, and further development of hospital ASPs.

7. References

1. Roberts SC, Zembower TR. Global increases in antibiotic consumption: a concerning trend for WHO targets. Lancet Infect Dis 2020, 21, 10–11.

2. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. JAMA Internal Medicine 2017, 177, 1308-1315.

3. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, Colomb-Cotinat M, Kretzschmar ME, Devleesschauwer B, Cecchini M, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019, 19, 56-66.

4. European Centre for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA – Annual Epidemiological Report 2019. Stockholm: ECDC; 2020.

5. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report 2019. Stockholm: ECDC; 2020.

6. Organisation for Economic Co-operation and Development. Antimicrobial Resistance - Tackling the Burden in the European Union. Paris: OECD; 2019.

7. Baraka MA, Alsultan H, Alsalman T, Alaithan H, Islam MA, Alasseri AA. Health care providers' perceptions regarding antimicrobial stewardship programs (AMS) implementation-facilitators and challenges: a cross-sectional study in the Eastern province of Saudi Arabia. Ann Clin Microbiol Antimicrob 2019, 18, 26.

8. Sutthiruk N, Considine J, Hutchinson A, Driscoll A, Malathum K, Botti M. Thai clinicians' attitudes toward antimicrobial stewardship programs. Am J Infect Control 2018, 46, 425-430.

9. Hayat K, Rosenthal M, Zhu S, Gillani AH, Chang J, Bogale AA, Kabba JA, Yang C, Jiang M, Zhao M, et al. Attitude of clinicians towards hospital-based antimicrobial stewardship programs: a multicenter cross-sectional study from Punjab, Pakistan. Expert Rev Anti Infect Ther 2019, 17, 661-669.

10. Perozziello A, Lescure FX, Truel A, Routelous C, Vaillant L, Yazdanpanah Y, Lucet JC. Prescribers' experience and opinions on antimicrobial stewardship programmes in hospitals: a French nationwide survey. J Antimicrob Chemother 2019, 74, 2451-2458.

11. Salsgiver E, Bernstein D, Simon MS, Eiras DP, Greendyke W, Kubin CJ, Mehta M, Nelson B, Loo A, Ramos LG, et al. Knowledge, Attitudes, and Practices Regarding Antimicrobial Use and Stewardship Among Prescribers at Acute-Care Hospitals. Infect Control Hosp Epidemiol 2018, 39, 316-322.

12. Wee LE, Chung SJ, Tang SLS, Liew YX, Tan LY, Cherng PZB, Kwa LHA, Chlebicki MP. Who listens and who doesn't? Factors associated with adherence to antibiotic stewardship intervention in a Singaporean tertiary hospital. J Glob Antimicrob Resist 2020, 22, 391-397.

13. Tamma PD, Avdic E, Keenan JF, Zhao Y, Anand G, Cooper J, Dezube R, Hsu S, Cosgrove SE. What Is the More Effective Antibiotic Stewardship Intervention: Preprescription Authorization or Postprescription Review With Feedback? Clinical Infectious Diseases 2016, 64, 537-543.

14. Van Schooneveld TC, Rupp ME. Antimicrobial stewardship strategies: preauthorization or postprescription audit and feedback? Infect Control Hosp Epidemiol 2014, 35, 1100-1102.

15. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev 2017, 2, CD003543.

16. Spernovasilis N, Ierodiakonou D, Milioni A, Markaki L, Kofteridis DP, Tsioutis C. Assessing the knowledge, attitudes and perceptions of junior doctors on antimicrobial use and antimicrobial resistance in Greece. J Glob Antimicrob Resist 2020, 21, 296-302.

17. Martin E, Philbin M, Hughes G, Bergin C, Talento AF. Antimicrobial stewardship challenges and innovative initiatives in the acute hospital setting during the COVID-19 pandemic. J Antimicrob Chemother 2021, 76, 272-275.

18. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clin Infect Dis 2020, 71, 2459-2468.

19. Spernovasilis NA, Kofteridis DP. COVID-19 and antimicrobial stewardship: What is the interplay? Infect Control Hosp Epidemiol 2020, 1-2.

20. Garcia-Vidal C, Sanjuan G, Moreno-García E, Puerta-Alcalde P, Garcia-Pouton N, Chumbita M, Fernandez-Pittol M, Pitart C, Inciarte A, Bodro M, et al. Incidence of co-infections and superinfections in hospitalized patients with COVID-19: a retrospective cohort study. Clin Microbiol Infect 2020, 27, 83–88.

21. Rawson TM, Wilson RC, Holmes A. Understanding the role of bacterial and fungal infection in COVID-19. Clin Microbiol Infect 2020, 27, 9–11.

22. Dyar OJ, Beović B, Pulcini C, Tacconelli E, Hulscher M, Cookson B. ESCMID generic competencies in antimicrobial prescribing and stewardship: towards a European consensus. Clin Microbiol Infect 2019, 25, 13-19.

23. Cotta MO, Robertson MS, Tacey M, Marshall C, Thursky KA, Liew D, Buising KL. Attitudes towards antimicrobial stewardship: results from a large private hospital in Australia. Healthcare infection 2014, 19, 89-94.

24. Leone M, Pulcini C, De Waele J. Improving care for the ICU patient with suspected infection: a multidisciplinary perspective. Clin Microbiol Infect 2020, 26, 6-7.

25. Romei C, De Liperi A, Bartholmai BJ. COVID-19: The Importance of Multidisciplinary Approach. Academic radiology 2020, 27, 1327-1328.

26. Manning ML, Septimus EJ, Ashley ESD, Cosgrove SE, Fakih MG, Schweon SJ, Myers FE, Moody JA. Antimicrobial stewardship and infection prevention-leveraging the synergy: A position paper update. Am J Infect Control 2018, 46, 364-368.

CHAPTER V

Overview Discussion

1. Summary of main findings

Our work clearly demonstrated, through repeated point prevalence surveys and continuous surveillance, the positive impact of the implementation of this carbapenem-focused ASP in the University Hospital of Heraklion, Greece, on the quality of the antimicrobial prescribing [1]. In addition, the intervention *per se* comprised a retrospective-prospective, before–after, quasi-experimental cohort study, which showed a reduction in the carbapenems consumption without a concurrent increased of other broad-spectrum antibiotics with activity against Gram-negative bacteria, with the exemption of piperacillin-tazobactam [2]. Importantly, this reduction in carbapenems use was accompanied with an improvement in patient outcomes [2]. Furthermore, it was shown through a cross-sectional study that the aforementioned carbapenem-focused ASP had a beneficial impact on hospital's doctor perceptions and attitudes regarding the management of patients with MDRO infections [3]. Notably, it should be emphasized that the intervention described in this dissertation was implemented in a hospital setting of high endemicity for MDR GNB during the initial phase of the COVID-19 pandemic, which at that time was causing a tremendous pressure on health systems and healthcare workers, disrupting the majority of antimicrobial stewardship activities worldwide [4-6].

1.1 Quality of antibiotic prescribing

The quality of healthcare can be measured by using quality indicators (QIs), which are defined as "measurable elements of practice performance for which there is evidence or consensus that they can be used to assess the quality of care provided" [7,8]. QIs can be

categorized as structure-, process- and outcome indicators [7]. This acknowledges the relationship between comprehensive structures, adequate processes, and favorable outcomes.

The majority of reports on the effects of ASPs have focused on the decrease in antibiotic consumption following the deployment of various stewardship interventions [9,10]. If used alone, this approach entrains modest results. Any ASP should strive to evaluate the adequacy of antimicrobial prescribing, focused not only on administrating fewer antimicrobials but also on using them optimally. It is the appropriate use of antibiotics, and not only their reduction, which has been related to fewer adverse events and better clinical outcomes [10,11]. Furthermore, although the magnitude of the antibiotic use contributes to the emergence and spread of resistance to some extent, the inappropriate use of antibiotics is one of the most significant aggravating factors. Thus, reducing both overall antibiotic consumption and improper use of the antibiotics is an effective approach to slow the pace of the emergence of AMR [12,13].

Specifically for hospital ASPs, over two hundred QIs have been described in the medical literature, addressing a broad range of areas of ASPs in the hospital setting [14]. A recent, multidisciplinary, international consensus procedure led to the development of 51 generic QIs for antibiotic use in the inpatient setting, that are meant to be generally relevant, independent of the type of infectious disease, location, or socioeconomic environment. The majority of these IQIs were categorized as process, nearly one-third as structure, and only two as patient outcome indicators [13].

Continuous surveillance and PPS are the methods of choice to assess the quality of prescribing in hospital settings. When resources and time do not permit ongoing monitoring, PPS

have shown to be helpful in evaluating prescription quality and determining the reasons behind the inappropriate use of antibiotics [10]. These two methods provide targets for stewardship interventions, also enabling the evaluation of the results of these interventions.

1.1.1 Process indicators

This dissertation included both a continuous surveillance, through the prospective arm of the quasi-experimental cohort study, and a repeated PPS before and after the implementation of the ASP [1, 2]. The latter was based on the Global-PPS 2019 methodology [15], with some adaptations. The implementation of the ASP took into account several issues related to antimicrobial prescribing quality that were detected during the initial PPS. These issues included process indicators, specifically compliance to treatment guidelines and documentation of indication/diagnosis and stop/review date of antimicrobial treatment in patient files. Prior to the implementation of the ASP, the rates of the complete adherence to treatment guidelines and of the recording in patient files of the justification for therapy and the stop/review date of antimicrobial treatment were considered as being low compared to the majority of other similar studies [16-19]. In the second PPS, after the stewardship intervention, these rates were significantly increased, reflecting the effectiveness of the carbapenem-focused ASP on the quality of the overall antimicrobial prescribing in our hospital [1]. However, we could not examine all the process QIs that are reported in the literature, as the Global-PPS 2019 methodology does not include all of them [15].

1.1.2 Patient outcome indicators

The limited number of patient outcome QIs identified in the literature reflects the challenges of ASPs to precisely measure and demonstrate their influence on patient outcomes [20,21]. Even though expert panels developing QIs for hospital ASPs appraise patient outcome measures as quite important [20,22], there is a reluctance to include such measure in the proposed QI sets because of the existence of confounding factors that may be quite difficult to be adjusted reliably [23]. Such factors include, among others, random changes in the patterns of bacterial prevalence in the hospital setting and modification of the infection control activities [14]. Furthermore, concern exists that specific patient outcomes, including mortality, may be intrinsic insensitive to improvement after various stewardship interventions, for example i.v. to oral switching [22]. As a result, the most recent set of QIs developed for antimicrobial stewardship activities includes only two patient outcome indicators, the clinical outcomes of patients receiving antibiotics and the rates of nosocomial CDIs, whereas bacterial and resistance outcomes of patients on antibiotics are not included [13].

A 2017 Cochrane systematic review showed that stewardship interventions are probably associated with lower use of antibiotics and reduced length of hospital stay without increasing patient mortality [24]. A later systematic review also found that the majority of studies, that were included and evaluated the corresponding parameters, reported a decrease in length of hospital stay, re-admission rate, and all-cause and infection-related mortality [25].

In accordance with the results of the aforementioned systematic reviews, following the ASP implementation in the context of this distinctive (due to the unprecedented conditions of the COVID-19 pandemic in a hospital setting of pre-existing high rates of AMR) project, there was a statistically significant decrease in the infection-related readmission rate compared to the pre-

implementation period, while no significant changes in all-cause in-hospital mortality and 30-day mortality after carbapenem initiation were observed. Importantly, the analysis of the patient outcomes of the post-implementation cohort showed that the acceptance of the stewardship team recommendation was associated with reduced in-hospital and 30-day mortality after carbapenem initiation, as well as better treatment outcome. The optimization of diagnostic testing and antimicrobial therapy brought about by accepting the intervention, which reflected the advantages of ID consultation on this parameter, is likely the main factor that caused the difference in treatment outcomes between cases with accepted and non-accepted interventions in the post-implementation subgroup of patients [2].

Contrarily to the majority of the studies included in the above-mentioned systematic reviews, we found that, on average, patients in the post-implementation group had a longer hospital length of hospital stay than those in the pre-implementation group. A possible reason may be the fact that the proportion of admitted patients who received carbapenems decreased during the intervention period, indicating that treating physicians used them more sparingly at that time and only reserved them for severe cases, which, however, required longer hospitalization compared to the cases in the pre-intervention period [2]. Finally, we preferred not to evaluate the impact of the ASP on AMR or the incidence of CDI, because we considered that the strengthening of infection prevention and control measures due to COVID-19 pandemic during the post-implementation period would be an important and difficult-to-adjust confounder.

1.2 Quantity of antibiotic prescribing

Many studies before the COVID-19 pandemic showed that the implementation of carbapenem-focused ASPs result in decreased carbapenem use without having a negative impact on patient outcomes [26-29]. None of these studies assessed the effect of a carbapenem-focused stewardship intervention on the use of newer, non-carbapenem, antibiotics with efficacy against MDR-GNB. In this project, a decrease in carbapenem use was achieved safely, with a concurrent increase only in the use of piperacillin/tazobactam, while the consumption of colistin, tigecycline, ceftolozane/tazobactam and ceftazidime/avibactam was not significantly affected [2]. Our research provides additional scientific evidence because it shows that a reduction in carbapenem use is feasible and safe, even during a pandemic, without a concurrent increase of other broad-spectrum antibiotics with comparable ecological impact with carbapenems on AMR. The fact that this observation included the recently licensed antibiotics ceftolozane/tazobactam and ceftazidime/avibactam is of great importance, because it is necessary to use these newer compounds wisely in order to maintain their effectiveness.

1.3 Prescribers' perceptions, attitudes, and practices regarding the management of infections caused by MDROs.

Through the survey study that we performed eleven months after the ASP implementation, shortly before the end of the intervention period, we assessed fruitfully the impact of the ASP on prescribers' way of thinking and acting. The findings were quite encouraged, since the great majority of the doctors of our hospital perceived the intervention as a contributing factor for improved patient outcomes, which was later confirmed by the analysis of the ASP's data. In addition, in-person ID consultation was viewed as an educational interaction which increased their awareness regarding the appropriate use of antimicrobials in their daily clinical

practice. Furthermore, the 98.5% of the respondents wanted the ASP to be continued and further developed despite the fact that their workload had already been increased due to the COVID-19 pandemic at that time [3]. The above-mentioned findings implied a positive effect of the stewardship intervention on the behavior of the doctors of our hospital with regard to the management of patients suffering infections caused by MDR bacteria.

2. Directions and challenges for future research

There is considerable design heterogeneity of the different antimicrobial stewardship interventions in the literature [24] and, therefore, there is an unmet need for a comprehensive framework to inform the design and planning of the ASPs. Moreover, studies on antimicrobial stewardship have primarily focused on process and structural indicators until now [14], with little progress made in developing outcome indicators. Future research is required to introduce appropriate outcome indicators or to link effectively structural and process indicators to outcomes in order to evaluate the stewardship interventions reliably through the development of benchmarks. Finally, few ASPs to date have included behavioral theory or behavior modification methodologies into their design, assessment, and reporting processes [30]. This is one of the key shortcomings of current stewardship interventions. Behavioral science should be incorporated in every antimicrobial stewardship intervention in order to optimize the implementation of these interventions and, thus, their positive impact.

3. Conclusions

More research is needed to fully evaluate the true value of these programs, particularly in real-world settings across a variety of geographies and resource settings. The carbapenem-focused ASP that we implemented in our hospital was associated with improvement of the quality of the antimicrobial prescribing, significant decrease in the carbapenem utilization, better patient outcomes, and positive impact on the attitudes and practices of the treating physicians with regard to the management of infections caused by difficult-to-treat bacteria. The findings of this project may guide future research and policy regarding effective stewardship interventions.

4. References

1. Spernovasilis N, Kritsotakis EI, Mathioudaki A, Vouidaski A, Markaki I, Psaroudaki D, et al. Antimicrobial Prescribing before and after the Implementation of a Carbapenem-Focused Antimicrobial Stewardship Program in a Greek Tertiary Hospital during the COVID-19 Pandemic. Antibiotics (Basel). 2022;12.

2. Spernovasilis N, Kritsotakis EI, Mathioudaki A, Vouidaski A, Spanias C, Petrodaskalaki M, et al. A carbapenem-focused antimicrobial stewardship programme implemented during the COVID-19 pandemic in a setting of high endemicity for multidrug-resistant Gram-negative bacteria. J Antimicrob Chemother. 2023;78:1000-8.

3. Spernovasilis N, Ierodiakonou D, Spanias C, Mathioudaki A, Ioannou P, Petrakis EC, et al. Doctors' Perceptions, Attitudes and Practices towards the Management of Multidrug-Resistant Organism Infections after the Implementation of an Antimicrobial Stewardship Programme during the COVID-19 Pandemic. Trop Med Infect Dis. 2021;6.

4. Spernovasilis NA, Kofteridis DP. COVID-19 and antimicrobial stewardship: What is the interplay? Infect Control Hosp Epidemiol. 2021;42:378-9.

5. Ashiru-Oredope D, Kerr F, Hughes S, Urch J, Lanzman M, Yau T, et al. Assessing the Impact of COVID-19 on Antimicrobial Stewardship Activities/Programs in the United Kingdom. Antibiotics (Basel). 2021;10.

6. Hashad N, Stewart D, Perumal D, Abdulrazzaq N, Tonna AP. The impact of COVID-19 on antimicrobial stewardship programme implementation in hospitals - an exploration informed by the Consolidated Framework for Implementation Research. J Hosp Infect. 2022;129:144-52.

7. Donabedian A. The quality of care. How can it be assessed? Jama. 1988;260:1743-8.

8. Lawrence M, Olesen F. Indicators of Quality in Health Care. European Journal of General Practice. 1997;3:103-8.

9. Patel D, Lawson W, Guglielmo BJ. Antimicrobial stewardship programs: interventions and associated outcomes. Expert Rev Anti Infect Ther. 2008;6:209-22.

10. Retamar P, Luisa Martín M, Molina J, del Arco A. Evaluating the quality of antimicrobial prescribing: Is standardisation possible? Enfermedades Infecciosas y Microbiología Clínica. 2013;31:25-30.

11. Davey PG, Marwick C. Appropriate vs. inappropriate antimicrobial therapy. Clin Microbiol Infect. 2008;14 Suppl 3:15-21.

12. Davey P, Sneddon J, Nathwani D. Overview of strategies for overcoming the challenge of antimicrobial resistance. Expert Rev Clin Pharmacol. 2010;3:667-86.

13. Monnier AA, Schouten J, Le Maréchal M, Tebano G, Pulcini C, Stanic Benic M, et al. Quality indicators for responsible antibiotic use in the inpatient setting: a systematic review followed by an international multidisciplinary consensus procedure. J Antimicrob Chemother. 2018;73:vi30-vi9.

14. O'Riordan F, Shiely F, Byrne S, Fleming A. Quality indicators for hospital antimicrobial stewardship programmes: a systematic review. J Antimicrob Chemother. 2021;76:1406-19.

15. Global Point Prevalence Survey of Antimicrobial Consumption and Resistance. Global Point Prevalence Survey (PPS)—Year 2019 (GLOBAL PPS). Available from: https://www.global-pps.com/wp-content/uploads/2019/01/Data-collection-form-Global-PPS-2019.pdf

16. German GJ, Frenette C, Caissy JA, Grant J, Lefebvre MA, Mertz D, et al. The 2018 Global Point Prevalence Survey of antimicrobial consumption and resistance in 47 Canadian hospitals: a cross-sectional survey. CMAJ Open. 2021;9:E1242-e51.

17. Fowotade A, Fasuyi T, Aigbovo O, Versporten A, Adekanmbi O, Akinyemi O, et al. Point Prevalence Survey of Antimicrobial Prescribing in a Nigerian Hospital: Findings and Implications on Antimicrobial Resistance. West Afr J Med. 2020;37:216-20.

18. Frenette C, Sperlea D, German GJ, Afra K, Boswell J, Chang S, et al. The 2017 global point prevalence survey of antimicrobial consumption and resistance in Canadian hospitals. Antimicrob Resist Infect Control. 2020;9:104.

19. Gürtler N, Erba A, Giehl C, Tschudin-Sutter S, Bassetti S, Osthoff M. Appropriateness of antimicrobial prescribing in a Swiss tertiary care hospital: a repeated point prevalence survey. Swiss Med Wkly. 2019;149:w20135.

20. Bumpass JB, McDaneld PM, DePestel DD, Lamp KC, Chung TJ, McKinnon PS, et al. Outcomes and metrics for antimicrobial stewardship: survey of physicians and pharmacists. Clin Infect Dis. 2014;59 Suppl 3:S108-11.

21. Scobie A, Budd EL, Harris RJ, Hopkins S, Shetty N. Antimicrobial stewardship: an evaluation of structure and process and their association with antimicrobial prescribing in NHS hospitals in England. J Antimicrob Chemother. 2019;74:1143-52.

22. Moehring RW, Anderson DJ, Cochran RL, Hicks LA, Srinivasan A, Dodds Ashley ES. Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings. Clin Infect Dis. 2017;64:377-83.

23. McGowan JE. Antimicrobial stewardship--the state of the art in 2011: focus on outcome and methods. Infect Control Hosp Epidemiol. 2012;33:331-7.

24. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2(2):Cd003543.

25. Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. Antimicrob Resist Infect Control. 2019;8:35.

26. García-Rodríguez JF, Bardán-García B, Peña-Rodríguez MF, Álvarez-Díaz H, Mariño-Callejo A. Meropenem antimicrobial stewardship program: clinical, economic, and antibiotic resistance impact. Eur J Clin Microbiol Infect Dis. 2019;38:161-70.

27. Faraone A, Poggi A, Cappugi C, Tofani L, Riccobono E, Giani T, et al. Inappropriate use of carbapenems in an internal medicine ward: Impact of a carbapenem-focused antimicrobial stewardship program. Eur J Intern Med. 2020;78:50-7.

28. García-Rodríguez JF, Bardán-García B, Juiz-González PM, Vilariño-Maneiro L, Álvarez-Díaz H, Mariño-Callejo A. Long-Term Carbapenems Antimicrobial Stewardship Program. Antibiotics (Basel). 2020;10.

29. López-Viñau T, Peñalva G, García-Martínez L, Castón JJ, Muñoz-Rosa M, Cano Á, et al. Impact of an Antimicrobial Stewardship Program on the Incidence of Carbapenem Resistant Gram-Negative Bacilli: An Interrupted Time-Series Analysis. Antibiotics (Basel). 2021;10.

30. Lorencatto F, Charani E, Sevdalis N, Tarrant C, Davey P. Driving sustainable change in antimicrobial prescribing practice: how can social and behavioural sciences help? J Antimicrob Chemother. 2018;73:2613-24.

SUPPLEMENTARY

Supplementary I

Supplementary Statistical Tables of Chapter III

Table S1. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on all-cause hospital mortality. This is an ITT analysis comparing the pre-implementation cohort (n=842) to the post-implementation cohort (n=426).

	csHR	Std. error	95% CI	Wald Z	p-value
ITT analysis					
Pre- implementation group	1.00	0.00			
Post- implementation group	0.99	0.12	[0.79, 1.24]	-0.10	0.922
Sex					
Female	1.00	0.00			
Male	0.97	0.11	[0.77, 1.22]	-0.25	0.805
Age (years)	1.04	0.00	[1.03, 1.05]	9.04	<0.001
Ward of hospitalisation					
Intensive care	2.71	0.53	[1.85, 3.97]	5.14	<0.001
Medicine	2.17	0.38	[1.53, 3.07]	4.38	<0.001
Surgery	1.00	0.00			
Other specialty	5.23	5.33	[0.71, 38.59]	1.62	0.104
Hospitalisation in previous 3 months					
No	1.00	0.00			
Yes	1.61	0.19	[1.28, 2.04]	4.04	<0.001

Abbreviations: csHR, cause-specific hazard ratio

Table S2. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on hospital discharge alive. This is an ITT analysis comparing the pre-implementation cohort (n=842) to the post-implementation cohort (n=426).

	csHR	Std. error	95% CI		Wald Z	p-value
ITT analysis						
Pre-implementation group	1.00	0.00				
Post-implementation group	0.80	0.06	[0.70,	0.92]	-3.16	0.002
Sex						
Female	1.00	0.00				
Male	0.97	0.07	[0.85,	1.11]	-0.40	0.690
Age (years)	1.00	0.00	[1.00,	1.01]	1.48	0.139
Ward of hospitalisation						
Intensive care	0.33	0.05	[0.25,	0.43]	-8.05	<0.001
Medicine	0.96	0.07	[0.83,	1.12]	-0.48	0.630
Surgery	1.00	0.00				
Other specialty	2.90	1.12	[1.36,	6.19]	2.76	0.006
Hospitalisation in previous 3 months						
No	1.00	0.00				
Yes	1.16	0.08	[1.02,	1.33]	2.27	0.023

Abbreviations: csHR, cause-specific hazard ratio

Note. In this analysis, a low csHR for discharge alive reflects a low daily rate of discharge, resulting in prolonged hospital stay.

Table S3. Results of multivariable Logistic regression quantifying the effects of the antimicrobial stewardship intervention on all-cause mortality within 30 days of initiation of carbapenem therapy. This is an ITT analysis comparing the pre-implementation cohort (n=842) to the post-implementation cohort (n=426).

	OR	Std. error	95% CI	Wald Z	p-value
ITT analysis					
Pre-implementation group	1.00	0.00			
Post-implementation group	1.26	0.18	[0.95, 1.67]	1.61	0.107
Sex					
Female	1.00	0.00			
Male	1.06	0.15	[0.80, 1.41]	0.42	0.672
Age (years)	1.03	0.01	[1.02, 1.04]	6.61	<0.001
Ward of hospitalisation					
Intensive care	9.34	2.29	[5.78, 15.09]	9.12	<0.001
Medicine	2.04	0.39	[1.39, 2.97]	3.68	<0.001
Surgery	1.00	0.00			
Other specialty	1.50	1.66	[0.17, 13.05]	0.37	0.714
Hospitalisation in previous 3 months					
No	1.00	0.00			
Yes	1.22	0.18	[0.93, 1.62]	1.42	0.156

Intercept	0.01	0.01	[0.01, 0.03]	-10.65	<0.001

Table S4. Results of multivariable Logistic regression quantifying the effects of the antimicrobial stewardship intervention on infection-related readmission within 30 days of hospital discharge alive. This is an ITT analysis comparing the pre-implementation cohort (n=842) to the post-implementation cohort (n=426).

	OR	Std. error	95% CI	Wald Z	p-value
ITT analysis					
Pre-implementation group	1.00	0.00			
Post-implementation group	0.60	0.11	[0.42, 0.86]	-2.76	0.006
Sex					
Female	1.00	0.00			
Male	1.44	0.25	[1.02, 2.03]	2.09	0.037
Age (years)	1.01	0.01	[1.00, 1.02]	1.40	0.163
Ward of hospitalisation					
Intensive care	1.16	0.47	[0.52, 2.57]	0.36	0.716
Medicine	2.04	0.41	[1.37, 3.02]	3.53	<0.001
Surgery	1.00	0.00			
Other specialty	1.35	1.51	[0.15, 12.04]	0.27	0.786
Hospitalisation in previous 3 months					
No	1.00	0.00			
Yes	1.82	0.32	[1.30, 2.56]	3.46	0.001

Intercept	0.07	0.03	[0.03, 0.15]	-6.64	<0.001

Table S5. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on all-cause hospital mortality. This is a modified ITT analysis comparing the pre-implementation cohort (n=842) to the post-implementation cohort excluding patients for whom the intervention was not accepted (n=380).

	csHR	Std. error	95% CI	Wald Z	p-value
Modified ITT analysis					
Pre-implementation group	1.00	0.00			
Post-implementation intervention-accepted group	0.91	0.11	[0.71, 1.16]	-0.76	0.450
Sex					
Female	1.00	0.00			
Male	0.95	0.12	[0.75, 1.20]	-0.45	0.652
Age (years)	1.04	0.00	[1.03, 1.05]	8.81	<0.001
Ward of hospitalisation					
Intensive care	2.85	0.58	[1.91, 4.25]	5.13	<0.001
Medicine	2.26	0.42	[1.56, 3.27]	4.34	<0.001
Surgery	1.00	0.00			
Other specialty	5.64	5.77	[0.76, 41.80]	1.69	0.090
Hospitalisation in previous 3 months					
No	1.00	0.00			

Yes	1.65	0.20	[1.29, 2.10]	4.04	<0.001

Abbreviations: csHR, cause-specific hazard ratio

Table S6. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on hospital discharge alive. This is a modified ITT analysis comparing the pre-implementation cohort (n=842) to the post-implementation cohort excluding patients for whom the intervention was not accepted (n=380).

	csHR	Std. error	95% CI		Wald Z	p-value
Modified ITT analysis						
Pre-implementation group	1.00	0.00				
Post-implementation intervention-accepted group	0.83	0.06	[0.72,	0.95]	-2.62	0.009
Sex						
Female	1.00	0.00				
Male	0.97	0.07	[0.84,	1.11]	-0.50	0.616
Age (years)	1.00	0.00	[1.00,	1.01]	1.78	0.075
Ward of hospitalisation						
Intensive care	0.33	0.05	[0.25,	0.43]	-8.09	<0.001
Medicine	0.96	0.07	[0.83,	1.12]	-0.50	0.614
Surgery	1.00	0.00				
Other specialty	2.88	1.11	[1.35,	6.13]	2.74	0.006
Hospitalisation in previous 3 months						
No	1.00	0.00				

Yes	1.17	0.08	[1.02,	1.34]	2.31	0.021

Abbreviations: csHR, cause-specific hazard ratio

Note. In this analysis, a low csHR for discharge alive reflects a low daily rate of discharge, resulting in prolonged hospital stay.

Table S7. Results of multivariable Logistic regression quantifying the effects of the antimicrobial stewardship intervention on all-cause mortality within 30 days of initiation of carbapenem therapy. This is a modified ITT analysis comparing the pre-implementation cohort (n=842) to the post-implementation cohort excluding patients for whom the intervention was not accepted (n=380).

	OR	Std. error	95% CI	Wald Z	p-value
Modified ITT analysis					
Pre-intervention group	1.00	0.00			
Post-implementation intervention-accepted group	1.10	0.17	[0.82, 1.49]	0.65	0.513
Sex					
Female	1.00	0.00			
Male	1.06	0.16	[0.79, 1.42]	0.40	0.691
Age (years)	1.03	0.01	[1.02, 1.04]	6.35	<0.001
Ward of hospitalisation					
Intensive care	10.00	2.53	[6.09, 16.43]	9.10	<0.001
Medicine	2.13	0.43	[1.43, 3.18]	3.73	<0.001
Surgery	1.00	0.00			
Other specialty	1.68	1.86	[0.19, 14.66]	0.47	0.636
Hospitalisation in previous 3 months					

No	1.00	0.00				
Yes	1.25	0.18	[0.94,	1.67]	1.51	0.130
Intercept	0.01	0.01	[0.01,	0.03]	-10.37	<0.001

Table S8. Results of multivariable Logistic regression quantifying the effects of the antimicrobial stewardship intervention on infection-related readmission within 30 days of hospital discharge alive. This is a modified ITT analysis comparing the pre-implementation cohort (n=842) to the post-implementation cohort excluding patients for whom the intervention was not accepted (n=380).

	OR	Std. error	95% CI	Wald Z	p-value
Modified ITT analysis					
Pre-implementation group	1.00	0.00			
Post-implementation intervention-accepted group	0.57	0.11	[0.39, 0.83]	-2.93	0.003
Sex					
Female	1.00	0.00			
Male	1.37	0.24	[0.97, 1.94]	1.78	0.075
Age (years)	1.01	0.01	[1.00, 1.02]	1.24	0.216
Ward of hospitalisation					
Intensive care	1.16	0.47	[0.52, 2.57]	0.36	0.720
Medicine	1.99	0.41	[1.33, 2.97]	3.37	0.001
Surgery	1.00	0.00			
Other specialty	1.31	1.46	[0.15, 11.65]	0.24	0.809
Hospitalisation in previous 3 months					

No	1.00	0.00			
Yes	1.80	0.32	[1.27, 2.54]	3.34	0.001
Intercept	0.08	0.03	[0.03, 0.17]	-6.32	<0.001

Table S9. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on all-cause hospital mortality. This is an analysis per protocol, comparing patients who did not receive the intervention in either the pre- or the post-implementation period (n=888) to those who received the intervention (n=380).

	csHR	Std. error	95% CI	Wald Z	p-value
Per-protocol analysis					
Non-intervention group	1.00	0.00			
Intervention group	0.87	0.11	[0.69, 1.11]	-1.14	0.256
Sex					
Female	1.00	0.00			
Male	0.97	0.11	[0.77, 1.22]	-0.28	0.779
Age (years)	1.04	0.00	[1.03, 1.05]	9.09	<0.001
Ward of hospitalisation					
Intensive care	2.74	0.53	[1.87, 4.00]	5.18	<0.001
Medicine	2.17	0.38	[1.53, 3.06]	4.38	<0.001
Surgery	1.00	0.00			
Other specialty	5.47	5.58	[0.74, 40.39]	1.67	0.095
Hospitalisation in previous 3 months					
No	1.00	0.00			
Yes	1.59	0.19	[1.26, 2.01]	3.93	<0.001

Abbreviations: csHR, cause-specific hazard ratio

Table S10. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on hospital discharge alive. This is an analysis per protocol, comparing patients who did not receive the intervention in either the pre- or the post-implementation period (n=888) to those who received the intervention (n=380).

	csHR	Std. error	95% CI		Wald Z	p-value
Per-protocol analysis						
Non-intervention group	1.00	0.00				
Intervention group	0.85	0.06	[0.74,	0.98]	-2.29	0.022
Sex						
Female	1.00	0.00				
Male	0.97	0.07	[0.85,	1.11]	-0.40	0.692
Age (years)	1.00	0.00	[1.00,	1.01]	1.35	0.178
Ward of hospitalisation						
Intensive care	0.33	0.05	[0.25,	0.44]	-7.99	<0.001
Medicine	0.97	0.07	[0.84,	1.12]	-0.44	0.659
Surgery	1.00	0.00				
Other specialty	2.91	1.12	[1.36,	6.19]	2.77	0.006
Hospitalisation in previous 3 months						
No	1.00	0.00				
Yes	1.17	0.08	[1.03,	1.34]	2.36	0.018

Abbreviations: csHR, cause-specific hazard ratio

Note. In this analysis, a low csHR for discharge alive reflects a low daily rate of discharge, resulting in prolonged hospital stay.

Table S11. Results of multivariable Logistic regression quantifying the effects of the antimicrobial stewardship intervention on all-cause mortality within 30 days of initiation of carbapenem therapy. This is an analysis per protocol, comparing patients who did not receive the intervention in either the pre- or the post-implementation period (n=888) to those who received the intervention (n=380).

	OR	Std. error	95% CI	Wald Z	p-value
Per-protocol analysis					
Non-intervention group	1.00	0.00			
Intervention group	1.03	0.15	[0.77, 1.38]	0.19	0.852
Sex					
Female	1.00	0.00			
Male	1.06	0.15	[0.80, 1.41]	0.40	0.686
Age (years)	1.03	0.00	[1.02, 1.04]	6.65	<0.001
Ward of hospitalisation					
Intensive care	9.38	2.30	[5.80, 15.16]	9.14	<0.001
Medicine	2.04	0.39	[1.40, 2.98]	3.70	<0.001
Surgery	1.00	0.00			
Other specialty	1.59	1.74	[0.18, 13.70]	0.42	0.676
Hospitalisation in previous 3 months					
No	1.00	0.00			

Yes	1.21	0.17	[0.92,	1.61]	1.36	0.174
Intercept	0.01	0.01	[0.01,	0.03]	-10.51	<0.001

Table S12. Results of multivariable Logistic regression quantifying the effects of the antimicrobial stewardship intervention on infection-related readmission within 30 days of hospital discharge alive. This is an analysis per protocol, comparing patients who did not receive the intervention in either the pre- or the post-implementation period (n=888) to those who received the intervention (n=380).

	OR	Std. error	95% CI	Wald Z	p-value
Per-protocol analysis					
Non-intervention group	1.00	0.00			
Intervention group	0.57	0.11	[0.39, 0.83]	-2.96	0.003
Sex					
Female	1.00	0.00			
Male	1.43	0.25	[1.02, 2.02]	2.05	0.040
Age (years)	1.01	0.01	[1.00, 1.02]	1.37	0.172
Ward of hospitalisation					
Intensive care	1.19	0.48	[0.53, 2.63]	0.42	0.674
Medicine	2.05	0.41	[1.38, 3.04]	3.56	<0.001
Surgery	1.00	0.00			
Other specialty	1.38	1.54	[0.15, 12.29]	0.29	0.774
Hospitalisation in previous 3 months					
No	1.00	0.00			

Yes	1.84	0.32	[1.31,	2.59]	3.52	<0.001
Intercept	0.07	0.03	[0.03,	0.15]	-6.63	<0.001

Table S13. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on all-cause hospital mortality. This analysis is restricted in the post-implementation period and compares patients for whom the intervention was accepted (n=380) to patients for whom the intervention was not accepted (n=46).

	csHR	Std. error	95% CI	Wald Z	p-value
Intervention acceptance					
Intervention non-accepted group	1.00	0.00			
Intervention accepted group	0.49	0.12	[0.30, 0.80]	-2.85	0.004
Sex					
Female	1.00	0.00			
Male	0.98	0.19	[0.66, 1.43]	-0.13	0.898
Age (years)	1.03	0.01	[1.02, 1.05]	4.72	<0.001
Ward of hospitalisation					
Intensive care	2.97	0.96	[1.57, 5.60]	3.36	0.001
Medicine	2.35	0.68	[1.34, 4.15]	2.96	0.003
Surgery	1.00	0.00			
Other specialty	9.04	9.53	[1.15, 71.28]	2.09	0.037
Hospitalisation in previous 3 months					
No	1.00	0.00			
Yes	1.99	0.40	[1.34, 2.95]	3.41	0.001

Abbreviations: csHR, cause-specific hazard ratio

Table S14. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on hospital discharge alive. This analysis is restricted in the post-implementation period and compares patients for whom the intervention was accepted (n=380) to patients for whom the intervention was not accepted (n=46).

	csHR	Std. error	95% CI	Wald Z	p-value
Intervention acceptance					
Intervention non-accepted group	1.00	0.00			
Intervention accepted group	1.32	0.28	[0.87, 2.00]	1.32	0.187
Sex					
Female	1.00	0.00			
Male	1.04	0.13	[0.82, 1.33]	0.36	0.718
Age (years)	1.00	0.00	[0.99, 1.01]	-0.07	0.944
Ward of hospitalisation					
Intensive care	0.40	0.09	[0.26, 0.63]	-3.94	<0.001
Medicine	1.08	0.15	[0.83, 1.42]	0.58	0.562
Surgery	1.00	0.00			
Other specialty	3.52	2.11	[1.09, 11.39]	2.10	0.036
Hospitalisation in previous 3 months					
No	1.00	0.00			
Yes	1.37	0.17	[1.08, 1.74]	2.62	0.009

Abbreviations: csHR, cause-specific hazard ratio

Note. In this analysis, a low csHR for discharge alive reflects a low daily rate of discharge, resulting in prolonged hospital stay.

Table S15. Results of multivariable Logistic regression quantifying the effects of the antimicrobial stewardship intervention on all-cause mortality within 30 days of initiation of carbapenem therapy. This analysis is restricted in the post-implementation period and compares patients for whom the intervention was accepted (n=380) to patients for whom the intervention was not accepted (n=46).

	OR	Std. error	95% CI	Wald Z	p-value
Intervention acceptance					
Intervention non-accepted group	1.00	0.00			
Intervention accepted group	0.36	0.12	[0.18, 0.70]	-3.02	0.003
Sex					
Female	1.00	0.00			
Male	0.94	0.22	[0.59, 1.49]	-0.27	0.786
Age (years)	1.03	0.01	[1.01, 1.04]	3.37	0.001
Ward of hospitalisation					
Intensive care	6.54	2.59	[3.01, 14.19]	4.75	<0.001
Medicine	1.66	0.51	[0.90, 3.04]	1.63	0.103
Surgery	1.00	0.00			
Other specialty	2.22	2.69	[0.21, 23.80]	0.66	0.511
Hospitalisation in previous 3 months					
No	1.00	0.00			

Yes	1.19	0.28	[0.75,	1.89]	0.73	0.462
Intercept	0.09	0.06	[0.02,	0.33]	-3.56	<0.001

Table S16. Results of multivariable Logistic regression quantifying the effects of the antimicrobial stewardship intervention on infection-related readmission within 30 days of hospital discharge alive. This analysis is restricted in the post-implementation period and compares patients for whom the intervention was accepted (n=380) to patients for whom the intervention was not accepted (n=46).

	OR	Std. error	95% CI		Wald Z	p-value
Intervention acceptance						
Intervention non-accepted group	1.00	0.00				
Intervention accepted group	0.57	0.30	[0.20,	1.61]	-1.06	0.290
Sex						
Female	1.00	0.00				
Male	1.78	0.63	[0.89,	3.56]	1.64	0.102
Age (years)	1.02	0.01	[1.00,	1.05]	2.06	0.039
Ward of hospitalisation						
Intensive care	1.34	0.98	[0.32,	5.62]	0.40	0.689
Medicine	1.92	0.79	[0.86,	4.31]	1.58	0.113
Surgery	1.00	0.00				
Other specialty	1.00	0.00				
Hospitalisation in previous 3 months						
No	1.00	0.00				

Yes	2.09	0.72	[1.06,	4.11]	2.13	0.033
Intercept	0.02	0.02	[0.00,	0.14]	-3.88	<0.001

Table S17. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on all-cause hospital mortality. This analysis is restricted in the post-implementation period and compares patients for whom the intervention was accepted (n=380) to patients for whom the intervention was not accepted (n=46).

	csHR	Std. error	95% CI	Wald Z	p-value
Intervention acceptance					
Intervention non-accepted group	1.00	0.00			
Intervention accepted group	0.74	0.23	[0.40, 1.37]	-0.96	0.337
Sex					
Female	1.00	0.00			
Male	0.97	0.23	[0.61, 1.55]	-0.12	0.906
Age (years)	1.02	0.01	[1.01, 1.04]	2.62	0.009
Ward of hospitalisation					
Intensive care	3.18	1.36	[1.37, 7.37]	2.70	0.007
Medicine	1.69	0.62	[0.82, 3.49]	1.42	0.155
Surgery	1.00	0.00			
Other specialty	2.90	3.11	[0.35, 23.70]	0.99	0.321
Hospitalisation in previous 3 months					
No	1.00	0.00			
Yes	1.46	0.36	[0.90, 2.37]	1.52	0.127

Abbreviations: csHR, cause-specific hazard ratio

Table S18. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on new or recurrent infection. This analysis is restricted in the post-implementation period and compares patients for whom the intervention was accepted (n=380) to patients for whom the intervention was not accepted (n=46).

	csHR	Std. error	95% CI		Wald Z	p-value
Intervention acceptance						
Intervention non-accepted group	1.00	0.00				
Intervention accepted group	0.26	0.14	[0.09,	0.74]	-2.53	0.011
Sex						
Female	1.00	0.00				
Male	1.02	0.55	[0.36,	2.92]	0.04	0.966
Age (years)	1.02	0.02	[0.99,	1.05]	1.09	0.275
Ward of hospitalisation						
Intensive care	0.88	0.78	[0.15,	4.98]	-0.15	0.881
Medicine	0.69	0.39	[0.22,	2.11]	-0.66	0.512
Surgery	1.00	0.00				
Other specialty	0.00	0.00	[0.00,	.]	-0.00	>0.999
Hospitalisation in previous 3 months						
No	1.00	0.00				
Yes	0.42	0.22	[0.14,	1.20]	-1.63	0.103

Abbreviations: csHR, cause-specific hazard ratio

Table S19. Results of multivariable Cox proportional hazards regression quantifying the effects of the antimicrobial stewardship intervention on favourable treatment outcome. This analysis is restricted in the post-implementation period and compares patients for whom the intervention was accepted (n=380) to patients for whom the intervention was not accepted (n=46).

	csHR	Std. error	95% CI		Wald Z	p-value
Intervention acceptance						
Intervention non-accepted group	1.00	0.00				
Intervention accepted group	2.45	0.54	[1.59,	3.77]	4.09	<0.001
Sex						
Female	1.00	0.00				
Male	1.00	0.12	[0.80,	1.26]	0.04	0.969
Age (years)	1.00	0.00	[0.99,	1.00]	-1.35	0.177
Ward of hospitalisation						
Intensive care	0.60	0.12	[0.41,	0.89]	-2.53	0.012
Medicine	0.86	0.11	[0.66,	1.12]	-1.14	0.255
Surgery	1.00	0.00				
Other specialty	0.81	0.48	[0.25,	2.61]	-0.35	0.728
Hospitalisation in previous 3 months						
No	1.00	0.00				
Yes	0.88	0.10	[0.70,	1.10]	-1.14	0.254

Abbreviations: csHR, cause-specific hazard ratio

Supplementary II

Questionnaire of Chapter IV

Questionnaire

General information

1. Age: ☐

2. Gender:

Male ☐
Female ☐

3. What is your professional status?

Resident doctor ☐
Specialist doctor ☐

4. What is your specialty?

Vascular surgery ☐	Haematology ☐	Gastroenterology ☐
General practice ☐	General surgery ☐	Dermatology ☐
Endocrinology ☐	Cardiology ☐	Cardiac surgery ☐
Neurology ☐	Neurosurgery ☐	Nephrology ☐
Orthopedic ☐	Urology ☐	Ophthalmology ☐
Internal medicine ☐	Oncology ☐	Obstetrics & Gynaecology ☐
Plastic surgery ☐	Respiratory medicine ☐	Rheumatology ☐
Psychiatry ☐	ENT ☐	Thoracic surgery ☐
ICU ☐	Craniofacial surgery ☐	

5. How many years of experience do you have as a doctor? (If you are a specialist doctor, please report only the years of experience you have as a specialist doctor) ☐

6. Do you have previous experience (>3 months) with antimicrobial stewardship programmes (ASPs)?

Yes ☐ No ☐

7. How often do you have patients with multidrug-resistant (MDR) Gram-negative infections under your care?

Not at all ☐
1-4 times/month ☐
5-10 times/month ☐
>10 times/month ☐

8. How often do you seek ASP consultation for patients with MDR Gram-negative infections who are under your care?

Not at all ☐
1-4 times/month ☐
5-10 times/month ☐
>10 times/month ☐

9. How often do you accept the recommendations provided by the ASP team?

Never ☐
Rarely ☐
Sometimes ☐
Often ☐
Always ☐

Perceptions

10. How much do you disagree or agree with each of the following statements?

1 = Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly agree

- Prospective audit and feedback strategy is more effective than preauthorization strategy in improving patients' outcome

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Prospective audit and feedback strategy is more educational for me than preauthorization strategy

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Preauthorization strategy suits a Greek hospital better than prospective audit and feedback strategy

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Preauthorization strategy should substitute prospective audit and feedback strategy in our hospital

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Regardless of the strategy followed, the implementation of an ASP improves patients' outcome compared to the absence of such a program

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

11. How much do you disagree or agree with each of the following statements regarding in-person consultation as the followed practice for the ASP in our hospital?

1 = Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly agree

- It is the preferred practice for the ASP

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- It can be largely replaced by telephone or electronic communication

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- It is welcome as often as possible
  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- It is also a very useful educational process for me regarding prudent use of antimicrobials
  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- It disrupts my daily life in the clinic
  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

12. How helpful do you find each of the following interventions for the improvement of the current ASP?

1 = Not helpful, 2 = Slightly helpful, 3 = Somewhat helpful, 4 = Very helpful, 5 = Extremely helpful

- Availability of hospital resistance data and development of hospital guidelines for the treatment of infections caused by multidrug-resistant organisms
  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- More educational sessions and training regarding optimal use of antimicrobials
  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Stewardship-focused mobile/tablet applications
  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- More contact via telephone with ASP team members
  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Communication via hospital's electronic systems
  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

13. During COVID-19 pandemic, the ASP must be:

continued and further developed ☐
postponed ☐

Attitudes and Practices

14. The existence of the ASP in our hospital:

1 = Not at all, 2 = Slightly, 3 = Moderately, 4 = Significantly, 5 = Extremely

- Increased my concern regarding overuse/misuse of antimicrobials and antimicrobial resistance

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Amplified my awareness regarding appropriate use of antimicrobials in my daily clinical practice

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Stimulated me to seek further knowledge on selecting the optimal antimicrobial, whenever it is needed, and its dosage, route and duration of administration

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Reinforced my acknowledgement of the importance of microbiological analyses for infections' diagnosis and treatment

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Incited me to perform closer monitoring of the microbiological data of my patients

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Enriched my way of thinking about the diagnosis and treatment of infections caused by multidrug-resistance organisms

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Affected me towards multidisciplinary and personalised care of patients with infections caused by multidrug-resistant organisms

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

- Influenced my daily practice towards more rigorous implementation of infection prevention and control measures

  ☐1 ☐ 2 ☐ 3 ☐4 ☐5

15. Would you be willing to participate more actively in the ASP in the future?

Yes ☐ No ☐

LIST OF PUBLICATIONS

DERIVED FROM THIS DISSERTATION

List

1. Spernovasilis N, Kritsotakis EI, Mathioudaki A, Vouidaski A, Markaki I, Psaroudaki D, Ioannou P, Kofteridis DP. Antimicrobial Prescribing before and after the Implementation of a Carbapenem-Focused Antimicrobial Stewardship Program in a Greek Tertiary Hospital during the COVID-19 Pandemic. Antibiotics (Basel). 2022 Dec 27;12(1):39. doi: 10.3390/antibiotics12010039. (Presented in Chapter II of this dissertation).

2. Spernovasilis N, Kritsotakis EI, Mathioudaki A, Vouidaski A, Spanias C, Petrodaskalaki M, Ioannou P, Chamilos G, Kofteridis DP. A carbapenem-focused antimicrobial stewardship programme implemented during the COVID-19 pandemic in a setting of high endemicity for multidrug-resistant Gram-negative bacteria. J Antimicrob Chemother. 2023 Apr 3;78(4):1000-1008. doi: 10.1093/jac/dkad035. (Presented in Chapter III of this dissertation).

3. Spernovasilis N, Ierodiakonou D, Spanias C, Mathioudaki A, Ioannou P, Petrakis EC, Kofteridis DP. Doctors' Perceptions, Attitudes and Practices towards the Management of Multidrug-Resistant Organism Infections after the Implementation of an Antimicrobial Stewardship Programme during the COVID-19 Pandemic. Trop Med Infect Dis. 2021 Feb 5;6(1):20. doi: 10.3390/tropicalmed6010020. (Presented in Chapter IV of this dissertation).