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GENERAL PRACTITIONERS' ANTIBIOTIC PRESCRIBING PRACTICES IN MALTA: understanding drivers to inform the implementation of a social marketing behaviour change intervention

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GENERAL PRACTITIONERS' ANTIBIOTIC PRESCRIBING PRACTICES IN MALTA: understanding drivers to inform the implementation of a social marketing intervention

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To my cherished family

“Gentlemen, it is the microbes who will have the last word.”

– Louis Pasteur (1822-1895)

PREFACE

My life so far has taken me on some rather big but interesting twists and turns. Since I was a young child I have always been very inquisitive. I remember distinctly asking my mother over and over again, "But why? But why? But why?!" Her exasperated answer would always finally be, "Because pigs don't fly!" Of course that response did not satisfy me at all, and I continued to relentlessly question pretty much everything. As I grew older, I became particularly interested in medicine. People would often ask me, "What do you want to be when you grow up?" and I would typically answer, "A veterinarian!" or "A doctor!" When I eventually entered nursing school instead, people did question my decision. Some, to my dismay, seemed disappointed that I chose not to pursue medicine anymore. Others encouraged me to follow my dreams and work hard to achieve my goals. Nursing did not just teach me numerous technical skills, it also taught me about patience, empathy, kindness and compassion. My decision brought me to where I am today and for that I am grateful.

My interest in infection prevention and control probably peaked when I got the opportunity to participate in a student exchange in Stockholm towards the end of my nursing studies. Over the course of four months I worked side by side with Swedish colleagues at Karolinska Universitetssjukhuset in Huddinge. It was during this time that I could witness stark differences between infection control practices in Sweden versus Malta and I was adamant that I wanted to be part of a change; to change infection prevention and control practices back home in Malta. Eventually, I was awarded a scholarship to pursue post-graduate education and moved to Stockholm to do my Master's degree in Global Health at Karolinska Institutet where I was soon after employed as a research assistant.

Realising the devastating consequences a world without antibiotics would cause, and that antibiotic use and resistance in Malta was among the highest in Europe, it stood to reason that building a project in my home country was a good place to start. So when I got the opportunity to devise my own doctoral project, I could not allow the chance slip me by. Starting from the ground up certainly posed its challenges but with a great deal of perseverance the project was up and running and I was eventually registered as a doctoral student.

I sincerely hope that sharing my findings will help add another piece to the incredibly complex puzzle that is antibiotic resistance. I hope that it will not only help raise a lot more awareness on the current antibiotic prescription practices in Malta, but that it will also inform future research and policy.

Looking back, now that the project has drawn to an end, I realise that all the twists and turns that brought me to this place have been well worth it. I have grown and learnt so much throughout this entire process, and my inquisitive nature and critical mind has only intensified. Now that I have reached another crossroads in my life, I wonder what my next turn will be and where life will take me.

ABSTRACT

Background: Antibiotic resistance is a leading global public health problem and complex challenge. Although a multitude of factors affect its development, antibiotic use is a key driver. In fact, in Europe, a positive correlation between antibiotic use and resistance has been shown. The largest volumes of antibiotics are prescribed in the community setting and respiratory tract infections (RTIs) remain the most common diagnoses despite often being self-limiting. Malta has one of the highest antibiotic consumption rates in Europe with the top two reasons being sore throat and the flu. Since most antibiotics are obtained through a medical prescription, this suggests that antibiotics are overprescribed by doctors, and general practitioners (GPs) in particular are a suitable target group for interventions to improve antibiotic prescribing. However, prescribing decisions are often complex and influenced by numerous interrelated factors. Therefore changing prescribing behaviour first necessitates an in-depth understanding of antibiotic prescribing practices and factors that impact this behaviour. To date, large knowledge gaps remain in Malta which makes the implementation of evidence-based interventions targeting prescribers challenging.

Aim: The aim of this thesis, which forms part of a larger intervention project, was to explore GPs' views on antibiotic use and resistance in Malta, and to gain a better understanding of their antibiotic prescribing patterns for RTIs including the factors that influence their prescribing behaviour.

Methods: Data were derived from two pre-intervention studies; one qualitative [Papers I & II] and one quantitative [Papers III & IV]. For the qualitative study, individual face-to-face interviews were held in 2014 with a quota sample of 20 GPs. Interviews were audio recorded and transcribed verbatim. Data were analysed iteratively using manifest and latent content analysis [Paper I] and phenomenography [Paper II]. The quantitative study was a repeated cross-sectional surveillance study for which 30 GPs and 3 GP trainees collected monthly data for all patients with an acute respiratory tract complaint during predetermined one week periods between May 2015 and April 2016. Descriptive statistics were used to examine patient, consultation and clinical characteristics, and to describe GPs' prescribing patterns [Paper III]. In Paper IV, the association between GP-, practice- and consultation-level factors, patient sociodemographic factors and patient health status factors, and antibiotic prescription (yes/no) was investigated using generalised estimating equations to estimate population-averaged effects.

Key findings: GPs' provided an antibiotic prescription to 45.7% of cases, the majority of which (99.6%) were broad-spectrum. Almost all (84.3%) were for immediate use, whilst 15.7% were delayed prescriptions. Through qualitative interviews five qualitatively different ways by which GPs perceived delayed antibiotic prescribing were described: (i) to maintain a good GP-patient relationship, retain patients and avoid doctor-shopping, (ii) to reach a compromise and provide treatment just in case, (iii) to provide the patient comfort and reassurance, (iv) to empower and educate patients, and limit antibiotic use, and (v) to retain GP

responsibility by employing a wait-and-see approach. Surveillance data also revealed that GPs' antibiotic prescribing is associated with a number of GP-, patient-, clinical- and consultation-level factors. This was largely corroborated by qualitative evidence that showed that antibiotic prescribing is impacted not only by intrinsic GP factors but several other factors, including but not limited to, diagnostic uncertainty, patient demand, interaction with drug reps, availability of guidelines and community resistance data, and access to diagnostic testing.

Conclusions: GPs' antibiotic prescribing for RTIs in Malta is high. The abundant use of broad-spectrum antibiotics is of particular concern and indicates that antibiotics are not being used appropriately. A number of factors were found to impact GPs' antibiotic prescribing behaviour. In order to improve this behaviour, targeted and coordinated implementation activities must address barriers identified at all levels of the system and provide GPs with the necessary tools to alleviate diagnostic uncertainty.

Trial registration number: NCT03218930

Key words: antibiotic prescription, primary care, general practitioners, respiratory tract infections, qualitative research, surveillance, barriers and facilitators, influencing factors, Malta

LIST OF SCIENTIFIC PAPERS

I. **Saliba-Gustafsson EA**, Nyberg A, Borg MA, Rosales-Klintz S, Stålsby Lundborg C
General practitioners' understanding of antibiotic use and resistance, and perceived barriers and facilitators to prudent antibiotic prescribing: a qualitative study
Manuscript.

II. **Saliba-Gustafsson EA**, Röing M, Borg MA, Rosales-Klintz S, Stålsby Lundborg C
General practitioners' perceptions of delayed antibiotic prescription for respiratory tract infections: a phenomenographic study
PLoS One, 2019, 14(11): e0225506.

III. **Saliba-Gustafsson EA**, Dunberger Hampton A, Zarb P, Borg MA, Stålsby Lundborg C
Antibiotic prescribing for respiratory tract complaints in Malta: a 1 year repeated cross-sectional surveillance study
J Antimicrob Chemother, 2019, 74(4): 1116-24.

IV. **Saliba-Gustafsson EA**, Dunberger Hampton A, Zarb P, Orsini N, Borg MA, Stålsby Lundborg C
Factors associated with antibiotic prescribing in patients with acute respiratory tract complaints in Malta: a 1-year repeated cross-sectional surveillance study
BMJ Open, 2019, 9(12): e032704.

These papers shall be referred to in text by their Roman numerals [I-IV].

OTHER SCIENTIFIC CONTRIBUTIONS

I. **Saliba-Gustafsson EA**, Borg MA, Rosales-Klintz S, Nyberg A, Stålsby Lundborg C
Maltese Antibiotic Stewardship Programme in the Community (MASPIC): protocol of a prospective quasiexperimental social marketing intervention
BMJ Open, 2017, 7(9): e017992.

II. Pathak A, **Saliba EA**, Sharma S, Mahadik VK, Shah H, Stålsby Lundborg C
Incidence and factors associated with surgical site infections in a teaching hospital in Ujjain, India
Am J Infect Control, 2014, 42(1): e11-5.

III. Rosales-Klintz S, **Saliba EA**, Zacharias C, Stålsby Lundborg C
Course on the development, implementation and evaluation of prudent antibiotic use campaigns: facilitator manual
Stockholm, Sweden: European Centre for Disease Prevention and Control; 2013.

IV. Rosales-Klintz S, **Saliba EA**, Zacharias C, Stålsby Lundborg C
Course on the development, implementation and evaluation of prudent antibiotic use campaigns: participant workbook
Stockholm, Sweden: European Centre for Disease Prevention and Control; 2013.

CONTENTS

LIST OF ABBREVIATIONS

aRTC	Acute respiratory tract complaint
ATC	Anatomical therapeutic chemical
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DAP	Delayed antibiotic prescription
DDD	Defined daily dose
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
EU	European Union
GP	General practitioner
IQR	Interquartile range
MASPIC	Maltese Antimicrobial Stewardship Programme in the Community
OR	Odds ratio
POCT	Point-of-care test
RTI	Respiratory tract infection
SD	Standard deviation
SM	Social marketing
WHO	World Health Organization

1 BACKGROUND

1.1 THE GROWING THREAT OF ANTIMICROBIAL RESISTANCE

1.1.1 Antimicrobials and antimicrobial resistance

Antimicrobial drugs comprise a vast range of drugs, including antibiotics, antifungals, antivirals, antimalarials and anthelmintics. These drugs can kill or inhibit the growth of specific microorganisms, including bacteria, fungi, viruses and parasites. Access to effective antimicrobial treatment is a prerequisite in medicine today. Unfortunately however, the hard-won gains achieved through the health-related Millennium Development Goals, are threatened by the increasing development of antimicrobial resistance.[1] Antimicrobial resistance has been a growing public health threat for several decades[2] and occurs when microorganisms counteract the exposure of antimicrobial drugs through a number of resistance mechanisms such as efflux, phosphorylation, hydrolysis, etc.[3] The reduced efficacy of these drugs makes the treatment of infections challenging and expensive, sometimes impossible.[2] This puts great strain on the sustainability of many public health interventions targeting communicable diseases.[1] If the necessary policies are not put into place to target antimicrobial resistance, it has been estimated that by 2050, antimicrobial resistance will cause ten million deaths worldwide per year, greater than the mortality attributed to cancer.[4] This chapter will narrow its focus on antibiotic use and the imminent threat of antibiotic resistance, including strategies to contain its spread.

1.1.2 Antibiotic resistance: a global and cross-sectoral crisis

The discovery of antibiotics by Sir Alexander Fleming in 1928 revolutionised the field of medicine, moving it from a diagnosis- and prognosis-focused field, to an interventional one.[5] It gave us the opportunity to carry out procedures that before then had posed immense risks on morbidity and mortality. Surgery became safer, previously lethal infections became curable and certain life-saving procedures such as chemotherapy became possible. However, already in his Nobel Prize speech in 1945, Sir Alexander Fleming cautioned that bacteria could develop resistance towards these remarkable drugs.[2] Indeed already in the 1950s, shortly after the introduction of penicillin in the 1940s, resistance to penicillin became a substantial clinical problem.[5,6] Although the development of antibiotic resistance is inevitable,[3] as it is a natural evolutionary process for bacteria,[7] their exposure to widespread antibiotic use exerts selective pressure on bacteria and accelerates resistance,[2] as is evident in Figure 1. Figure 1 illustrates a timeline of how rapidly antibiotic-resistant bacteria were detected after antibiotics were introduced to the market.

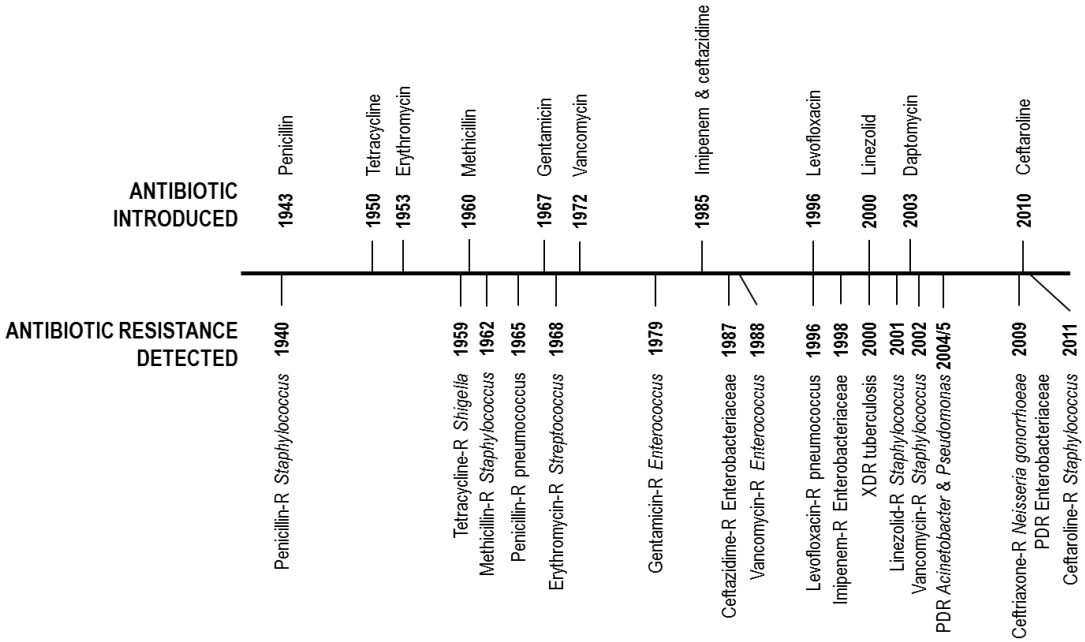

Figure 1. Timeline of the introduction of antibiotics and subsequent identification of antibiotic-resistant bacteria
This image has been modified from Ventola (2015).[6] *Dates are based on early evidence of resistance in the literature except for pan-drug-resistant Acinetobacter and Pseudomonas where dates are based on reports of healthcare transmission or outbreaks. Please note that penicillin was in limited use before its widespread use in 1943.*
NOTE. *PDR=pan-drug-resistant; R=resistant; XDR=extensively drug-resistant.*

Today, antibiotic resistance is one of the most pertinent and pressing global public health challenges of our time, that threatens modern medicine as we know it today and requires urgent action.[2] Whilst some improvements have been made, the problem is hardly subsiding.[8] Further exacerbating the problem is the fact that antibiotic resistance is a crisis that does not only concern human health, but spans across a number of sectors. Indeed, antibiotics have not only been misused in humans but also in the veterinary and food-production sectors. In addition, they have been released into the environment in an uncontrolled manner through, for example, inadequate treatment of sewage systems and pollution caused by the pharmaceutical industry.[7] With the realisation that human, animal and environmental health are closely interlinked, the One Health approach was launched almost two decades ago[9] and since then there have been many efforts to promote cross-sectoral and multidisciplinary collaboration to address antibiotic resistance across all sectors.[10]

Moreover, the rapid increase in antibiotic resistance worldwide pushed the issue to the forefront of top intergovernmental organisations' agendas, including the European Commission, World Health Organization (WHO) and World Economic Forum. Already in 2001, the WHO had proposed a global strategy for the containment of antimicrobial resistance to slow down its emergence and decrease the spread of resistant microorganisms.[11] Following the 68th World Health Assembly in May 2015, a global action plan on antimicrobial resistance was adopted, re-emphasising the need for adopting a One Health approach to ensure long-term, successful prevention and treatment of infectious diseases with safe and effective medicines that are used responsibly. It also set another objective, to have multi-sectoral national action plans prepared by Member States by the 2017 World Health Assembly.[1] By March 2018, 100 countries had drafted national action plans and 67 were in the planning phase.[12]

1.2 IMPACT OF ANTIBIOTIC RESISTANCE ON HUMAN HEALTH

Although the precise scale of this global problem and the impact of antibiotic resistance on human health and well-being is still largely unknown,[2] antibiotic resistance due to common bacterial pathogens has reached alarming levels in many countries worldwide.[2] Moreover, antibiotic development has declined markedly over the years, and many of the currently available treatment options are becoming increasingly ineffective in certain contexts.[2] This has led prescribers to resort to stronger, more toxic and expensive drugs, often with devastating side effects on the patient.[6] Unfortunately, reports of resistance towards last-line drugs like colistin, fosfomycin and ceftazidime-avibactam in the treatment of multidrug-resistant and extensively-drug-resistant Gram-negative bacteria are becoming more frequent.[13]

Antibiotic-resistant infections pose considerable burden on patient outcomes and healthcare expenditure, both on a societal but also on an individual level.[2,14] They lead to significantly longer hospital stays, increased morbidity and mortality,[6] among a host of other negative consequences. It has been found that hospital stays are prolonged by 6.4 to 12.7 days as a result of antibiotic-resistant infections, resulting in a total of eight million extra hospital days.[14] In the United States, nearly two million patients develop healthcare-associated infections each year, resulting in 99,000 deaths that are largely a consequence of antibiotic-resistant pathogens.[15] Furthermore, in 2006, it was reported that healthcare-associated sepsis and pneumonia caused the deaths of nearly 50,000 patients and cost the healthcare system more than US$8 billion.[16]

In a European Union (EU) report based on 2007 data from EU member states, Iceland and Norway, the burden of resistance in six multidrug-resistant bacteria was investigated and estimated to cost society approximately €1.5 billion per year in extra healthcare costs and productivity losses.[17]A more recent EU-/European Economic Area (EEA)-wide study estimated the burden of antibiotic resistance in eight bacterial species and found that they accounted for approximately 33,000 deaths and over 850,000 disability-adjusted life-years in 2015.[18] Patients younger than one and over 65 years were most afflicted, and a substantial proportion of the burden was estimated to have been caused by community-associated infections.

1.3 DRIVERS OF ANTIBIOTIC RESISTANCE

It is evident that antibiotic resistance is a complex and multidimensional problem, driven by many interrelated factors.[2] Antibiotic use, misuse and overuse, as well as unregulated consumer access to antibiotics, are recognised key drivers of antibiotic resistance.[19–24] Prolonged and low dose antibiotic therapy, and broad-spectrum antibiotics in particular, promote its development.[25] Antibiotic use in turn, is impacted by a multitude of factors, including knowledge, attitudes, perceptions, expectations, communication between prescribers and patients, time constraints, economic incentives, cultural factors, health system characteristics and regulations.[19,26–30] The degree to which these factors impact antibiotic use in particular

settings varies, and contextual factors must be considered when implementing antibiotic stewardship activities to improve antibiotic use.

1.4 ANTIBIOTIC USE AND RESISTANCE IN EUROPE

1.4.1 Public knowledge and awareness

Knowledge on antibiotics varies depending on the context but remains below par. Indeed, a recent systematic review that included studies from all over the globe, found that 33.7% of people were not aware that antibiotics are used to treat bacterial infections and 53.9% did not know that antibiotics do not work against viruses. Whilst 59.4% were aware of antibiotic resistance, 26.9% did not know that antibiotic misuse can aggravate the problem.[31] In Europe specifically, the latest Eurobarometer report, for which the general public in 28 EU Member States were interviewed, showed that although there has been some improvement in the overall knowledge on antibiotics among Europeans since 2016, there is room for improvement.[32] The report demonstrated that only 25% of respondents correctly responded to the knowledge questions on antibiotics, with the highest knowledge scores achieved in Finland and Sweden, and the lowest in Latvia and Romania. Overall, only 43% of Europeans knew that antibiotics are ineffective against viruses despite 85% being aware that unnecessary antibiotic use makes them become ineffective. Another European-wide study found that certain southern European countries like Malta and Italy, had significantly less appropriate attitudes, beliefs and knowledge compared to Swedish respondents.[33]

It is evident that awareness on prudent antibiotic use among the general public must be improved, particularly in countries with weaker knowledge and attitudes levels, by strengthening educational campaigns and encouraging doctors to provide patients with information.[31,34] Encouraging better antibiotic use through increased public knowledge and awareness could also have positive implications on actual and perceived patient demand,[29] which has been shown to impact physicians' antibiotic prescribing behaviour.[35,36]

1.4.2 Impact of culture on antibiotic use

In Europe, there is an evident geographical variation in antibiotic consumption and resistance. Antibiotics are used more in southern and eastern European regions.[37] These regions tend to have higher antibiotic resistance levels than other parts of Europe with lower rates of antibiotic use.[38] In fact, a correlation between outpatient antibiotic consumption and antibiotic resistance has been shown in Europe,[39,40] with a stronger correlation in southern European countries where antibiotic consumption rates are among the highest.[41]

Arguably, cultural drivers have provided the best understanding of this geographical variation in antibiotic use in Europe.[26,42,43] The most accepted approach used to analyse behavioural differences among countries is Geert Hofstede's anthropological model of cultural dimensions. The model describes how cultures vary along six fundamental dimensions: uncertainty avoidance, power distance, masculinity, individualism, long-term orientation and indulgence.[44] Table 1 briefly describes each of these dimensions.

Table 1. Description of Geert Hofstede's national cultural dimensions[45]

National cultural dimensions	Description
Uncertainty avoidance	The degree to which people within a society feel discomfort when faced with uncertain and ambiguous situations. Countries that exhibit high uncertainty avoidance scores are intolerant of uncertainty and ambiguity whilst societies with weak scores have a more laid back attitude.
Power distance	The degree to which people with less power within a society accept and expect unequal distribution of power. In societies with high power distance scores, people accept hierarchies without question, whereas in societies with low power distance scores, people do their utmost to distribute power equitably and demand justification when power is not distributed equally.
Masculinity versus femininity	Masculine societies are typically more competitive. They provide material rewards for success, praise achievements, heroism and assertiveness. In feminine societies, people prefer cooperation, modesty, caring for the weak and quality of life. Such societies are usually more consensus-oriented.
Individualism versus collectivism	In individualistic societies, individuals are expected to take care of themselves and their immediate family. Conversely, in collectivist societies, individuals are also expected to care for extended family or members of a particular group of people.
Long-term orientation versus short-term normative orientation	Societies that score low in this dimension prefer to preserve traditions and norms and view societal change with suspicion. Those that score high are more pragmatic, encouraging thrift and modern education as they pave the way to the future.
Indulgence versus restraint	Indulgent societies allow deriving satisfaction from basic and natural human drives related to enjoying life and having fun. Restrained societies suppress this gratification by means of strict social norms.

The dimension that has been correlated most consistently with the overuse or inappropriate use of antibiotics is uncertainty avoidance.[26,30,46] People in countries with high uncertainty avoidance scores tend to feel threatened and anxious by uncertain and ambiguous situations, and do not tolerate them well. As a result, doctors may feel compelled to act promptly rather than wait and see,[30] prescribing antibiotics "just in case" when faced with uncertain clinical presentations.[47] This provides a subconscious reassurance of certainty to both the patient and prescriber.[26] In such contexts it is also more likely that wide-spectrum antibiotics are prescribed and for longer durations.[47] A positive correlation between power distance and antibiotic use has also been shown.[48] In fact, Scandinavian countries like Sweden that have low rates of antibiotic use, score low in uncertainty avoidance but also power distance. Conversely countries in the Mediterranean region, such as Malta, are characterised by high uncertainty avoidance and power distance scores.[47]

1.4.3 Antibiotic prescription

The largest volumes of antibiotics prescribed for systemic use in Europe are provided in the community setting,[49] and despite most respiratory tract infections (RTIs) being self-limiting, they remain the most common indication.[39,50] Although antibiotic prescription rates vary greatly by context and prescriber, studies have shown staggeringly high prescription rates for upper RTIs in outpatient settings, despite being seldom required.[39,51–56] Indeed, antibiotics confer little benefit in most upper RTIs and the overall risk of developing complications by

withholding antibiotic treatment is small.[57–60] Furthermore, antibiotic use exposes patients to unnecessary side effects and costs, and can have long-lasting impact on gut microbiota, which could propagate conditions such as obesity and allergies, particularly when used in infancy.[61]

1.5 TURNING THE LENS ON MALTA

In order to assist EU/EEA countries to outline and implement national action plans and strategies to contain antimicrobial resistance and promote prudent antimicrobial use, the European Centre for Disease Prevention and Control (ECDC) conducts country visits upon invitation by national authorities. These visits are intended to discuss and assess the country's situation regarding the prevention and control of antimicrobial resistance through appropriate antibiotic use and infection control.[62] ECDC conducted a country visit to Malta, an archipelago situated in the centre of the Mediterranean Sea, in July 2017, where they assessed progress made since the first country visit in November 2009. Whilst good progress was observed in some areas such as a decrease in methicillin-resistant *Staphylococcus aureus* bacteraemia cases at the local public hospital (Mater Dei Hospital) and less access to oral antibiotics over-the-counter, little difference was noted in other areas. Notably, it was reported that broad-spectrum antibiotic use is still considerably high in the community.[62]

At the time of ECDC's country visit, the Maltese national action plan and strategy against antimicrobial resistance for 2017-2025 had been drafted but required further discussion with key stakeholders. Today, the national action plan for 2020-2025 has been drafted, discussed with key stakeholders (including the veterinary sector) and opened for public consultation. It is now awaiting final formal ministerial approval for its official launch.

1.5.1 Public knowledge and awareness

Although knowledge has increased slightly since the 2009 Eurobarometer survey,[32,63] the general public still lacks adequate knowledge on appropriate antibiotic use, particularly when compared to other EU countries. In 2018, only 30% (EU28 average = 43%) of Maltese knew that antibiotics do not kill viruses and 46% (EU28 average = 66%) knew that antibiotics are ineffective against colds.[32] In contrast, 92% (EU28 average = 85%) were aware that unnecessary antibiotic use makes them become ineffective.

1.5.2 Community antibiotic consumption

European Surveillance of Antimicrobial Consumption Network (ESAC-Net) reports have shown that community antibiotic consumption in Malta typically hovers around EU/EEA average but has not improved over the past decade,[37] despite a reduction in over-the-counter sales.[64] In contrast, Eurobarometer reports, which provide self-reported data on antibiotic consumption among EU Member States, portray a different picture, with antibiotic consumption consistently among the highest in Europe. According to the 2013 report, 48% of the population consumed antibiotics during the previous year; the highest reported antibiotic consumption at the time.[65] Although the most recent report has shown a reduction to 42%, antibiotic consumption remains high.[32] Furthermore, the top two reported indications were sore

throat (22%; EU28 average = 14%) and the flu (14%; EU28 average = 12%).[32] Figure 2 shows the trend in antibiotic consumption (using wholesale data) in the community between 2009 and 2018 according to ESAC-Net reports.

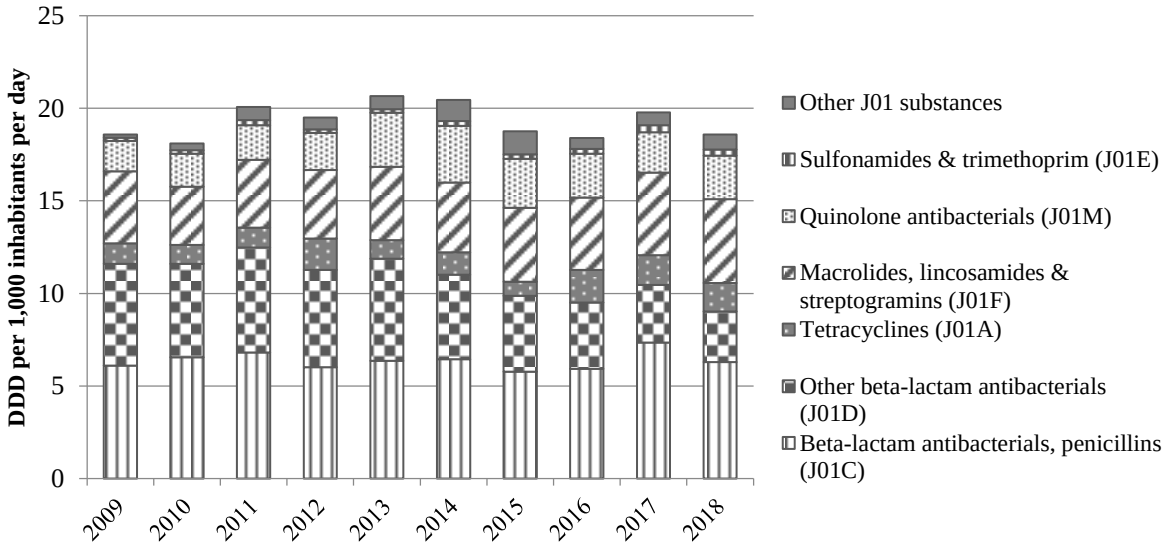

Figure 2. Antibiotic consumption (ATC group J01) in the community in Malta between 2009 and 2018, expressed in defined daily dose (DDD) per 1,000 inhabitants per day[66]

1.5.3 Antibiotic prescribing in the community

Although diagnosis-specific data on antibiotics prescribed in the community are unavailable, community antibiotic consumption data indicate that Maltese prescribers rely primarily on broad-spectrum antibiotics from four different antibiotic classes; penicillins with β-lactamase inhibitors, 2nd-generation cephalosporins, macrolides and fluoroquinolones.[64] This is not justified neither by evidence-based international guidelines nor by local resistance patterns.[64] A potential contributing factor to the unnecessary prescription of broad-spectrum agents is inaccurate perceptions of resistance due to insufficient knowledge of the local epidemiology[39] but also that narrow-spectrum antibiotics recommended by national antibiotic guidelines are reportedly unavailable from community pharmacies.[62] Since it is recognised that broad-spectrum antibiotics contribute to resistance more than narrow-spectrum antibiotics, the negligible prescription of narrow-spectrum antibiotics is concerning.[39]

1.6 BEHAVIOUR CHANGE INTERVENTIONS

In view of this complex problem and the fact that most antibiotics consumed in Malta are the result of a medical prescription,[32] research on effective strategies to change prescribers' knowledge and behaviour is needed to encourage appropriate antibiotic use.[39,67] However, changing behaviour is complex, and whilst awareness campaigns and education are often recommended,[21,40] interventions that aim to change behaviour are more likely to be effective.

1.6.1 Social and behaviour change communication: an ecological perspective to behaviour change

Pivotal to the success of any behaviour change intervention is a thorough understanding of people and the various factors that impact their behaviour.[68] With the realisation that an individual's behaviour is not only impacted by the individual him/herself but also the society and environment in which the individual is embedded, there has been a paradigm shift in how behaviour change researchers and programme implementers address behaviour change. In order to achieve sustainable behaviour change, there is a need to move beyond simply addressing individual behaviour through information and education, to tackling the problem from an ecological perspective, by understanding the interaction and interdependence of factors at all levels of the problem.[69,70]

Social and behaviour change communication is a theory-based and research-driven process that builds upon behaviour change communication and is used to achieve behaviour change beyond just the individual level, by using targeted approaches that also impact the physical, socioeconomic and cultural environment.[69] Social and behaviour change communication uses a socioecological model to identify critical areas in need of change in order to facilitate behaviour and address barriers to it. The socioecological model described by McLeroy *et al.*[71] is a theory-based framework used to understand personal and environmental processes and interactions that determine behaviour, and identify leverage points for change at five levels: intrapersonal, interpersonal, organisational, community and public policy. Such models can be used to address barriers and inform public health practice.[72] Table 2 provides a description of each level of the socioecological model together with a few examples of factors that may have an impact on antibiotic prescription.

Table 2. Description of factors that may impact behaviour at each level of the socioecological model [27,71]

Level	Description	Examples related to antibiotic prescription
Intrapersonal	Individual's characteristics, including knowledge, attitudes, behaviour, self-efficacy, age, etc.	Knowledge, attitudes and beliefs of the individual doctor
Interpersonal	Formal and informal social networks and support systems, including family, colleagues and friends	Doctor-patient and doctor-pharmacist relationships
Organisational	Social institutions with organisational characteristics and both formal and informal rules and regulations	Antibiotic guidelines and regulations
Community	Relationships among organisations, institutions and informal networks within distinct boundaries	Social networks and societal norms
Public policy	Local, state and national laws and policies	Adherence to laws and regulations, e.g. prescription-only medicines

Various strategies, theories and models can be used to address behaviour change at each level of the socioecological model. Since each level of influence may impact behaviour,[70] the most successful approaches combine activities at all levels.[73] However, these multi-level interventions are rather complex and expensive to implement.[74] Figure 3 depicts the five levels of the socioecological model grouped into three levels of change (i.e. the intrapersonal-, interpersonal- and community-levels) with corresponding strategies and behavioural theories and models that can be used to better understand behaviour at each level of influence.

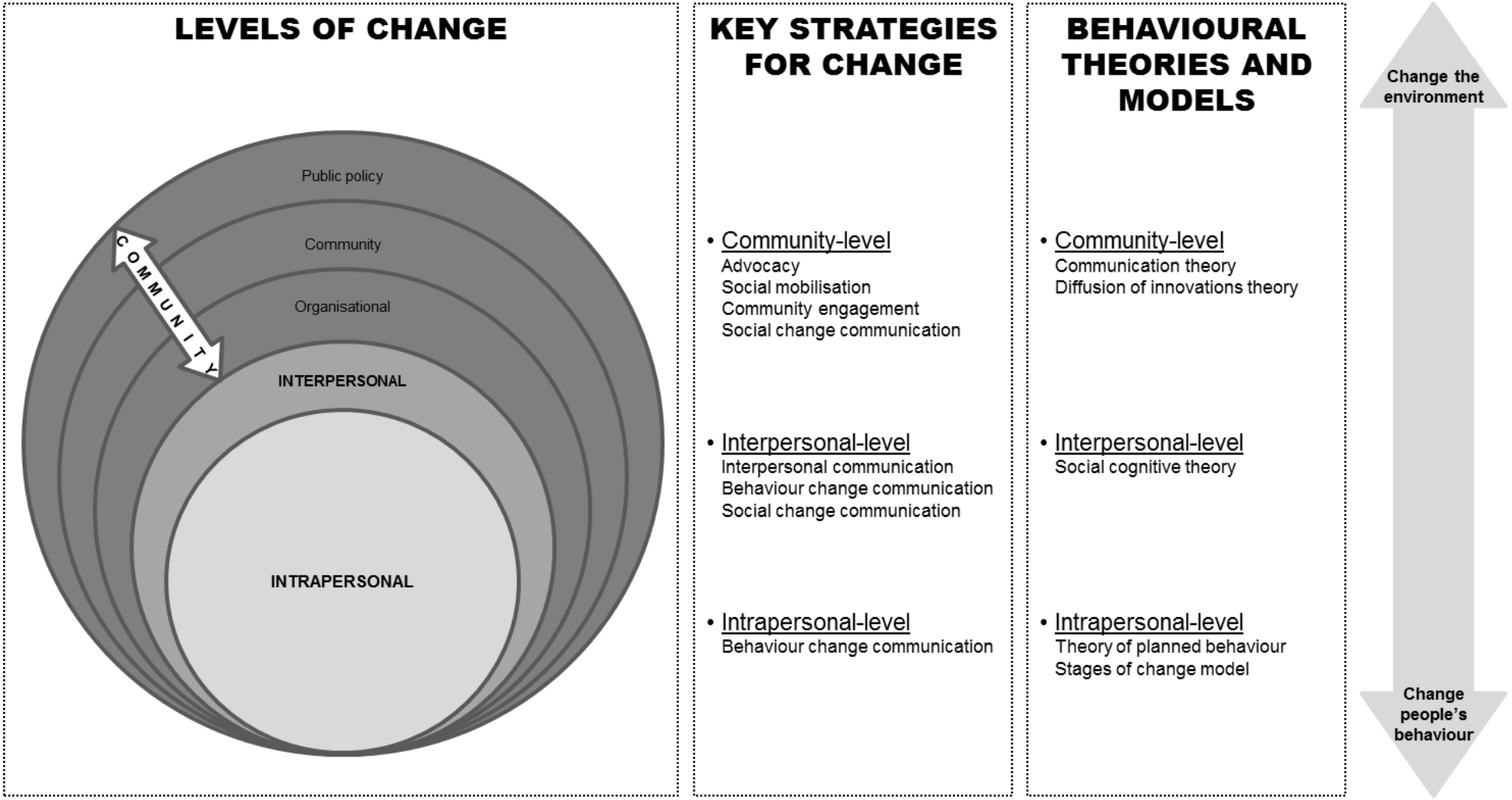

Figure 3. Key strategies for behaviour change at each level of the socioecological model and corresponding behavioural theories and models that can be used to understand behaviour[70,73]

Behavioural theories and models like the theory of planned behaviour[75] and stages of change model,[76] are suitable approaches that can be used to better understand factors that influence prescribing practices. These methods have so far been underutilised in the development of interventions targeting antibiotic prescribing.[77] In Europe and other high-income settings, several interventions and campaigns have attempted to use a behaviour change approach to promote appropriate antibiotic use, however, most did not consider the behavioural determinants related to antibiotic use and prescription.[77] Social marketing (SM) may provide a different insight on the development of behaviour change interventions targeting antibiotic use.

1.6.2 Bridging theory and practice: social marketing and its role in public health interventions

SM is an approach used to promote behaviour change by applying marketing theories and techniques to plan, implement and evaluate interventions to encourage voluntary behaviour change within a target audience.[70,78] It combines concepts from commercial marketing and health education, and breaks them down into the following principles: measurable behavioural objectives, "customer" or "consumer" orientation, segmentation (i.e. tailoring), competition (i.e. understanding benefits and barriers), exchange (i.e. emphasising the benefits of change), marketing mix (the "4Ps" of marketing – product, price, place and promotion), and long-term planning. It also takes context-specific issues into consideration in order to tailor interventions to one's particular needs and increase the chance of success.[78] When applied correctly, SM interventions can provide the right tools that are conducive to sustained behaviour change among targeted populations[67] by identifying competing behaviours, and barriers and facilitators to change, but also offering optimal conditions for exchange, i.e. offering target audiences something they consider worthwhile in exchange for them changing their behaviour. Therefore, SM interventions should ensure that activities maximise benefits whilst minimising barriers that are considered important to the target group.[79] Despite its potential, the utilisation of SM for the prevention and control of communicable diseases in Europe is still limited.[78]

1.7 STRATEGIES TO COMBAT ANTIBIOTIC RESISTANCE

A number of important strategies have been outlined in an effort to combat antibiotic resistance. However, their application is impacted by several contextual issues that must be addressed for their successful uptake. Interventions that attempt to improve antibiotic prescribing also tend to be more successful when they combine doctor, patient and public education and when the design is multi-faceted.[50,80–83] A recent systematic review that focused on antibiotic use for RTIs, found that multiple interventions that contained at least educational materials for doctors were most effective.[50] The other element/s to be included will be highly dependent on the local context.[50] Some of the suggested approaches are explained below.

1.7.1 Surveillance

The establishment of effective surveillance is critical for national and international efforts to contain antimicrobial resistance.[21] There are currently large knowledge gaps on the distribu-

tion and magnitude of antibiotic resistance in many regions of the world due to a lack of adequate surveillance systems.[21] Often, routine surveillance is performed on patients with severe infections, particularly those that are healthcare-related and for whom first-line antibiotic treatment was unsuccessful.[2] Community-acquired infections are usually underrepresented among samples, leading to gaps in reporting among important patient groups.[2] A more coordinated and synchronised surveillance system to monitor antibiotic resistance at national, regional and global level, is urgently needed. This, together with the development of internationally-agreed standards for data collection and reporting across all sectors, i.e. human health, veterinary care and agriculture.[1] Such data would help develop a better understanding of antibiotic resistance trends, monitor the situation to identify key areas that can be addressed in interventions to contain resistance, monitor the impact of interventions, determine optimal treatment options for patients, and inform public health policy.[2,21]

At European level, ECDC coordinates and funds the European Antimicrobial Resistance Surveillance Network (EARS-Net), a network of national surveillance systems that provide reference data on antimicrobial susceptibility of seven bacterial pathogens from 30 countries.[84] It also coordinates ESAC-Net, an interactive database that provides European reference data on antimicrobial consumption, both in the community and hospital sectors.[66] Malta participates in both networks. However, whilst resistance and consumption data are routinely collected within tertiary care, Malta can only provide wholesale data for the community; pharmacies do not keep electronic records of prescriptions dispensed and therefore community antibiotic consumption data at prescription-level are unavailable.[64]

1.7.2 Audit and feedback

Prescription audit and feedback has been incorporated in many recent studies that provide data at an individual- or practice-level. However, there is limited evidence supporting the long-term impact of this strategy.[50,85] In the Audit Project Odense model, Swedish general practitioners (GPs) recorded their consultations at two time points and received feedback in between. The medical audit resulted in a 10% decrease in antibiotic prescription within the intervention group.[86] Providing individual prescribing feedback has also been shown to lead to improvements in guideline adherence.[87,88] However, Gerber *et al*. found that although initial reductions in antibiotic use were seen following an educational seminar and quarterly individual feedback, these were not maintained and antibiotic use returned to baseline after one and a half years without audit and feedback.[89,90] This stresses the importance of maintaining audit and feedback if one is to sustain long-term improvements in antibiotic prescribing.

1.7.3 Antibiotic prescribing guidelines

Prescribing guidelines help clinicians translate the best evidence into practice. Although national antibiotic guidelines have been issued by several countries, few studies have assessed their impact on antibiotic prescribing behaviour.[85] It has however been shown that guideline dissemination alone is not sufficient to reduce antibiotic prescribing rates.[50] Studies from the United States have shown that despite some improvements in antibiotic selection, issuing

antibiotic guidelines had little effect on antibiotic prescribing for a number of upper RTIs.[91,92] A Belgian study showed that introducing guidelines led to short-term improvements in guideline-concordant antibiotic prescription, but that prescription returned to baseline levels after a 17-month washout period.[93]

1.7.4 Delayed antibiotic prescribing

Delayed antibiotic prescribing is a method typically used by doctors to postpone or reduce antibiotic consumption. There are different ways by which doctors usually handle such prescriptions. The doctor may, (i) provide an antibiotic prescription with the condition that the antibiotic should only be taken if symptoms persist or the patient's condition worsens within a given time period (typically between 48 and 72 hours) (patient-led approach), (ii) post-date (forward-date) the prescription, meaning that the patient is unable to acquire the antibiotic before a specified date, or (iii) ask the patient to return to the clinic to either collect the prescription or to be re-consulted by the doctor.[94] Despite some national guidelines recommending delayed antibiotic prescribing, its application in clinical practice remains low[95,96] and the motivation behind its use varies. Some use it to manage diagnostic uncertainty or avoid patient conflicts (particularly with those who pressure their doctors to prescribe), others use it as a tool for patient education and to promote shared decision-making.[96,97] Some prescribers feel uncomfortable shifting clinical responsibility onto their patients and therefore dislike the approach.[96]

1.7.5 Educational materials for patients

Over the past decade, the use of patient information leaflets in primary care has been increasing in popularity.[85] Doctors can use them during consultations to help explain concepts to patients and patients may take them home to read later.[85] Studies have shown that patient information booklets can not only help lower antibiotic prescribing rates,[98] but also increase awareness on antibiotic use and give patients valuable information on, for example, the usual duration of different infections and how to recognise signs of severe illness.[99,100] They can also increase knowledge and confidence among GPs, although some GPs report barriers such as lack of time and difficulty altering their consultation style.[99]

1.7.6 Educational sessions for doctors

A review of interventions targeting doctors to improve antibiotic use for RTIs showed that educational sessions, although arduous, appear to be more effective than audit and feedback, and circulation of written patient information.[50] Educational sessions can include: information on the core principles of prudent antibiotic use, introduction to new tools (guidelines for example), diagnostic skills training and sessions on patient communication.[85] A few studies have shown that sessions incorporating these subject areas can lead to sustained improvement in antibiotic use that can last longer than two to four years.[101,102] The degree of impact in other studies has generally been rather modest.[100,103–106]

1.8 RATIONALE FOR THIS THESIS

Given that Malta has among the highest antibiotic consumers in Europe,[32,107] targeting antibiotic overuse and misuse in this community is imperative. In Malta, most antibiotics for systemic use are provided in the community setting. The top two reasons for which antibiotics are consumed are sore throat and the flu, for which antibiotics are largely unnecessary.[32] Furthermore, it has been shown that 96% of antibiotics consumed are the result of a medical prescription.[32] Since the Maltese consider doctors the most trustworthy source of information on antibiotics,[32] they are important role models for their patients. GPs are therefore a key target group in this particular setting.

Successful interventions must identify key local drivers of antibiotic prescribing and integrate incentives for behaviour change.[108] However, we currently lack knowledge on what factors, particularly contextual ones, facilitators and barriers impact GPs' antibiotic prescribing behaviour in Malta, particularly for RTIs. Moreover, no antibiotic prescribing data are available. As a result, we do not know the extent to which antibiotics are prescribed by GPs specifically. Neither are we able to determine their diagnosis-specific antibiotic prescribing rates. Developing a more in-depth understanding of both GPs' actual prescribing behaviour and the factors that influence their prescribing is pivotal to determine the appropriateness of antibiotic prescription and to develop suitable targeted interventions.

2 AIM AND OBJECTIVES

2.1 AIM

The overall aim of this thesis was to explore general practitioners' views on antibiotic use and resistance in Malta, and to gain a better understanding of their antibiotic prescribing patterns for respiratory tract infections including the factors that influence their prescribing behaviour.

The overarching goal was to identify and inform appropriate social marketing strategies in order to design, implement and evaluate a social marketing behaviour change intervention to improve general practitioners' antibiotic prescribing practices in Malta.

2.2 OBJECTIVES

The specific objectives were to:

a) explore general practitioners' understanding of antibiotic use and resistance, and describe their perceived barriers and facilitators to prudent antibiotic prescribing for respiratory tract infections **[Paper I]**
b) explore and describe the perceptions of delayed antibiotic prescription for respiratory tract infections among general practitioners **[Paper II]**
c) determine the one year antibiotic prescribing patterns by general practitioners for acute respiratory tract complaints **[Paper III]**
d) identify factors that influence general practitioners' oral antibiotic prescribing for acute respiratory tract complaints **[Paper IV]**

3 METHODS

This doctoral thesis forms part of a larger intervention project entitled the Maltese Antibiotic Stewardship Programme in the Community (MASPIC) for which a study protocol has been published (Appendix I).[109] For the purpose of this thesis, only pre-intervention phase results are included. Nonetheless, a brief description of MASPIC is included here.

A quasi-experimental multi-faceted SM intervention was implemented in Maltese primary care clinics to assess whether SM can influence GPs' antibiotic prescribing for acute respiratory tract complaints (aRTCs). In order to design a tailored intervention, understanding key concerns, particularly contextual ones, that influence GPs' antibiotic prescribing, is essential. Furthermore, for any SM intervention to be successful, an in-depth understanding of the target audience is required.[110] Therefore the SM intervention was developed following a BEHAVE-based marketing plan[111] (Figure 4). Through the BEHAVE framework critical questions could be addressed prior to selecting which interventions to implement, namely (i) who is the audience? (ii) what do we want them to do? and (iii) what factors influence their behaviour?[111] Formative research is the best way to gain insight into the practices, views and attitudes of target audiences and can be attained through, for example, focus group discussions and individual interviews. Therefore formative research findings from the pre-intervention phase could thereafter be used to inform subsequent studies and develop a SM intervention that addressed competing behaviours as well as barriers and facilitators to behaviour change. A short description of the intervention, which was delivered between October 2016 and March 2017, can be found in Appendix II. The intervention materials used have also been attached (Appendices III-V).

3.1 THE MALTESE ARCHIPELAGO

Malta is a Mediterranean archipelago that consists of five islands of which only three are inhabited, Malta (the largest), Gozo and Comino.[112] Malta is the smallest EU Member State in size (316 km^2) and population, yet has the highest population density.[113] The nation has two official languages, Maltese and English. Table 3 provides a few population and health indicators for Malta in 2017 and 2018.

Table 3. Population and health indicators for Malta in 2017 and 2018[113]

Indicator	2017	2018
Total population size	460,297	475,701
Population aged 0-14 years (% of total)	14.1	13.9
Population aged 65 years and over (% of total)	18.8	18.8
Population density	1495.2	-
Life expectancy (years) at birth (male/female)	80.2/84.6	-
Total fertility rate	1.26	-
Infant mortality rate	6.7	-

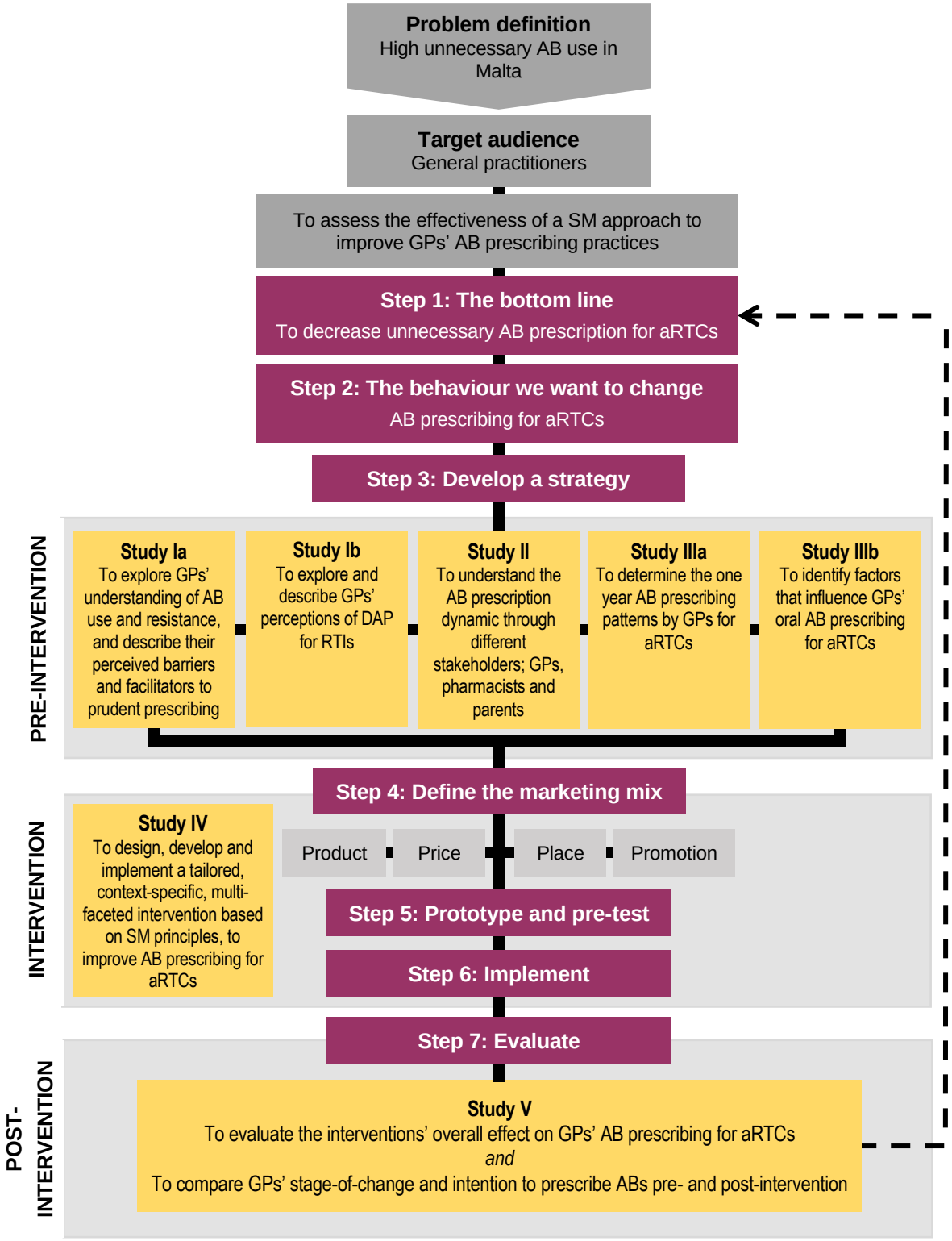

Figure 4. The project's BEHAVE-based social marketing framework

NOTE. *AB – antibiotic; aRTC – acute respiratory tract compliant; DAP – delayed antibiotic prescription; GP – general practitioner; RTI – respiratory tract infection; SM – social marketing*

3.1.1 Health system organisation and financing

Provision of health services, regulation and standards, and occupational health and safety are governed by the Ministry for Health with the Permanent Secretary as administrative head, accountable to the Prime Minister. S/he is responsible to support general policies and priorities set by the government. The Chief Medical Officer is responsible for the Department for Policy in Health and is chief adviser to the Minister of Health on issues related to government health policies. The Department for Health Services is led by the Director General for Health Services who ensures that health services are delivered effectively and efficiently. The Superintendent of Public Health leads the Department for Health Regulation and is responsible for safeguarding public health, licensing, monitoring and inspecting health services provision in terms of quality and safety, and provides advice to the Minister of Health on public health issues.[112] Figure 5 provides an overview of the organisation of Malta's health system, relevant to this thesis.

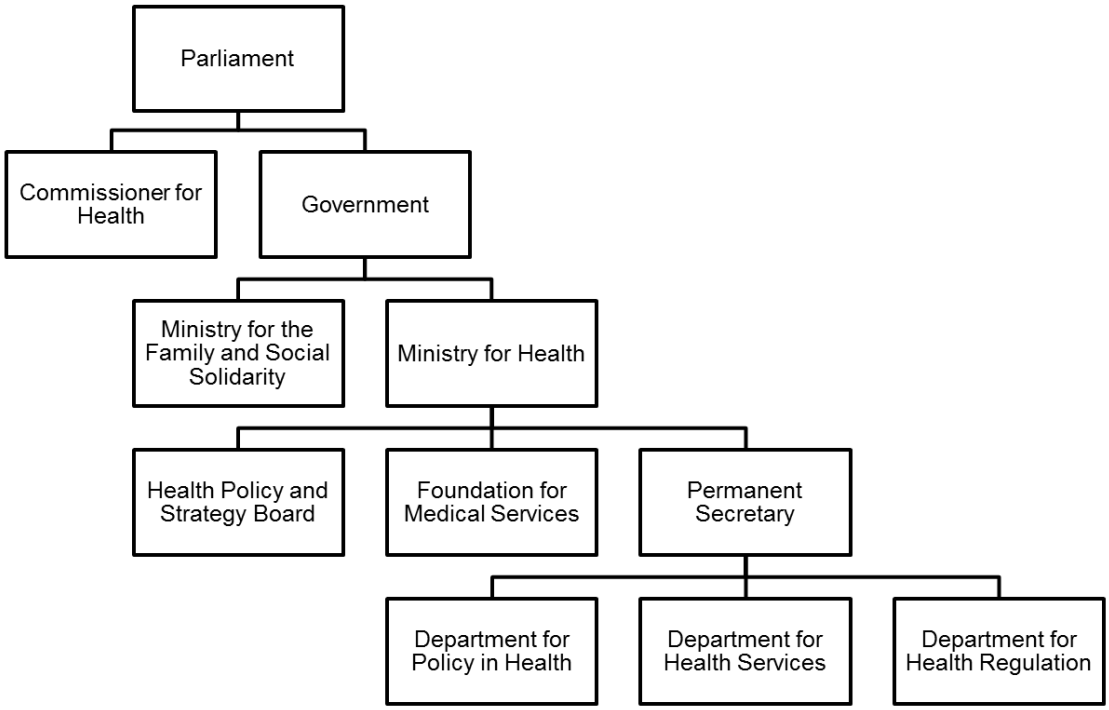

Figure 5. Malta's health system organisation.
Adapted from Azzopardi-Muscat N. (2017)[112]

Malta has an integrated health system organised at national level. It is primarily funded by taxation but is complemented by private financing.[114] Health services are mainly provided by the public sector and are free-of-charge at point-of-care to Maltese residents covered by the Maltese Social Security Act. This usually covers all workers and their dependents, pensioners and persons on benefits due to their inability to work. It also provides care to irregular immigrants and alien employees with valid work permits.[112]

Secondary and tertiary care are provided largely by specialised public hospitals although acute general services (ambulatory, inpatient and intensive care) are provided by a centrally-located teaching hospital (Mater Dei Hospital).[112] The private sector complements health services provided by the public sector, particularly in primary care, and services are financed

through out-of-pocket payments and/or voluntary health insurance.[112] No reimbursement system exists, although a small percentage of the population are entitled to receive a restricted list of medicines, including antibiotics, directly from government pharmacies free-of-charge.

3.1.2 Primary healthcare services and general practice

As from 2003, qualified doctors who wish to work in primary care are expected to specialise in family medicine. However, GPs who began practising prior to 2003 were granted certified specialisation based on acquired experience and were therefore not required to undergo specialist training.[115] In 2015, there were 83 registered GPs per 100,000 population.[112]

It is estimated that approximately two-thirds of primary care is provided by GPs in the private sector.[112] Patients are free to choose their own doctor and are therefore not registered to a particular GP. In the public sector patients are seen by whichever doctor is present on the day and do not generally develop a specific relationship with one GP; thus hindering continuity-of-care. In the private sector, patients typically choose their own family doctor with whom they tend to have strong family ties. In fact, many private sector GPs often treat several generations within a family and it is still rather common for GPs to maintain close contact with regular patients throughout the duration of their illness.

Public sector services are accessible mainly through nine public district healthcare centres in Malta and one in Gozo (Figure 6). Smaller local health clinics, staffed by their respective district healthcare centre, also provide services. Three of the healthcentres in Malta are open 24 hours a day to cater for patients requiring urgent care between 8pm and 8am. General practice services are provided on a walk-in basis and home visits are provided in urgent cases if the patient lacks transportation.[112] Private sector GPs predominantly operate through solo practices from private clinics and/or clinics situated within retail pharmacies; few work in group practices.[112] House visits are still in great demand and fairly common.[114] Despite associated out-of-pocket costs, private GPs are generally favoured by patients due to better continuity-of-care and scheduling convenience.[112] Finally, private sector GPs are not obliged to keep patient records, although some do so for personal use.

Over the last three decades there have been many attempts to reform primary care to improve continuity-of-care in both the public and private sectors through patient registration. However, these reforms have been met with opposition. Successful reforms have resulted in the expansion of service provision, infrastructure and equipment.[112] Moreover, since 2012, GPs working in the private sector have been given increased access to public healthcare services and are now able to refer patients to the public sector for imaging and laboratory investigations. Laboratory tests are sent to and analysed at Mater Dei Hospital. Private sector GPs are also able to access electronic patient records for services provided in the public sector, including laboratory results and radiology reports.[112]

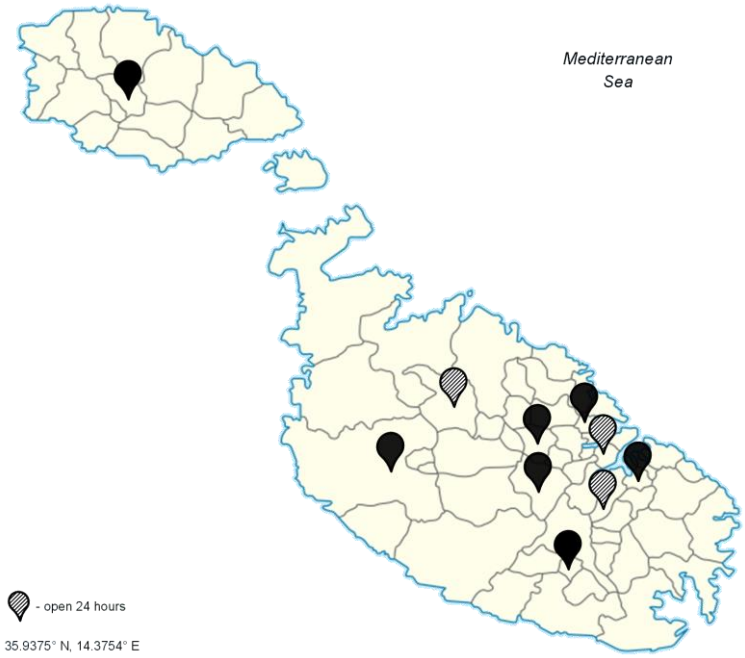

Figure 6. Map of Malta showing the ten district healthcare centres that provide primary healthcare services in the public sector.

3.1.3 Regulation and governance of pharmaceuticals

Pharmaceuticals can only be sold within licensed pharmacies in Malta.[112] Antibiotics are prescription-only medicines by law[116] and more than 90% of antibiotics distributed are procured by private community pharmacies.[64] Antibiotic prescriptions are considered invalid ten days after their date of issue[117] and single-use prescriptions should be retained by the pharmacist upon dispensation.[118] According to legislation, unless a prescriber specifically requests that an originator drug is to be dispensed, pharmacists can substitute the product so long as the product has the same active ingredient, dose and dosage form prescribed.[112]

3.2 OVERVIEW OF THE PAPERS INCLUDED IN THIS THESIS

To fulfil the aim and objectives of this thesis, a mixed methods approach was used. Table 4 summarises the methods used in all four papers.

Table 4. Overview of the papers included in this thesis

Paper	Main topic	Study design	Sampling and data collection	Data analysis
I	Barriers and facilitators to prudent antibiotic prescribing	Qualitative	▪ Quota sample ▪ Individual semi-structured interviews	Manifest and latent content analysis
II	Delayed antibiotic prescription			Phenomenographic analysis
III	Antibiotic prescribing patterns for aRTCs	Repeated cross-sectional surveillance	▪ Total population sample ▪ One-year prospective surveillance	Descriptive analysis
IV	Factors associated with antibiotic prescribing for aRTCs			Population averaged models using generalised estimating equations

NOTE. *aRTC – acute respiratory tract complaint*

3.3 INTERVIEWS WITH GENERAL PRACTITIONERS [PAPERS I & II]

3.3.1 Interview guide development

Following a thorough literature search and based on the co-authors' expertise in the subject area, a semi-structured interview guide with prompts (Appendix VI) was developed in English and adapted to the local context. The guide was pilot tested with six GPs in March 2014 and revised accordingly. Interview topics were broad and focused mainly on GPs' views on: (i) antibiotic resistance and antibiotic use for RTIs, (ii) factors that influence their antibiotic prescribing, (iii) delayed antibiotic prescription (DAP), (iv) drug reps (also known as pharmaceutical sales representatives) and the pharmaceutical industry, (v) use of diagnostic testing for RTIs, and (vi) patient education.

3.3.2 Study participants

GPs registered on the Malta Medical Council's Specialist Register were considered eligible for participation if they worked as GPs in the public and/or private healthcare sectors, irrespective of whether they worked part- or full-time. Registered GPs were called and invited to participate using quota sampling. In quota sampling, the researcher wants to ensure that the strata within the sample being investigated are proportional to those of the population under study, so that the sample of interviewees is as representative of the population characteristics as possible.[119] All eligible GPs to whom a phone number was available were listed and subsequently divided into strata based on the following characteristics and in the following order: (i) years of experience as a GP, (ii) sex and (iii) locality of residence. A total of 30 GPs from within each stratum were contacted by phone in a stepwise fashion and invited to participate in this study. Four no longer worked as GPs and were considered ineligible whilst six declined participation. Ultimately 20 GPs participated, of whom 14 were male. GPs' age (years) ranged from 32 to 70 and their years' of experience ranged from 7 to 45. Table 5 summarises the GPs' characteristics.

Table 5. Characteristics of general practitioners participating in interviews (n=20)

		n
Sex	male	14
	female	6
Age (years)	30-39	2
	40-49	4
	50-59	11
	60-69	2
	70-79	1
Years of experience as a general practitioner	<10	2
	10-19	3
	20-29	10
	30-39	3
	40-49	2
Healthcare sector of practice	public	4
	private	14
	both	2

3.3.3 Data collection

Individual interviews were conducted in August and September 2014 by the author of this thesis, a Maltese registered nurse who did not work clinically in Malta at the time of the interviews and had no prior interaction with the participating GPs. The interviews were primarily held in English, however respondents were free to reply in Maltese, without inhibiting the interview's flow, as the interviewer was fluent in both languages. GPs often expressed themselves using a combination of the two languages.

GPs chose the time and place of the interview; often at their own workplace outside patient hours. Before the interview commenced, data on the GPs' demographics, training and experience, and their healthcare sector of practice, were collected by the interviewer (Appendix VII). The face-to-face interviews lasted between 25 and 67 minutes (median = 40 minutes). Participants were encouraged to think out loud and speak openly about their views and experiences, without being inhibited by the interviewer. GPs were also encouraged to provide concrete examples of patient encounters. Data were collected until no new information was gained and saturation was reached. Interviews were audio recorded and subsequently transcribed verbatim by the interviewer. Maltese to English translation of responses was also performed. Phrases that were hard to interpret or translate were discussed with a licensed Maltese proof-reader, although this was seldom necessary.

3.3.4 Data analyses

Pilot interviews were excluded from all analyses. Therefore ultimately, 20 interview transcripts were included in the analysis of both Papers I and II.

3.3.4.1 Content analysis [Paper I]

Interview transcripts were analysed iteratively and independently by the author of this thesis and another co-author using manifest and latent content analysis with an inductive approach.[120,121] In manifest analysis, the researcher remains very close to the text and describes what the interviewees say whilst latent analysis involves deeper interpretation with the researcher seeking to find the underlying meaning of the text.[122] In brief, the two co-analysts read and re-read the interview transcripts (the unit of analysis) to familiarise themselves with the data. Meaning units were then extracted from the transcripts and subsequently condensed. Codes were derived from the condensed meaning units and similar codes grouped into subcategories. Sub-categories were subsequently sorted and merged into categories. The tentative categories were discussed between the co-analysts and revised. Finally the underlying meaning, or latent content, of the categories were abstracted into themes. Findings were discussed among all co-authors, until a consensus was reached. Table 6 presents a sample of the content analysis procedure employed to our data.

3.3.4.2 Phenomenographic analysis [Paper II]

In Paper II, data were analysed using a phenomenographic approach.[123] Phenomenography is a qualitative research method that aims to empirically identify the qualitative variations of how people perceive, understand, conceptualise or experience a particular phenomenon.[124] It was first developed to investigate learning in tertiary education but was later applied to other research fields, including understanding the various ways medical practitioners view different diseases, medical practice and antibiotic resistance.[125–130]

Table 6. Sample of the content analysis procedure used in Paper I

Condensed meaning unit	Code	Sub-Category	Category	Sub-theme	Theme
If someone believed that I should have prescribed an antibiotic but I do not, he will go round the corner to another doctor. Doctor-shopping. That happens, I know it happens. I hope that it does not really happen in my practice but it happens yes.	Doctor-shopping	Pressure placed on GPs through patient demand and expectations	General practitioners' views on patient behaviour, knowledge and awareness, and their impact on general practitioners' antibiotic prescribing	Finding the right balance: addressing patient behaviour, knowledge and awareness through education and information provision	General practitioners' antibiotic prescribing decisions are complex and impacted by numerous barriers and facilitators at the intrapersonal, interpersonal, organisational, community and policy level
There's another problem when it comes to rapid tests in Malta, time. As GPs we work single-handedly. Sometimes we have to see long lists of people. If you do this test and that test you must have the infrastructure otherwise you would end up taking about half an hour to see one patient and in half an hour people start complaining.	Rapid point-of-care tests can be time consuming	Views on rapid point-of-care tests	Access to and use of diagnostic testing in general practice	Organisation and delivery of primary healthcare services, and the impact of public policy, regulation and guidelines on general practitioners' antibiotic prescribing	

Every understanding of the phenomenon has two characteristics, the structural and referential.[131] The structural aspect explains the individual's *focus* of attention, or awareness, whilst the referential elucidates the meaning of the phenomenon to the individual, or how *meaning* is generated.[131] Therefore a phenomenon is typically perceived in about three to seven alternative ways, with distinct variations in focus and meaning.[128]

Data were analysed iteratively by the author of this thesis and another co-author whilst bracketing their own preconceptions. Preliminary results were discussed with the remaining co-authors and minor adjustments were made following their input. Finally, an outcome space was created. This graphical representation illustrates how different conceptions or perceptions relate to one another to form a phenomenon.[132] Since some perceptions may be more complex or include several aspects of a phenomenon, the outcome space is often presented in a hierarchy. A step-by-step summary of the data analysis process is outlined in Table 7.

Table 7. The step-by-step phenomenographic analysis process used in Paper II

1	**Familiarisation**	Transcripts were read repeatedly and independently by two co-analysts to gain an overview of the material.
2	**Compilation and condensation**	Every transcript was analysed individually by the co-analysts and the most significant statements where GPs described their views on and experiences with DAP were extracted and condensed. Transcripts were read with these questions in mind: What does this tell me about the way the GP perceives DAP? What does DAP *mean* to the GP and what is the *focus*? Next, important elements of the different conceptions were identified.
3	**Comparison, grouping and preliminary description**	Similarities and dissimilarities between significant statements were identified, compared and grouped using preliminary labels. Preliminary descriptions of the various DAP perceptions were composed and labelled for *every* interview.
4	**Formulation and labelling of different categories of description**	The different ways of understanding in *all* interviews were collated and compared, searching for similarities and differences. They were subsequently labelled and described as different categories of description. Preliminary categories of description were compared during discussions between the co-analysts to determine whether the descriptions truly captured the variations in GPs' views and experiences.
5	**Final categories of description and outcome space**	Preliminary categories of description were presented to and discussed among all co-authors until consensus was reached and the final categories of description were determined. Lastly an outcome space was created.

NOTE. *DAP – delayed antibiotic prescription; GP – general practitioner*

3.4 ANTIBIOTIC PRESCRIBING SURVEILLANCE [PAPERS III & IV]

3.4.1 Development of surveillance data collection form

The surveillance data collection form was developed and tailored to the local context based on tools used in previous research[133,134] and data collected from earlier qualitative studies within the MASPIC project. The form was piloted with eight GPs and checked for face validity, after which no major changes were made. The final form (Appendix VIII) included data on: (i) patient characteristics such as age, comorbidities and lifestyle factors, (ii) clinical characteristics such as duration of symptoms and signs and symptoms, (iii) diagnostic testing, (iv) suspected aetiology and diagnosis, and (v) prescribed medicines.

3.4.2 Study participants

All GPs registered on the Malta Medical Council's Specialist Register and GP trainees were invited to partake. GPs were considered eligible if they were actively working as GPs full- or part-time. Of the 378 registered GPs and 34 trainees, 404 (98%) were invited. Eight were excluded as they were inactive or ineligible as they were already involved in the project.

In November 2014, postal invitations with a six-week reminder were sent to registered GPs and trainees whose postal addresses were available online. In an attempt to target those who could not be reached by postal mail, e-mail invitations were sent out via local professional associations and a public invitation was distributed through a local medical professional network called TheSynapse (www.thesynapse.eu). Invitations were also sent out through the Malta College of Family Doctors to target trainees enrolled in the specialist training programme. Finally, phone calls were made to follow up with as many GPs as possible.

Seventy registered GPs and trainees replied, of whom 35 agreed to participate. The remainder either declined participation (n=21) or were no longer practising GPs and were thus considered ineligible for participation (n=14). Before surveillance commenced, a further two registered GPs became ineligible; one transferred to non-clinical work and the other quit working as a GP. Ultimately, 30 GPs and 3 trainees participated (Table 8). GPs exhibited variation across various factors, including locality and sector of practice, years of practice as a GP, age and sex. Most GPs were male (n=24; 73%). Mean age (years) was 49±12 and mean years of practice as a GP was 23±11.

Table 8. Characteristics of general practitioners (GPs) participating in antibiotic prescribing surveillance (n=33)

		n
Sex	male	24
	female	9
Age (years)	28-39	7
	40-49	9
	50-59	14
	60-76	3
Years of practice as a GP (n=32)	<10	6
	10-19	5
	20-29	14
	≥30	7
GP trainee	no	30
	yes	3
Type of employment	part-time	11
	full-time	22
Practice location	public healthcentre clinic	13
	private clinic	14
	private pharmacy clinic	11
Type of practice*	group	16
	solo	17

NOTE. *GPs working in public healthcentre clinics were defined as group practice practitioners*

3.4.3 Data collection

During enrolment, GPs were asked to complete and submit a background information sheet, which included information on demographics, training and experience, and service delivery organisation (Appendix VII). They were also provided with a surveillance pack, which included all the tools they required to complete the one-year surveillance study, including an instruction sheet, twelve pre-paid envelopes, data collection forms and tally charts.

The study was carried out in both the public and private healthcare sectors. GPs personally registered all patients seen for an aRTC during twelve pre-determined surveillance weeks (one week/month with no substitutions) between May 2015 and April 2016. Forms were filled during first consultations with all patients suffering from any aRTC (lower- and upper-RTIs, allergies and exacerbation of chronic obstructive pulmonary disease (COPD)/asthma/bronchitis). Data on the total number of patients seen per day, irrespective of complaint, were also collected using the tally charts provided. In order to promote compliance, close communication was maintained with GPs throughout the surveillance year. Each surveillance week, GPs received three text messages; one prior to surveillance initiation to remind them to prepare for data collection, another on the first surveillance day to remind them to initiate it and a third on the last surveillance day to remind them to conclude it and send completed sheets using pre-paid envelopes. GPs were also called at most four times throughout the year, to offer encouragement and address queries. Finally, GPs were e-mailed quarterly individual- and aggregate-level feedback reports on their prescribing patterns.

3.4.4 Data analyses

In total, data from 4,831 aRTC cases were recorded and input in Microsoft® Excel 2010. Data were later transferred to Stata/IC® 13.1 for further data management and analyses.

3.4.4.1 General patient eligibility criteria

Only cases diagnosed with an aRTC were considered eligible for analysis. Cases had to have been consulting with the participating GP for the first time for that presenting complaint. Any follow-up visits recorded were automatically omitted from analysis. Cases where two or more aetiologies and/or diagnoses were provided were also excluded from analysis.

3.4.4.2 General practitioners' antibiotic prescribing patterns for acute respiratory tract complaints [Paper III]

Following data cleaning, 190 cases (3.9%) were excluded from analysis using the general patient eligibility criteria outlined above, resulting in 4,641 aRTC cases (96.1%) eligible for analysis. Descriptive statistics were used to examine patient, consultation and clinical characteristics, and to describe GPs' antibiotic prescribing patterns. The WHO's 2017 Anatomical Therapeutic Chemical (ATC) classification system was used to classify antibiotics.[135] Antibiotic prescribing indicators were calculated using WHO's manual on investigating drug use[136] and the ECDC, European Food Safety Authority and European Medicines Agency's updated quality indicators for outpatient antibiotic use in Europe.[137] To determine the extent of broad-spectrum antibiotic prescription, the following ratio was used, ratio of broad-spectrum pen-

icillins, cephalosporins, macrolides and fluoroquinolones (J01[CR+DC+DD+(F-FA01)+MA]) to narrow-spectrum penicillins, cephalosporins and macrolides (J01[CA+CE+CF+DB+FA01]).[137]

3.4.4.3 Factors associated with general practitioners' antibiotic prescribing for acute respiratory tract complaints [Paper IV]

In addition to the general patient eligibility criteria defined above, all cases diagnosed with pneumonia and patients consulted over the phone were also excluded from this dataset. As a result, 313 aRTC cases (6.5%) were excluded from this analysis, reducing the final sample size to 4,518 (93.5%).

Variables pertaining signs and symptoms, diagnostic testing, symptomatic treatment and other miscellaneous variables (Appendix VIII – Sections 6, 7, 11 and 12 respectively) that were not marked by GPs were assumed not present and analysed as absent, not tested or not provided. Analyses were conducted using complete case analysis. Descriptive statistics were calculated using frequencies and percentages, means and standard deviations (SDs), medians and interquartile ranges (IQRs) as appropriate. The outcome of interest was antibiotic prescription (yes/no), defined as an oral antibiotic prescribed for an aRTC during an in-person consultation, irrespective of the number of antibiotics given. It included both immediate and delayed antibiotic prescriptions. It did not include 'delayed instruction', i.e. instruction to follow-up should symptoms persist or worsen.

To control for clustering at GP level, potential predictors of antibiotic prescription were analysed using generalised estimating equations to estimate population-averaged effects. Frequency distributions of explanatory variables of interest were calculated and univariable associations between each variable and antibiotic prescription were assessed using unadjusted odds ratios (ORs) and 95% confidence intervals (CIs). All continuous variables were categorised since linearity to the outcome could not be assumed. Individual signs and symptoms variables were investigated if at least 5% of aRTC cases presented with that symptom. Multivariate Wald-type tests were performed on multi-level categorical variables to test the hypothesis of the overall association. Finally, potential predictors were included in the multivariable model if significant at $p<0.2$ at univariable level and excluded if there were collinearity issues. A predictor was kept in the multivariable model if it improved the model and its p-value was <0.05. Ultimately 4,425 aRTC cases were included in the final multivariable model.

3.5 ETHICAL CONSIDERATIONS

Ethical approval for each study was sought from the University of Malta's Research Ethics Committee. The ethical considerations are described below.

3.5.1 Interviews with general practitioners [Papers I & II]

Following the research ethics committee's assessment, it was decided that since the study pertained medical professionals and no sensitive topics were to be discussed, it was exempt

from ethical approval. Despite this decision, standard ethical considerations were adhered to. During recruitment, participants were verbally informed about the study's purpose and what their involvement would entail. Just before the interview, participants were given information letters outlining the study, its purpose, their role and the estimated duration of the interview. The letter also requested their permission to audio record the session. GPs were also given the opportunity to pose queries about the study. Informants were told that their participation is voluntary and that they were free to withdraw at any time and without justification or consequences. No financial incentives were provided, however in return for their participation, GPs were offered certificates of participation that they could use to apply for continuing medical education credits through the Malta College of Family Doctors.

GPs who agreed to participate were asked to sign an informed consent form, which both they and the researcher received a signed copy of, signed by both parties. Participants were each given individual codes that were kept in a separate file, accessible to only one member of the research team. Furthermore, all collected data were made confidential so as not to reveal GPs' identities, and stored in a safe location. Signed consent forms were stored separately. There were no anticipated risks associated with participation, rather informants could have benefitted from being given the opportunity to reflect on their antibiotic prescribing practices and factors that may influence their prescribing decisions.

3.5.2 Antibiotic prescribing surveillance [Papers III & IV]

For this study, ethical approval was granted by the University of Malta's Research Ethics Committee. GPs were sent information letters and consent forms to participate in this study, followed by one reminder. The information letter included information on the study's purpose, data collection method, a template of the data collection sheet and their role as participants. It informed them that they were free to withdraw from the study at any time without justification or consequences. It also informed them that in return for their participation they would be offered certificates of participation at the end of the surveillance year, based on the degree of their participation. This would allow them to apply for continuing medical education credits through the Malta College of Family Doctors. Those interested were requested to submit their signed consent.

During the one-year surveillance, doctors submitted surveillance sheets that were individually coded and confidential. Codes were stored in a separate file that could be accessed by only one member of the research team. Moreover, although the surveillance sheet included patient records, none of the information gathered risked compromising the patients' identities since no names and/or identifiable data were collected. There were no major anticipated risks associated with participation apart from the time GPs had to dedicate to filling in and submitting the sheets. However, all doctors were aware of this and the sheet was specifically designed to be very user-friendly.

4 KEY FINDINGS

This chapter presents the key findings identified through Papers I-IV. The results are integrated below to highlight important aspects of each finding.

4.1 ANTIBIOTIC PRESCRIBING PATTERNS

Of the 4,641 aRTC cases that were eligible for analysis in Paper III, just over half were female (n=2,462; 53.1%) and median age was 29 years (IQR=12-49). The most frequently reported signs and/or symptoms were sore throat (n=2,189; 47.2%), rhinorrhoea (n=1,701; 36.7%), productive cough (n=1,481; 31.9%), non-productive cough (n=1,447; 31.2%) and fever (n=1,363; 29.4%). The top five most common diagnoses were common cold (n=1,536; 33.1%), pharyngitis (n=743; 16.0%), bronchitis (n=570; 12.3%), tonsillitis (n=434; 9.4%) and sinusitis (n=305; 6.6%).

Figure 7 shows the suspected aetiology by diagnosis as reported by participating GPs in Paper III. Despite GPs in Paper I suggesting that the majority of upper RTIs (approximately 70-90%) are viral in aetiology and would thus not necessitate an antibiotic, GPs in Paper III suspected a viral aetiology in only 49.7% (n=2,307) aRTC cases. The rest were considered to have bacterial (n=1,280; 27.6%) or mixed (n=735; 15.8%) aetiologies.

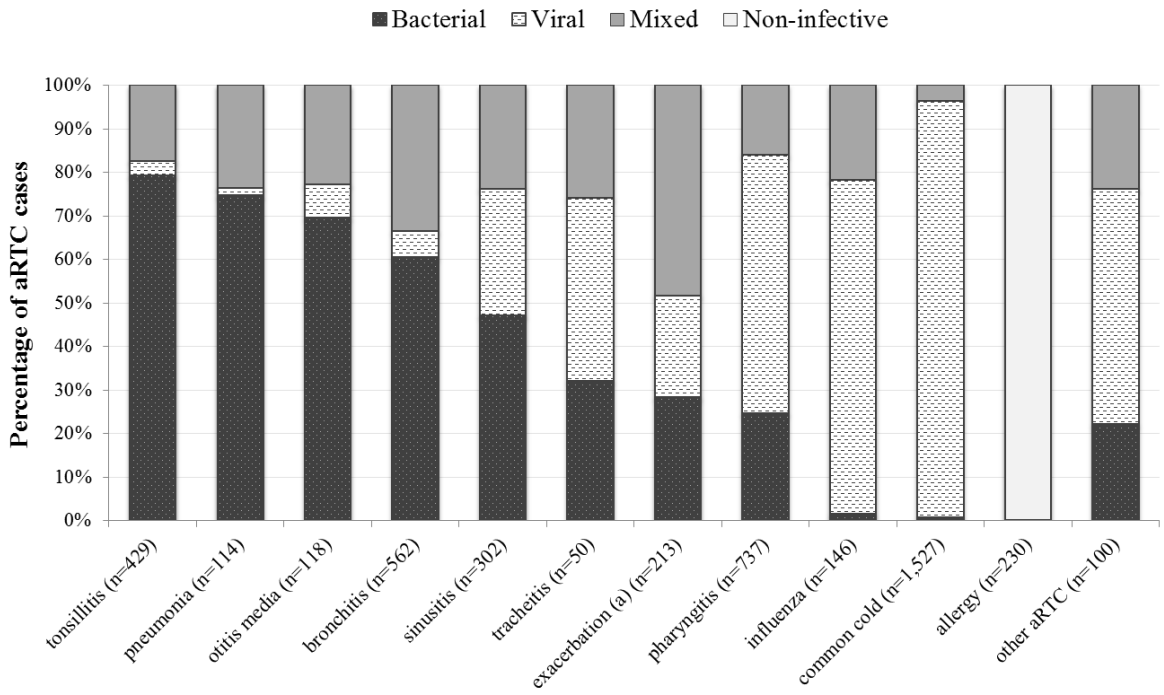

Figure 7. Suspected aetiology by diagnosis as reported by participating general practitioners
(a) Exacerbation of chronic obstructive pulmonary disease/asthma/bronchitis

The antibiotic prescription rate, as indicated in Paper III, was rather high. In total, 45.7% (n=2,122) of aRTC cases received an antibiotic prescription. Of these, 84.3% (n=1,789) were for immediate use, the rest (n=333; 15.7%) were DAPs. The greatest proportion of antibiotic treatment was prescribed to cases with a suspected bacterial aetiology (n=1,213; 94.8%), fol-

lowed by a suspected mixed aetiology (n=603; 82.0%). Nevertheless, 11.6% (n=268) of cases with a suspected viral infection were given an antibiotic prescription, the majority of which were delayed (n=231; 86.2%). In terms of diagnosis, the highest proportion of antibiotic prescriptions were provided to patients diagnosed with tonsillitis (n=418; 96.3%), otitis media (n=111; 92.5%) and bronchitis (n=499; 87.5%). Similarly in Paper I, GPs reported that they typically prescribe antibiotics for tonsillar infections, otitis media, bronchitis, pneumonia, sinusitis (particularly if prolonged) and bacterial pharyngitis, reflecting their actual antibiotic prescribing behaviour as observed in Paper III.

GPs prescribed broad-spectrum antibiotics in the majority of cases (99.6%). The most frequently prescribed antibiotics were macrolides [J01FA] (n=757; 35.5%), followed by penicillins with β-lactamase inhibitors [J01CR] (n=709; 33.2%) and 2nd-generation cephalosporins [J01DC] (n=302; 14.2%). Eleven cases (1%), diagnosed with pneumonia (n=4), bronchitis (n=4) and acute exacerbation of COPD/asthma/bronchitis (n=3), received combination treatment i.e. two antibiotics from different classes. These combinations included penicillins with β-lactamase inhibitors together with macrolides [J01CR & J01FA] (n=7) or 2nd-generation cephalosporins together with macrolides [J01DC & J01FA] (n=4). Figure 8 below shows GPs' antibiotic prescribing rate by diagnosis (Paper III). It also illustrates how GPs' choice of antibiotic class varies by diagnosis.

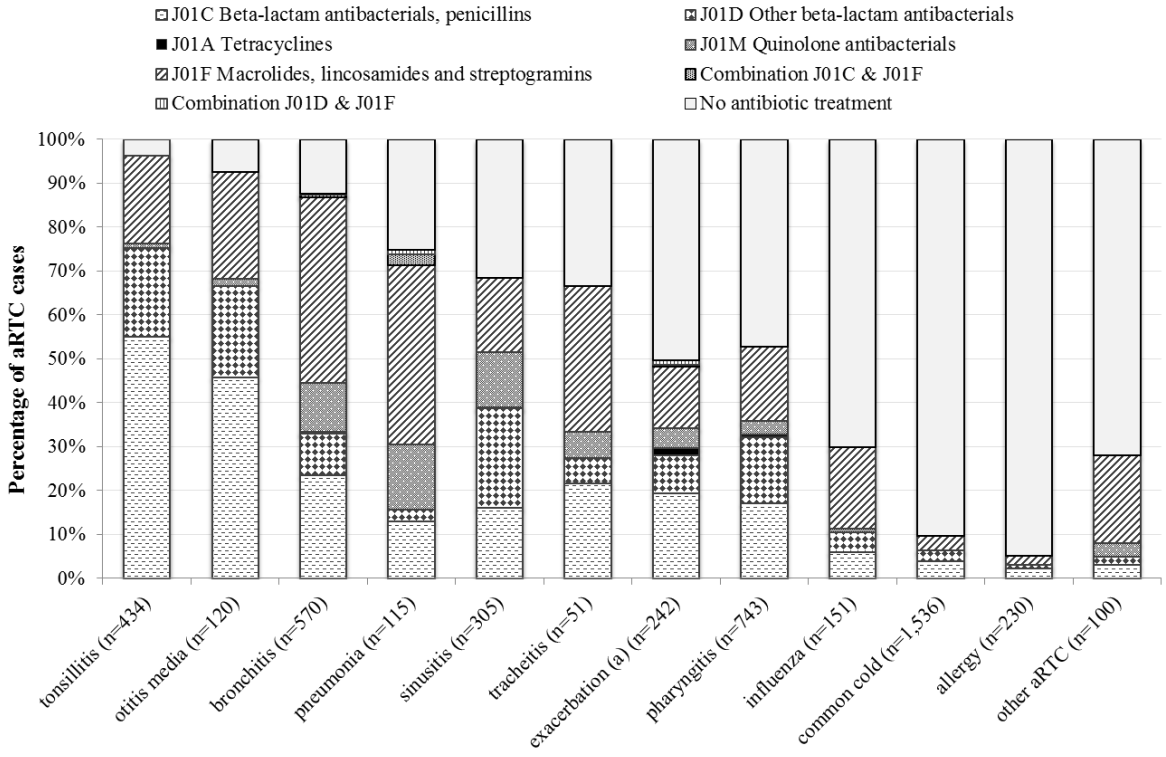

Figure 8. Antibiotic classes prescribed by general practitioners for each diagnosis, by antibiotic class
[(a)] Exacerbation of chronic obstructive pulmonary disease/asthma/bronchitis
NOTE. *This figure includes delayed antibiotic prescriptions*

4.2 DELAYED ANTIBIOTIC PRESCRIPTION: PRACTICES AND PERCEPTIONS

Results from Paper III showed that GPs do provide DAPs to patients with aRTCs. In fact, as mentioned earlier, of all patients who received an antibiotic prescription (n=2,122; 45.7%),

15.7% (n=333) were delayed. Through our findings we also showed that DAPs were provided mostly to patients with either a suspected viral (n=186; 58.3%) or mixed infection (n=102; 32.0%). Through Paper II we were able to further understand GPs' DAP practices by identifying five qualitatively different ways that GPs perceive delayed antibiotic prescribing. These varying perceptions were labelled and described under five categories of description and are outlined in further detail below.

4.2.1 "The Service Provider": maintaining a good general practitioner-patient relationship to retain patients and avoid doctor-shopping

"Service providers" feared losing patients from their practice and mainly perceived delayed antibiotic prescribing as a strategy to maintain a good GP-patient relationship thereby ensuring that patients return to the clinic. In this perception, GPs also focused on understanding why patients want immediate antibiotics; essentially to avoid a second visit for financial reasons. Therefore GPs provided DAPs to avoid being perceived as avaricious by asking patients to return for a second visit. Some GPs also thought that providing a DAP can help manage patient expectations for antibiotics and avoid doctor-shopping, i.e. when patients visit several GPs for the same illness episode in order to obtain antibiotics.

> "Don't forget this is not a free clinic. People have to pay. I don't want to be seen that I'm abusing them by telling them to come back in two days' time for a prescription and charging them a second time." (GP M)

GPs either used a patient-led approach or a post-dated approach with a one to two day delay. Two GPs were sceptical towards a post-dated approach; they suspected that pharmacists would nonetheless dispense the antibiotic, rendering the method ineffective. One GP who preferred a patient-led approach requested that patients call for advice before buying the antibiotic. Another used post-dated prescriptions but collaborated closely with pharmacists in order to ensure that post-dated antibiotic prescriptions were not dispensed prematurely.

4.2.2 "The Uncertainty Avoider": reaching a compromise and providing treatment just in case

DAP was perceived as a way of solving the "wait-and-see" dilemma by being careful and playing it safe when GPs were uncertain whether an immediate antibiotic prescription was warranted but suspected that antibiotic treatment could be needed within the coming days. GPs considered this a good compromise; ensuring that patients have access to treatment should they deteriorate within a few days. Ensuring that the patient will recover and not suffer complications brought comfort to the GP.

> "I think it's a good compromise… If I have a case where I think it's not severe enough to warrant antibiotics… I will give them a prescription and tell them that they should start it if they develop fever or feel worse after 48 hours…" (GP H)

Only one GP post-dated DAPs, otherwise GPs used a patient-led approach. Of note, GPs often selectively provided DAPs to patients they knew and trusted. They would rather follow-up with patients they considered untrustworthy or who they did not know well. To overcome

this challenge, one GP requested that patients call back before purchasing the antibiotic, providing an opportunity to reassess the situation and provide guidance over the phone.

4.2.3 "The Comforter": providing the patient comfort and reassurance

Providing a DAP was perceived as a way of being considerate and understanding towards patients who are anxious and fear that their condition may worsen and require antibiotic therapy. Similar to the "Uncertainty Avoiders", GPs wanted to play it safe, however their rationale differed. GPs focused on being receptive towards patients' needs and empathising with them. Therefore they provided DAPs to provide the patient comfort and reassurance knowing that they would have a prescription to fall back on should they deteriorate.

> "If you tell them [patients] I'm not going to prescribe you antibiotics… they freak out literally. So, I found that giving them a delayed prescription puts their mind at rest… they don't need to come back again if these things happen." (GP S)

DAPs were only provided to patients GPs considered trustworthy, had a certain level of understanding, and/or were regular clients. In fact, GPs questioned whether delayed antibiotic prescribing is indeed best practice as they have no guarantee that patients will follow their advice. Trust was therefore a dominating decisive factor and GPs would rather ask patients who do not fulfil these criteria to follow-up in person than provide them with a DAP. Some GPs overcame this challenge by asking patients to call back for advice prior to purchasing the antibiotic. They also provided a thorough verbal explanation to the patient and a written note on the prescription to avoid the pharmacist dispensing the antibiotic prematurely.

4.2.4 "The Conscientious Practitioner": empowering and educating patients, and limiting antibiotic use

"Conscientious Practitioners" were very concerned about antibiotic overuse in Malta and recognised antibiotic resistance as a threat. They showed a deeper understanding of delayed antibiotic prescribing and were avid users of this strategy. The DAP was perceived as a useful tool for educating and empowering patients, providing an opportunity to teach and persuade them that antibiotics are not always necessary. It was also perceived as a way of practising safer medicine by limiting antibiotic use when not required. GPs also reflected upon the impact delayed antibiotic prescribing has on their own practice, how patients are positive towards the approach and the resulting long-term societal gains.

> "I think it's [delayed antibiotic prescription] a useful tool, it's a tool especially for educating people as I said, you know they realise that the child got better without the antibiotic… it also gives the… patient power that he can be in charge… I think it's very educational… it's a good tool." (GP B)

Similar to other GPs, GPs in this category selectively provided DAPs to patients they trusted and to those who had a certain level of knowledge and awareness. One private sector GP collaborated with pharmacists to ensure that DAPs are dispensed appropriately and stressed the importance of communicating with patients when providing a DAP by keeping in touch in order to guide them when to purchase the antibiotic.

4.2.5 "The Holder of Professional Power": retaining general practitioner responsibility by employing a wait-and-see approach

GPs with this perception were very sure of themselves regarding when antibiotics should be prescribed and relied heavily on their training and expertise to determine whether a patient needed antibiotics. As the medical professional, they were of the opinion that it was their responsibility to ensure optimal patient outcomes. Therefore, in their perception, antibiotic prescribing decisions should not be transferred onto the patient, making delayed antibiotic prescribing an unsafe practice. To them, it was more important and justified to re-evaluate the patient in person should symptoms persist or deteriorate after the first consultation.

> "I usually don't do it [delay a prescription]. I usually caution the patient and tell him, look here, if you get a temperature, if the condition gets worse, just call again. Just to make sure that it's really needed... I don't do it on purpose; I think it's justified… to revise the situation." (GP C)

Therefore GPs in this category did not practise delayed antibiotic prescribing and were not interested in utilising this strategy in the future. GPs shared the view that patients are generally non-compliant to treatment and still maintain that they will not get better without antibiotics. As a result, these GPs expressed that they would not trust patients to abide by their advice should they provide a DAP.

4.2.6 The outcome space

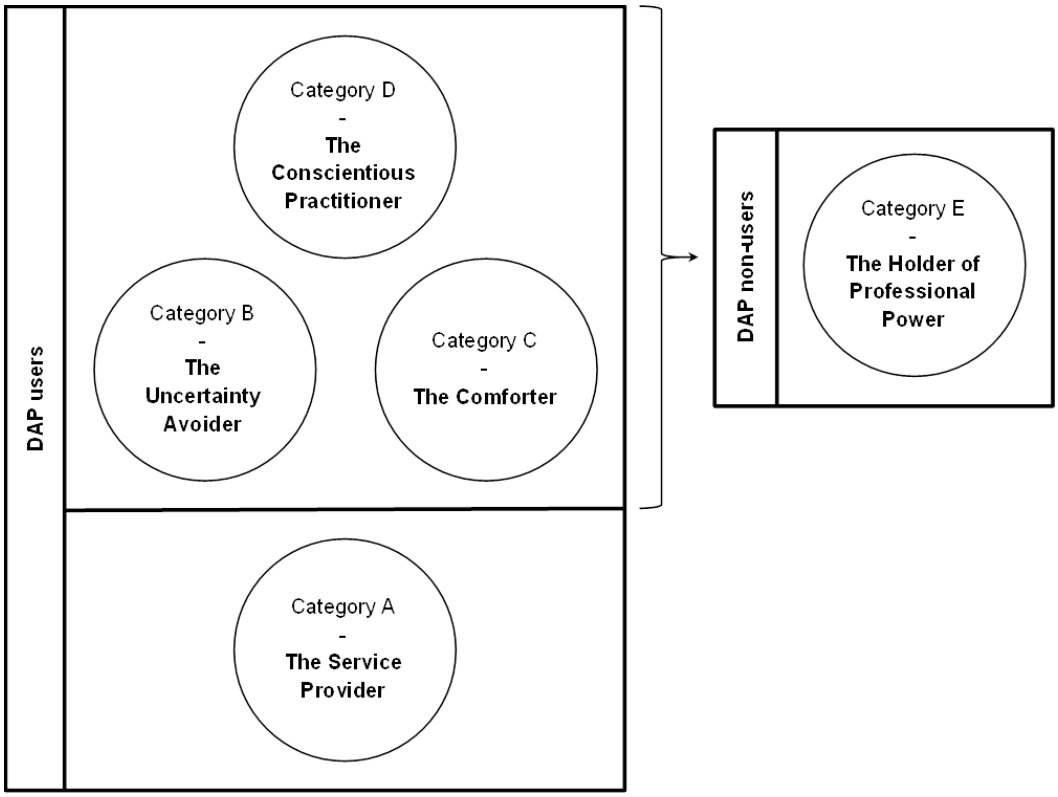

Figure 9. The outcome space

The outcome space (Figure 9) illustrates how each category of description relates to another and has been split into DAP users and non-users. "Holders of Professional Power", or non-users, were unwilling to share decision-making and used a wait-and-see strategy instead.

"Conscientious Practitioners", "Uncertainty Avoiders" and "Comforters" were selective DAP users. They used a wait-and-see approach whenever they considered a patient untrustworthy, unreliable, lacks certain levels of understanding and awareness, or perhaps they did not know the patient well-enough, reflecting similarities with the "Holders of Professional Power". "Conscientious Practitioners" possessed a deeper level of self-reflection and higher degree of awareness of DAP as a tool for decreasing antibiotic use. In contrast, "Services Providers" were non-selective DAP users whose focus was on ensuring patient satisfaction and maintaining a good GP-patient relationship, irrespective of who the patient is or his/her intentions.

4.3 BARRIERS AND FACILITATORS TO ANTIBIOTIC PRESCRIBING AND FACTORS THAT INFLUENCE GENERAL PRACTITIONERS' MANAGEMENT OF ACUTE RESPIRATORY TRACT COMPLAINTS

In Paper I, our findings revealed that GPs' antibiotic prescribing is impacted not only by their own knowledge, attitudes and awareness, but also by several external factors, including but not limited to patient demand and behaviour, information from drug reps, communication and collaboration with other healthcare professionals, availability of guidelines, access to diagnostic testing and ease of referral. It was evident that numerous barriers and facilitators influence GPs' antibiotic prescribing which led to the construction of one overarching theme, namely, *GPs' antibiotic prescribing decisions are complex and impacted by numerous barriers and facilitators at the intrapersonal, interpersonal, organisational, community and policy level*.

In Papers III and IV, through actual antibiotic prescribing data and following multivariable analysis, we were able to corroborate some of these findings through a better understanding of how GPs manage patients with aRTCs and identifying significant factors associated with antibiotic prescription. We were also able to identify other factors that were not raised in Paper I, including that female GPs were 2.3 times more likely to prescribe antibiotics (95% CI 1.22-4.26). Furthermore, compared to younger GPs aged between 28 and 39 years, GPs aged 50 to 59 (OR=2.1, 95% CI 1.19-3.77) or 60 years and older (OR=34.7, 95% CI 14.14-84.98) were more likely to prescribe antibiotics. Also, regular clients i.e. patients who tend to re-consult with the same GP, were 1.3 times more likely to receive an antibiotic prescription (95% CI 1.05-1.66).

In order to better illustrate and frame our findings, some of the factors identified to have an impact on GPs' antibiotic prescribing are depicted in a socioecological model (Figure 10). The findings are described in further detail below through the four sub-themes identified in Paper I with results from Papers III and IV incorporated where relevant.

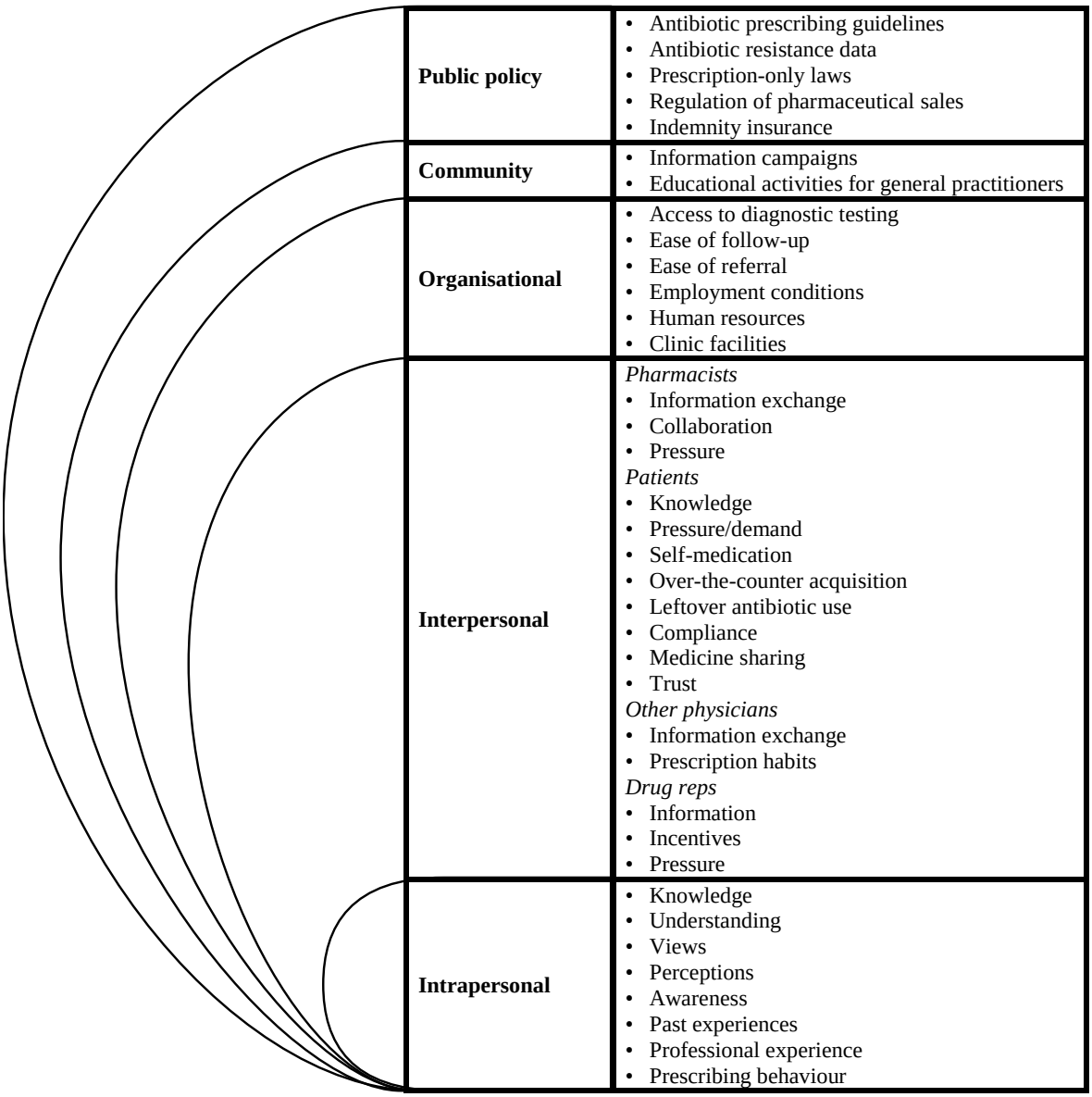

Figure 10. Overview of factors identified to have an impact on GPs' antibiotic prescribing at all levels of the socioecological model

4.3.1 General practitioners' knowledge, awareness, views and experiences, and the resulting management of respiratory tract infections (sub-theme I)

Whilst many GPs viewed antibiotics as important and precious tools that should be used appropriately and when recommended in guidelines, few of them seemed aware that effective antibiotic treatment options are running out. Even fewer acknowledged that antibiotics must be prescribed appropriately to halt the development of antibiotic resistance. However, most GPs were aware that antibiotic misuse accelerates antibiotic resistance and that consequently everybody is at fault – prescribers, pharmacists and the public.

Through increased awareness, many GPs felt that antibiotic use is improving in Malta. Nonetheless, many agreed that antibiotics are still misused, not just by prescribers but also by the general public who self-medicate through leftover use and over-the-counter acquisition of antibiotics, and are non-compliant to treatment. Although many GPs felt that over-the-counter

antibiotic dispensing has almost stopped, pharmacists were still blamed for contributing to the problem by dispensing antibiotics to patients without a prescription. Few GPs considered themselves high prescribers. However, many admitted to prescribing antibiotics without a focus of infection on occasion, particularly if in doubt or whenever they suspected that the patient may deteriorate. By doing so they safeguarded the patient and also themselves.

Many GPs felt that infections are becoming more serious and sometimes harder to treat, indicating that antibiotic resistance is on the rise in Malta. The rampant and repeated overuse and misuse of antibiotics, particularly for viral infections, and overuse of broad-spectrum antibiotics, were considered important contributing factors. Additionally, marketing of specific antibiotics by drug reps was also considered a driver. Nevertheless, few GPs felt that antibiotic resistance directly impacts their practice. In fact, several GPs reported achieving good patient outcomes when prescribing antibiotics; to them antibiotic resistance was not yet a cause for concern. Meanwhile, some GPs mentioned that they were forced to prescribe higher antibiotic doses and more broad-spectrum antibiotics as a result of antibiotic resistance.

Interestingly, although confirming whether non-response to antibiotic treatment was due to a viral infection or resistant pathogen was considered challenging by many GPs, several assumed that non-response was a result of an infection caused by a resistant pathogen. Consequently, GPs sometimes prescribed multiple antibiotic courses in an attempt to resolve an infection. Few GPs said that non-response to treatment could be the result of antibiotics being prescribed unnecessarily for a viral infection. GPs were more inclined to believe that even if an antibiotic was initially prescribed unnecessarily for a viral infection, subsequent non-response to treatment indicated progression to a secondary bacterial infection which would justify the prescription of another antibiotic.

> "It's very difficult to know whether an infection is resistant or whether they are non-responsive to treatment because they never needed antibiotics in the first place." (GP B, female public sector GP with 25 years' experience)

Indeed, most GPs believed that viral infections commonly progress to secondary bacterial infections and that the elderly are particularly vulnerable to this. Therefore, many GPs lowered their antibiotic prescribing threshold for such patients. In fact, in Paper IV we showed that increasing patient age increased the likelihood of receiving an antibiotic prescription, with patients over 64 years being the most likely (OR=2.3, 95% CI 1.71-3.18).

> "There is a tendency for old, frail patients with viral infections to get secondary bacterial infections… It would be indicated that it is a viral infection but being an old patient, prescribing an antibiotic won't do any harm." (GP A, male private sector GP with 30 years' experience)

Determining the aetiology of RTIs, particularly lower RTIs, was considered challenging by some GPs. Some considered the time since onset of infection to determine the aetiology of an infection. GPs typically waited between two to five days for a viral infection to resolve and if not, they would often review the patient to decide whether to prescribe an antibiotic for a suspected secondary bacterial infection.

GPs considered numerous other factors when deciding whether an RTI warrants an antibiotic prescription. According to GPs, they were more inclined to prescribe antibiotics to patients with high or intermittent fever, a sore throat with red and inflamed tonsils with pus, enlarged and tender lymph nodes, infected and tender sinuses, shortness of breath, crepitations, wheezing, productive and persistent cough, purulent/greenish phlegm, chest pain and generalised malaise. Results from Paper IV identified similar signs and symptoms that significantly increased the odds of a patient receiving an antibiotic prescription. More specifically, patients with tender cervical nodes (OR=2.2, 95% CI 1.57-3.05), fever >38.5^{o}C (OR=2.6, 95% CI 2.08-3.26), productive cough (OR=1.3, 95% CI 1.03-1.61) or otalgia (OR=1.3, 95% CI 1.01-1.76) were more likely to receive an antibiotic. In contrast, patients with a non-productive cough (OR=0.3, 95% CI 0.26-0.41), sore throat (OR=0.6, 95% CI 0.53-0.78), rhinorrhoea (OR=0.3, 95% CI 0.23-0.36) or dyspnoea (OR=0.6, 95% CI 0.41-0.83), were less likely to be prescribed antibiotics.

GPs also considered the patient's smoking status, occupation and co-morbidities. They believed that smokers are more susceptible to bacterial infections and were therefore more likely to prescribe antibiotics, particularly for suspected chest infections. In fact, smokers were 1.4 times more likely to receive an antibiotic (95% CI 1.13-1.71) [Paper IV]. As aforementioned, patient age was an important factor that GPs considered when determining whether an antibiotic prescription is warranted. Several GPs avoided antibiotics in children since to their knowledge they are more likely to contract viral infections. On the other hand, they were more likely to prescribe prophylactic antibiotics to the elderly, even if absent of signs that would indicate a bacterial infection, as they wanted to avoid complications. Indeed GPs mentioned that patients with multiple co-morbidities, such as impaired renal and/or liver function, diabetes, heart disease, chronic chest infections, emphysema, asthma or COPD, were more likely to require antibiotics early. According to some GPs, these patients typically deteriorate quicker and often develop more complications and even pneumonia.

> "My threshold for prescribing antibiotics is much lower in patients with asthma and COPD, the reason being that often when they get an infection it gets really bad, they get these infective exacerbations, and if you don't start treating immediately you'll end up with a very bad situation." (GP S, female public sector GP with 7 years' experience)

Finally, GPs mentioned that in order to improve patient compliance, they often adjusted their prescription to suit patients' needs and preferences. GPs typically tailored antibiotic therapy (if necessary even changing antibiotic class) if the patient mentioned having discomforting side effects in the past such as thrush, nausea/vomiting or diarrhoea. They also considered the flavour of the antibiotic (particularly in children), dosage form and regimen.

4.3.2 Finding the right balance: addressing patient behaviour, knowledge and awareness through education and information provision (sub-theme II)

According to some GPs, patient demand for antibiotics is decreasing in Malta. They attributed this to increasing awareness and more availability of information on the negative repercus-

sions of antibiotic overuse. In fact, in Paper III only 76 patients (2%) actively requested antibiotics. Nonetheless, GPs expressed that patients still expect and demand antibiotics and put pressure on them to prescribe. A few postulated that expectations and demand are aggravated by easy access to services, which can lead to premature and unnecessary antibiotic prescription. In fact, GPs reported that patients consult GPs upon onset of symptoms. Indeed most patients (n=3,397; 73.2%) consulted the GP within the first three symptomatic days [Paper III].

GPs reported that patients can sometimes exhibit aggressive attitudes towards them or return to blame them if they do not get better. They also threaten to consult other doctors who will give them what they want (doctor-shopping). Although most GPs expressed that they are largely unaffected by this behaviour, a few admitted that they do give in to patients on occasion, even if they know that antibiotics are unnecessary. Whilst some believed that doing this is harmless, others deliberately prescribed shorter antibiotic courses, narrow-spectrum antibiotics or gave DAPs, in an effort to reduce harm. In Paper III we showed that of the 76 patients who requested antibiotics, 51 (67%) were given an antibiotic prescription, either for immediate or delayed use. In fact, according to findings from Paper IV, these patients were 4.8 times more likely to be given an antibiotic prescription (95% CI 2.52-8.99).

> "Keeping your foot down is useless with people who keep insisting they want antibiotics. So I give them a very specific antibiotic, not broad-spectrum, so that I limit the damage as much as possible, and as short a course as possible with the lowest dose possible." (GP R, male private sector GP with 7 years' experience)

GPs felt that it is their responsibility to educate patients about the appropriate use of antibiotics, and that by doing so they can also address misconceptions and improve compliance, which they reckoned will have a positive impact on demand in the long run. Nonetheless, according to GPs some patients were impossible to persuade. GPs found certain concepts, such as how antibiotic resistance develops, hard to explain to patients, particularly those less educated. A few GPs felt that introducing educational tools in the clinic, like images and charts, that can be used to explain concepts, are necessary and would be appreciated.

4.3.3 Learning through interaction: the perceived importance of cooperation with other professionals (sub-theme III)

Many GPs felt that it is important to engage in discussion with other medical doctors, particularly when seeking advice. Whilst public sector GPs had such opportunities available to them, some private sector GPs felt isolated. Consequently, working closely with pharmacists was considered advantageous by several solo private practitioners who rented clinics within pharmacies. They used it to their advantage by discussing treatment plans and requesting advice when necessary. However, a few GPs mentioned that some pharmacists take advantage of this close professional relationship and make GPs feel obliged to prescribe medicines, despite not always being necessary.

GPs also interacted with drug reps rather frequently but had opposing views on them. Although most were largely positive towards them, several complained that they visited too of-

ten, which some regarded as a nuisance, mainly because they could make better use of their time consulting patients instead. However, to private GPs in particular, drug reps were viewed as important points of contact and a necessary educational resource, keeping them up-to-date with the latest medical advancements. Drug reps provided them with much desired information on new drugs on the market, new technologies, resistance patterns and recent recommendations. However, not all GPs agreed that the information provided to them is credible, reliable and scientifically sound. Some believed that it is biased, and some suspected that it is sometimes fabricated. The fact that their recommendations are based on foreign evidence and that drug reps claim that antibiotic resistance is on the rise and therefore antibiotic classes must be changed or doses increased, made them more cynical.

> "My views on medical reps in Malta are very mixed. On one hand they are a good source for information; if you have any problems with medications, they are a very good source of information and they are pharmacists too. But on the other hand we have no way of verifying whether some of the claims they make are true or false." (GP H, male private sector GP with 28 years' experience)

Not all GPs agreed that drug reps put pressure on them to prescribe antibiotics, and incentives were mostly mentioned as something that occurred in the past. Regardless, the majority of GPs insisted that they were uninfluenced by pressure from drug reps. A few disagreed, saying that regardless how hard one may try to remain uninfluenced by them, one's antibiotic prescribing choices are inevitably influenced by them.

4.3.4 Organisation and delivery of primary healthcare services in Malta, and the impact of public policy, regulation and guidelines on general practitioners' antibiotic prescribing (sub-theme IV)

Access to community antibiotic prescribing guidelines and data on local antibiotic resistance rates varied among GPs. Public sector GPs said that guidelines can be found online but few private sector GPs were aware of this resource. Only two GPs actively looked up guidelines on occasion, whilst others only referred to guidelines as a last resort. However, many GPs thought that it is important to use guidelines to help support diagnoses and treatment, particularly in complicated cases. To a few others, guidelines created more of a burden. A small number of GPs, particularly more experienced ones, valued experience more than guidelines.

> "Often when you reach my age, guidelines just make you laugh. If you want a frank and honest answer, I do not abide by guidelines. Sometimes they are stupid." (GP I, male private sector GP with 39 years' experience)

GPs also felt that current data on antibiotic resistance rates are irrelevant to the Maltese community setting since they are based on in-patient data, and that antibiotic prescribing guidelines are not up-to-date or based on local evidence. This made GPs rather sceptical about their applicability in Maltese primary care and many wished for more relevant antibiotic prescribing guidelines. Several GPs believed that the lack of antibiotic resistance data and local guidelines to help inform prescribing decisions, leads to more cautious but sometimes more aggressive antibiotic prescription strategies. This, according to some GPs, was aggravated by the introduction of compulsory professional indemnity insurance in 2014.

One GP insisted that antibiotics are not abused in Malta but rather overprescribed unintentionally since GPs are forced to prescribe blindly, without knowledge of what antibiotic to prescribe and the recommended dose. Consequently, GPs tend to play it safe, opting for the "usual" antibiotic, i.e. one they know is safe and effective, and provides good results.

> "We do not have any information on the current levels of antibiotic resistance in Malta… so we have to assume that whatever we're prescribing is appropriate for the current levels of resistance both in terms of the medication and dose. We have no clue, no information at our fingertips, about minimum inhibitory concentrations or which antibiotics are effective for what we're dealing with. So we sometimes have to make decisions which may not be appropriate." (GP H, male private sector GP with 28 years' experience)

Despite the lack of guidelines and uncertainty in antibiotic choices, GPs said that they seldom use diagnostic tests such as X-rays, C-reactive protein tests, throat swabs or sputum cultures, to help support their decisions, unless they considered the patient seriously ill. GPs in the public sector seemed more likely to use such services as they are more readily available to them. Usually however, many GPs prescribed antibiotics empirically first, occasionally prescribing a second antibiotic if the first antibiotic does not successfully resolve the infection. This was later corroborated in our surveillance study [Paper III] where diagnostic tests were indeed rarely performed (n=133; 2.9%).

> "We prescribe antibiotics without carrying out bacteriological tests so we use our clinical judgement to try form an idea of what the underlying bacteriology is and treat it accordingly with the best antibiotic to match the infection." (GP J, male private sector GP with 41 years' experience)

Very few GPs were familiar with rapid point-of-care tests (POCTs) for RTIs, and according to most they are unavailable in Malta. Consequently, almost all GPs had never used or considered using them. Only one GP used rapid strep tests regularly and intended to invest more in them to reduce antibiotic use. To him, rapid POCTs were good educational tools that allow patients to better understand their condition and treatment plan. Several GPs were positive towards introducing rapid POCTs in general practice. They believed that rapid POCTs could help guide antibiotic prescription, particularly when the aetiology is unclear, and consequently decrease antibiotic overuse. Some also felt that they could help negotiate a care plan with the patient. Others asserted that even if introduced, they were unlikely to use them. To them, their own clinical assessment and experience was sufficient to make a correct diagnosis.

> "I would use diagnostic tests if they were available. They would absolutely be very helpful. You can make your case for antibiotics. You can explain to patients that the results are positive which means you have a bacterial infection and what they need. It can be used to persuade the patient rather than basing it just on my clinical impression." (GP M, male public and private sector GP with 23 years' experience)

The main barriers to diagnostic testing (both rapid POCTs and other diagnostic tests) were time and lack of access. Whilst certain diagnostic facilities are readily available to GPs working in the public sector, private sector GPs must refer patients for most services. They considered this time-consuming and burdensome, particularly since it takes times for results to be issued. Occasionally they do not receive the results at all. GPs would therefore rather pre-

scribe antibiotics without knowing whether they are truly warranted, than wait and risk that in the meantime the patient develops complications. Another deterrent to diagnostic testing was cost. In private practice, where patients pay for services out-of-pocket, a few GPs said that it is illogical to charge for testing if the resulting cost is more than the consultation and an antibiotic prescription combined. They suspected that if they charge for such services, that they would lose patients to other GPs.

> "Near patient testing is an excellent idea but it takes time. I've tried it but it takes time. We do not have the luxury of having staff who can do it so we have to charge for our time. Although it is a good idea and although I have tried to integrate it, some take more time than others. It's not practical." (GP H, male private sector GP with 28 years' experience)

GPs encountered similar problems with feedback among the primary, secondary and tertiary sectors when referring patients, not just for diagnostic testing, but also other services. According to GPs, the lack of IT infrastructure resulted in poor feedback from specialists and hospitals regarding referred cases, causing time delays and impacting continuity-of-care.

5 DISCUSSION

Our studies have, for the first time, shed light on GPs' understanding of antibiotic use and resistance in Malta as well as their actual prescribing practices for aRTCs. We also further identified key barriers and facilitators that can be addressed when implementing strategies to contain antibiotic resistance and promote better antibiotic use in Malta. This is the one of the first crucial steps in SM; gaining a good understanding of one's target audience (also known as customer or consumer orientation) and the competition, i.e. barriers that discourage the adoption of preferred behaviours.[111]

5.1 GENERAL PRACTITIONERS' VIEWS ON ANTIBIOTICS AND ANTIBIOTIC RESISTANCE

Many GPs' were aware that antibiotic misuse promotes resistance, and that it is therefore important to use antibiotics appropriately. They believed that everyone (prescribers, the public and pharmacists alike) must take responsibility for the problem. Whilst they felt that awareness among all stakeholders is increasing, they nonetheless felt that self-medication, non-compliance to treatment, leftover antibiotic use and over-the-counter dispensing remain a problem. According to reports however, over-the-counter dispensing is low in Malta, and most people rather acquire their prescription through a medical professional.[32,116] Unfortunately, there are currently only a few authorised leftover medication disposal sites in Malta,[62] which could explain why leftover antibiotic use and self-medication remain a problem. Moreover, antibiotic packs sometimes contain more antibiotic doses than necessary. Since it is illegal to split packs, patients may end up with leftover antibiotics at home, with few places to dispose of them safely, which further promotes the misuse of leftover antibiotics.[62]

Antibiotic resistance was considered an increasingly important problem. However, similar to views shared by GPs in other studies,[138,139] few felt that it directly impacts their day-to-day practice. Consequently, some did not consider antibiotic resistance to be a cause for concern in Malta as of yet. Those who did believe that antibiotic resistance is getting worse locally attributed it to the repeated overuse and misuse of antibiotics, particularly broad-spectrum, and promotion of specific antibiotic classes by drug reps.

It is important to be mindful that GPs' heightened awareness on antibiotic resistance may have a negative impact on their antibiotic prescribing behaviour. It could lead GPs to practise more cautious prescribing behaviour such as using broad-spectrum antibiotics more freely.[139] It could also lead to more aggressive antibiotic prescription. In fact, a few GPs said that they sometimes provided combination antibiotic therapy to minimise the risk of promoting antibiotic resistance. Others attributed non-response to treatment to antibiotic resistance and consequently prescribed multiple antibiotic courses on occasion.

5.2 ANTIBIOTIC PRESCRIBING PATTERNS

5.2.1 Prescription of broad-spectrum antibiotics

In Paper III it was shown that 45.7% of aRTC cases were given an antibiotic prescription by a GP, closely reflecting the findings of the 2016 Eurobarometer report where 48% of Maltese participants reported taking an antibiotic during the past 12 months.[107] At the time, this was the highest reported antibiotic consumption rate in the EU/EAA, and although it has since decreased to 42%,[32] it remains high. A comparable antibiotic prescription rate of 46.8% was reported in (southern) Italy,[140] a Mediterranean country with similar sociocultural traits.[26]

Earlier reports have shown that prescription of narrow-spectrum antibiotics is negligible in Malta,[37,62,64] dissimilar to Sweden for example, where narrow-spectrum penicillins are the most frequently prescribed antibiotics in outpatient care.[141] Unsurprisingly, broad-spectrum antibiotic use was extremely high in our study [Paper III] at 99.6% and is similar to other southern European countries such as Spain and Greece.[142,143] According to the latest ECDC report on antimicrobial consumption,[37] Malta has had the highest ratio of broad- to narrow-spectrum antibiotic use in the EU/EAA for the past decade and it remains high at 24.0 (EU/EAA average = 2.9). In our study we observed an even higher ratio of 33.2. The fact that our data were limited to aRTC cases only, could explain this difference and suggests that aRTCs contribute greatly to the prescription of broad-spectrum antibiotics in Malta. Since broad-spectrum antibiotic use favours the development of antibiotic resistance,[25,64] their widespread use is of great concern.

Penicillins with β-lactamase inhibitors, 2nd-generation cephalosporins, broad-spectrum macrolides and fluoroquinolones, made up 90% of all antibiotics prescribed [Paper III]. These antibiotics are major drivers of resistance.[64] Previous reports have shown that broad-spectrum penicillins with β-lactamase inhibitors are the most commonly prescribed antibiotic in Malta.[37,49,64] In our study [Paper III] however, GPs showed a preference towards macrolides, similar to prescribers in Greece and the United States.[143,144] This finding raises concerns since the rates of *Streptococcus pneumoniae* invasive isolates resistant to macrolides are rather high in southern European countries like Malta.[38] Another concern is the increasing rates of *Escherichia coli* resistant to fluoroquinolones in Malta. Consequently, efforts need to be made to decrease the prescription of broad-spectrum antibiotics for respiratory pathogens, particularly macrolides and fluoroquinolones.

5.2.2 Factors associated with antibiotic prescription

5.2.2.1 General practitioners' age and years of practice

Older GPs were more likely to prescribe antibiotics [Paper IV]. Age reflects GPs' years of experience and it has similarly been shown that GPs with more years of practice are more likely to provide antibiotic prescriptions.[145] As aforementioned, family medicine was not recognised as a medical specialisation in Malta until 2004, after which doctors were obliged to undergo specialist training in family medicine. However, those doctors who practised as GPs

prior to November 2003 were exempt from specialist training.[115] Consequently, the fact that younger GPs had recently undergone specialist training could explain why they were lower antibiotic prescribers than their older, more experienced, peers. It is likely that older GPs engage in habitual prescribing behaviour and may require updated access to the latest antibiotic prescription guidelines as well as opportunities to participate in refresher courses on the topic.

5.2.2.2 Patient and clinical factors

Verbal reports from GPs [Paper I] as well as their actual prescribing behaviour [Paper IV] indicate that GPs in Malta are more likely to prescribe antibiotics to the elderly, and less likely to prescribe to children. This is consistent with similar studies where antibiotic treatment increased with patient age.[146–150] Interestingly, in England/Wales and Sweden, antibiotic treatment rates were high among both the elderly and children,[151,152] whilst in Norway, patients aged over 80 years were the least likely to receive an antibiotic prescription.[153] The prescribing behaviour of Maltese GPs reflects their beliefs that children are often afflicted by viral infections, and that the elderly are more susceptible to secondary bacterial infections and to deteriorate quicker as a result of complications. The elderly are also more likely to suffer from multiple co-morbidities like impaired renal and/or liver function, diabetes, heart disease, chronic chest infections, emphysema, asthma or COPD, which according to GPs, would lower their antibiotic prescribing threshold [Paper I], although this association was not found in Paper IV.

Being a current smoker has also been found to be associated with antibiotic prescription,[154–156] similar to our findings. Although there is no evidence that antibiotics confer better clinical outcomes in smokers,[155] GPs still believed that smokers are more likely to deteriorate without antibiotics [Paper I] and were in fact more likely to prescribe them [Paper IV].

A multi-country European study showed that GPs do not only consider risk factors like co-morbidities and age, but also signs and symptoms that they believe warrant an antibiotic prescription.[157] Indeed studies have shown that GPs consider a wide range of clinical factors when deciding whether to prescribe an antibiotic.[29] This is also evident in Papers I and IV. GPs in Paper I mentioned that they were more likely to prescribe antibiotics to patients with a number of different signs and/or symptoms, including enlarged and tender lymph nodes, fever, productive cough and sore throat with red, swollen tonsils and pus. In fact, in Study IV a number of similar factors that were independent predictors of antibiotic prescribing were identified. It is likely that GPs believe that these factors suggest a bacterial infection, or are an early warning sign of more severe illness which could explain why their antibiotic prescribing threshold decreases.

5.2.3 Diagnosis-specific antibiotic prescription

The most common indications that led GPs to prescribe antibiotics were acute tonsillitis, otitis media, bronchitis and sinusitis [Paper III], similar to Belgian prescribers.[158] More specifically, over 65% of patients with these diagnoses were prescribed antibiotics. In fact, GPs disclosed that they were more likely to prescribe antibiotics to patients with tonsillar infections,

otitis media, bronchitis and sinusitis, but also with pneumonia and pharyngitis [Paper I]. Similar research carried out in Spain and Sweden also found comparably high antibiotic prescription rates for tonsillitis, otitis media and sinusitis, however lower rates for bronchitis.[142,158] There is however limited evidence to justify antibiotic prescription for uncomplicated acute bronchitis and sinusitis.[159–161] Despite this, acute bronchitis in adults is one of the most common causes of inappropriate antibiotic prescribing.[162]

Notably, GPs not only reported a high variation in choice of antibiotic class by diagnosis but also suspected aetiology (by diagnosis) [Paper III]. Although many GPs believed that approximately 70-90% of upper RTIs are viral [Paper I], their behaviour suggests that GPs overestimate the degree to which certain RTIs are bacterial. Indeed, determining the aetiology of RTIs was considered challenging by many GPs [Paper I].

5.3 DIAGNOSTIC UNCERTAINTY

Diagnostic uncertainty was a major drawback to appropriate antibiotic prescription according to GPs [Paper I], and has often been reported to be a barrier,[163] correlated with antibiotic misuse and overuse.[26,30,46] The inability to determine the aetiology of infections due to lack of access to testing, relevant reports and guidelines, was an important issue raised by GPs and could partly explain their antibiotic prescribing behaviour observed in Papers III and IV, and their attitudes towards antibiotics. In fact, GPs often expressed [Paper I] that they found it hard to differentiate between viral and bacterial infections. As a result, they sometimes prescribed antibiotics "just in case" out of fear of negative repercussions, including patient complications and legal consequences, despite there being no added benefit of prescribing antibiotics prophylactically in viral infections.[164]

Several GPs also believed that non-response to antibiotic treatment is the result of an antibiotic-resistant infection or secondary bacterial infection. To many, viral infections commonly progress to secondary bacterial infections. Although possible for viral infections to progress to secondary bacterial infections,[165] given GPs' antibiotic prescribing patterns, it appears to be over-estimated, particularly since patients tend to consult GPs upon onset of symptoms, often within the first three symptomatic days [Paper III]. Moreover, GPs reported typically waiting at most five days before following up patients [Papers I & II] or considering the infection a secondary bacterial infection [Paper I]. However most uncomplicated viral RTIs last between five and seven days and peak in severity between days three and six.[166] In addition, for some self-limiting RTIs like bronchitis and sinusitis, it can take around three weeks (sometimes longer) for symptoms to resolve on their own,[161] therefore providing antibiotics this early is likely premature and risks that patients consume antibiotics unnecessarily.

GPs' beliefs, coupled with their antibiotic prescribing behaviour, seems to reflect their diagnostic uncertainty, with an antibiotic prescription reassuring GPs that should the infection aggravate, the patient is already being treated. The lack of current and relevant local antibiotic guidelines and data on antibiotic resistance rates in the community augmented their diagnostic uncertainty and was considered a serious barrier to appropriate prescription. In addition,

GPs were sceptical of the fact that recommendations are based on foreign evidence, which they considered irrelevant. There is therefore a critical need to establish community surveillance systems for antibiotic prescribing and to collect antibiotic resistance data from the community. This data must be disseminated to all GPs in a timely fashion to address this imminent need. Indeed, surveillance is one of the pillars of antibiotic resistance containment[1,4,21] and demands urgent attention in this context. Moreover, in cultures like Malta where diagnostic uncertainty is a dominant cultural trait (according to Hofstede's model of cultural dimensions Malta's uncertainty avoidance score is the second highest in Europe[44]), GPs may benefit from strategies that help alleviate uncertainty such as delayed antibiotic prescribing or decision-support tools like rapid POCTs. Formalising their use in Malta could help reduce unnecessary antibiotic prescription.

5.3.1 Delayed antibiotic prescribing

Delayed antibiotic prescribing is a strategy that has been shown to reduce antibiotic use for RTIs by 45-80%, with no major differences in re-consultation rates or significant negative repercussions on patients.[167–175] In spite of its potential, GPs' perceptions regarding the use of this strategy in practice varied greatly [Paper II]. Practical implementation varied too, with a patient-led approach being preferred by many GPs.

Using DAP strategies to address uncertainty was a dominating perception primarily described by "Uncertainty Avoiders" but also by "Comforters". Whilst to "Comforters" DAPs were a means of reassuring and comforting patients in uncertain situations, to "Uncertainty Avoiders", DAP was perceived as a strategy that guarantees that patients have antibiotic treatment available to them should their condition worsen. Other studies have also shown that GPs not only use DAPs to provide patients or caregivers reassurance and comfort, but also to provide reassurance to themselves.[96,176–178] It can also be considered a safety net or precautionary measure in situations that do not warrant immediate antibiotic use. Remarkably, studies from the UK and Norway also found that DAPs are provided to manage diagnostic uncertainty,[96,169,176,179] despite being cultures with comparably lower uncertainty avoidance scores than Malta.[30] The UK however has comparably lower antibiotic consumption and prescription rates for colds, flu and sore throat than Malta.[32]

Apart from DAP potentially being a useful tool to reduce unnecessary prescribing in countries with high uncertainty avoidance scores, DAPs are provided for other reasons too, as described earlier, and these varying perceptions must be considered if standardising the implementation of DAP in Malta. Studies have shown that doctors prescribe DAPs to safeguard patient relationships, although motivations vary.[96,177,180] For several GPs in Paper II ("Service Providers"), DAP was perceived as a means of ensuring a good GP-patient relationship, ensuring satisfaction and therefore keeping patients in the practice. This was more relevant for private sector GPs who expressed concern that dissatisfied patients may visit another GP should their expectations not be met. This could affect their income in the long run. Norwegian, UK and New Zealander GPs reported similar concerns, sometimes proving DAPs even when not medically indicated[96,97] to prevent patients from visiting another GP.[177] There is

conflicting evidence as to whether DAP impacts patient satisfaction. Several randomised trials have found no significant difference in patient satisfaction among various prescription groups.[167,168,174] Other studies have shown lower satisfaction rates among patients given a DAP than those given immediate antibiotics.[170,171,175] Conversely, in Norway, 89% of patients who received a DAP stated that they would appreciate receiving another in the future.[97] The impact of DAP on patient satisfaction in Malta has yet to be explored.

"Conscientious Practitioners" considered delayed antibiotic prescribing a means of empowering patients to make their own decisions and educating patients, as has been shown elsewhere.[96,97,177,178] They also recognised that DAPs can help reduce antibiotic use. Both Norwegian and Danish GPs stressed that DAP promotes shared decision-making, providing them with an educational opportunity.[97,178] It was also perceived as a good strategy to reduce antibiotic use by both Danish and New Zealander GPs.[177,178] Notably, UK prescribers expressed concern that DAP can potentially deliver contradictory messages to patients regarding when antibiotics should be used.[96,179] Indeed, British patients have reported receiving conflicting messages; being issued DAPs after having been informed that their infection was viral.[94] Arguably, since patients consult early in Malta, combined with the fact that GPs typically provide DAPs with just a one to three day delay, DAPs might actually provide contradictory messages and patients might incorrectly presume that antibiotics are warranted despite most likely suffering from a viral infection.[94,96] However, studies have shown that patients given a DAP are less likely to believe that antibiotics are beneficial for their given condition and exhibit lower intent of re-visiting a practitioner for the same infection in the future.[167,168,170,172,174] These important findings stress the importance of providing DAPs under the right circumstances and with a clear rationale, explanation and structured advice.

Finally it is important to consider that some GPs ("Holders of Professional Power") disagreed with DAP because to them, it is the GPs' responsibility to decide when antibiotics should be taken, not the patient's, which is why they considered DAP unsafe. Similarly, several studies found that prescribers deem it safer practice to follow-up the patient in person, and are also unwilling to include patients in the treatment decision.[96,178–180] This approach is congruent with cultures that score high in power distance; another Hofstede cultural dimension. In such cultures, the GP is considered the expert and may therefore hesitate to relinquish their expert power. Additionally, patients in such contexts expect to be told what to do therefore any hesitancy from the side of the expert may be perceived as a lack of confidence.[30] Consequently, by giving a DAP, GPs may be perceived by patients as indecisive, possibly explaining why they might avoid this strategy altogether. These prescribers are less likely to adopt DAP strategies, and may require a more targeted approach to address their key concerns.

5.3.2 Rapid point-of-care tests

Rapid POCTs may also contribute to reducing antibiotic use in Malta. Rapid POCTs provide fast results that can guide clinical management[181] and have been shown to decrease antibiotic use.[182] If used correctly they have the potential of facilitating diagnostic certainty, therefore

eliminating the need for an antibiotic prescription, including a delayed one. To-date, use of rapid POCTs in Malta is almost non-existent, primarily due to lack of access to such tests.

Although point-of-care C-reactive protein testing can lead to reductions in antibiotic prescription, as shown in a study carried out in Swedish and Norwegian primary care practices,[183] it does not guarantee appropriate prescription practices. Indeed, in Spain it was shown that despite negative rapid antigen detection tests for acute pharyngitis, antibiotics were still prescribed in more than 30% of cases.[182] Not surprisingly, this country exhibits rather high uncertainty avoidance scores. Conversely, another study carried out in Sweden showed that rapid POCTs are sometimes used excessively to avoid uncertainty, at the expense of guidelines.[184] Therefore rapid POCTs should be used appropriately and under justified circumstances according to established guidelines such as the Centor criteria.

Rapid POCTs can also provide GPs with better negotiating power particularly with persistent patients, as highlighted by GPs in Paper I and previous research.[185] In a Spanish study, access to POCTs was associated with an 18.9% lower antibiotic prescription rate among patients who request antibiotics.[186] Since rapid POCTs can help reduce uncertainty and support GPs' decisions not to prescribe antibiotics, this lessens the risk that they succumb to patient demands.[186,187] However, GPs expressed that integrating rapid POCTs into practice is impeded by time constraints, added costs, lack of resources and possible hesitancy from patients. Consequently, despite generally having a positive outlook towards rapid POCTs, some GPs insisted on relying on their clinical assessment and diagnosis. They believed that rapid POCTs would have little impact on their prescribing, as has been reported elsewhere.[185] Nonetheless, the introduction of rapid POCTs for RTIs in Malta should be considered, particularly since almost all patients with suspected tonsillitis received an antibiotic prescription. Their implementation will however need to address barriers to adoption in order to successfully roll-out such a strategy on a national level. Their introduction must avoid introducing new elements of uncertainty and be combined with training and support to encourage acceptance. Similarly, patients should be informed about the possibility of low-cost POCTs to avoid unnecessary antibiotic use, thereby safeguarding themselves and their future. Given GPs' concerns that rapid POCTs could burden patients financially, it is important to gain a better understanding of patients' views on rapid POCTs and further identify any other barriers to their uptake.

5.4 PATIENT DEMAND AND EXPECTATIONS

Another important aspect of antibiotic prescription is the impact of patient demand and expectations on GPs. It is reported that GPs experience and are impacted by actual and perceived patient pressure to prescribe antibiotics and that this could lead to unnecessary antibiotic prescription, particularly when they do not succeed at persuading patients otherwise.[35,36,46,163,188–191] GPs expressed that, although improving, they still experienced patient demand for antibiotics [Paper I]. According to some, patients expect antibiotics for a "quick fix", as has been found elsewhere.[163] However, our surveillance data revealed that patient demand is low and suggests that it may be overestimated by GPs. It is nonetheless important to address its impact on antibiotic prescribing as GPs were more likely to prescribe antibiotics

to patients who requested them [Paper IV]. In fact, a few GPs admitted to succumbing to the pressure of patient demand after failing to convince them otherwise. According to them, some patients are impossible to persuade and lack the necessary knowledge to understand when antibiotics are necessary. Indeed, lack of knowledge may lead to higher demand for antibiotics when they are not needed. Unfortunately, the general public's knowledge and awareness on appropriate antibiotic use remains low and is currently lower than other EU countries.[32] Shifting the public's mentality and improving knowledge will take time but must be drastically improved.

GPs also reported that patients express dissatisfaction if they do not get their way and sometimes threaten to consult elsewhere which could mean losing a patient to another GP. Similar concerns have been reported elsewhere.[36] One must consider that when patients pay for their visit out-of-pocket, GPs may feel more pressure to prescribe antibiotics to avoid losing clients, avoid reconsultation and/or ensure patient satisfaction.[192] However, contrary to some beliefs, providing an antibiotic prescription does not necessarily guarantee satisfaction. While some studies have shown that prescribing an antibiotic to such patients leads to better overall patient satisfaction,[189,193] others have indicated that a proper examination and receiving information (without antibiotics) leads to higher satisfaction.[194–197] This would explain why communication is sometimes considered more important by patients than a prescription.[198]

Consequently, whilst it is important to understand why patients expect antibiotics in Malta and what determines their satisfaction, GPs need to consider alternative strategies to ensure patient satisfaction without providing an unnecessary antibiotic, especially since receiving an antibiotic, particularly when expected, reinforces patients' desire for an antibiotic prescription and their belief that they should re-visit a GP for a similar problem.[199] Whilst national campaigns are important to address the public's knowledge and misconceptions, GPs are ideal educational vessels. They are often the first point of contact, providing a great opportunity to inform patients on appropriate antibiotic use. Importantly, GPs took pride in educating patients. However, certain concepts were considered hard to explain without educational resources. Communication skills training that teaches GPs the necessary skills to address patient concerns and expectations without compromising the GP-patient relationship, together with educational tools that facilitate decision-making and empower doctors to decline antibiotic requests, could be effective.[200]

5.5 INTERACTION WITH DRUG REPS

It is not uncommon for GPs' to encounter drug reps who effectively provide one-to-one information during regular outreach visits.[201–203] They also use other strategies to promote their products, such as information via postal mail, incentives and sponsored educational events.[203] GPs mentioned that drug reps use similar tactics in Malta [Paper I] and whilst some appreciated the informative and educational aspect of it, as seen in other studies,[204] others received them with scepticism. Some GPs were particularly hesitant to believe that all the information provided to them is true. However, as shown in other studies,[204] GPs rarely felt that drug reps directly impacted their prescribing. Yet exposure to information from pharmaceutical compa-

nies has been shown to have negative repercussions on the quality and quantity of GPs' antibiotic prescribing.[202,203,205,206] Indeed, as GPs themselves mentioned, they may be more inclined to favour a particular company's drugs, and prescribe them irrationally.[204] So far we lack evidence that continued exposure to promotional activities by pharmaceutical companies improves antibiotic prescribing, therefore it cannot be recommended.[203] Restricting the promotion of antibiotics through new legislations should be considered.

5.6 METHODOLOGICAL CONSIDERATIONS

In order to achieve a better understanding of GPs' views on antibiotic prescribing, their antibiotic prescription patterns as well as factors that drive their prescribing behaviour, a mixed methods approach was employed. Mixed methods research is particularly powerful when addressing complex, multifaceted issues, which is often the case in health services interventions.[207] By using this approach we were able to harness the strengths and offset the weaknesses of both quantitative and qualitative methodologies, in order to more comprehensively address our research questions. It also gave us the opportunity to triangulate our data (methodological triangulation) to corroborate our findings, thus strengthening their validity.[208,209]

We specifically used an exploratory sequential approach, meaning that our initial qualitative studies were used to inform the subsequent quantitative surveillance study and its analysis, as well as the intervention, enabling us to tailor it according to the needs identified in the preceding phase. Our results helped elucidate the quality and drivers of antibiotic prescribing and identify critical areas in need of improvement. Outlined below are some of the methodological issues considered in the studies included in this thesis. For ease of understanding, they have been broken down into three parts; general considerations for all papers, and specific considerations for the qualitative and quantitative research methodologies used.

5.6.1 General methodological considerations [Papers I-IV]

5.6.1.1 Self-selection bias

Despite the fact that GPs exhibited variation across factors of interest, the samples may not be representative of all GPs. Since GPs participated voluntarily, it is likely that they were more interested in the research topic and may therefore differ from non-participating GPs. However, diverse views on and experiences with antibiotic prescription were nonetheless captured. Additionally, despite that GPs may have had more interest in the research area, their antibiotic prescribing rates still exceeded recommendations which calls into question what the antibiotic prescribing patterns for aRTCs are like among non-participants.

5.6.1.2 Social desirability bias and the Hawthorne effect

When research subjects are conscious of the fact that they are being observed, they may adjust their responses to be viewed more positively by others. It is possible that GPs provided more socially-desirable answers or refrained from disclosing sensitive information during the interview. In an attempt to avoid this, the interviewer made sure to create a comfortable and safe environment for the GPs. The interviewer also asked open-ended questions with appro-

priate prompts to give GPs the space they need to open up and elaborate about their personal experiences and practices.

During the surveillance study, it is possible that GPs adjusted their diagnoses according to their intention to treat with antibiotics. Modifying behaviour when being held under observation is known as the Hawthorne effect.[210] Moreover, since audit and feedback is a behaviour change intervention in itself and since GPs were issued three-monthly feedback reports, this may have influenced their prescribing practices.[133] However, prescribers were never directly observed and the study took place over an extended time which should have allowed prescribers to resume their habitual behaviour. In fact, no evidence was found that GPs' prescribing patterns changed during the study period as a result of the reports.

5.6.1.3 Generalisability (external validity) and transferability

In order to facilitate readers to transfer our findings to other contexts, a thick description of the study settings, data collection procedures, participants and data analysis methods used was provided. Therefore, although our findings are context-specific, they remain relevant and the methods used could be transferred and adapted in other contexts with similar characteristics, particularly Mediterranean countries that share similar sociocultural traits as Malta.

5.6.2 Qualitative research: specific considerations [Papers I & II]

To attain a richer and more in-depth understanding of GPs' views on and experiences with antibiotic prescription, and to delve deeper into contextual issues that impact their behaviour, a qualitative research approach was considered most effective. It is customary in qualitative research to use small, non-probability samples. To achieve variation in background factors, we used a stratified non-probability sample technique called quota sampling. This strategy accounts for sizes and proportions of sub-samples, with sub-groups ultimately reflecting corresponding proportions in the actual population.[211] It permitted us to better illustrate the variation in the way antibiotic prescribing was perceived and experienced in our study setting.

In order to produce good-quality qualitative research, researchers seek to ensure trustworthiness of their findings by following certain criteria, namely: credibility, transferability (discussed above), dependability, confirmability and reflexivity.[212,213] Described below are a few other measures taken to ensure trustworthiness.

5.6.2.1 Credibility

Credibility corresponds to internal validity in quantitative research and different strategies can be used to ensure it depending on one's study design.[212] To increase confidence in the truth of our research findings, we used investigator triangulation. Whilst two researchers independently coded and analysed the data, results were later discussed among all co-authors, who came from different professional and cultural backgrounds. Incorporating the multiple perspectives of various co-authors is important to strengthen one's findings and ensure correct interpretation of the interviewees' views.

5.6.2.2 Reflexivity

The interviewer did not have any previous relationship with any of the interviewees and ensured to ask open-ended, objective questions with appropriate prompts so as to avoid directing GPs' responses. The research team also strove to bracket any preconceptions that might influence the interpretation of results, whilst concurrently allowing their pre-understanding of the research topic and context to facilitate deeper understanding of the findings.

5.6.3 Quantitative research: specific considerations [Papers III & IV]

Community antibiotic prescribing data from southern European countries is lacking, particularly diagnosis-specific data. Furthermore, knowledge on the drivers of antibiotic prescribing in southern European countries with high antibiotic consumption rates is also limited. This repeated, cross-sectional surveillance study was the first of its kind in Malta, and provided insight into diagnosis-specific treatment and factors that influence it, which is a major strength of this study. The study's design posed two major limitations however. Firstly, since the surveillance weeks were static, GPs were occasionally unable to report data during the allocated week. Secondly, it was impossible to trace whether patients eventually purchased the antibiotic and whether they were compliant to treatment. Described below are measures taken to improve the study's validity and reliability, and assure data quality.

5.6.3.1 Validity, reliability and measurement error

To ensure the validity (i.e. accurate measurement of the problem)[214] of the research instrument, the data collection tool was developed based on previous research and prior knowledge of the study setting. This was done in collaboration with experienced researchers involved in the project. The tool was subsequently pilot tested for face validity and adapted accordingly.

Measures were also taken to ensure the reliability (i.e. consistent measurement) of the data collection tool.[214] To reduce measurement errors (systematic bias and random error), participating GPs were given detailed instruction sheets on how to use the data collection instruments. This was explained verbally to the GPs by the same researcher during a one-to-one meeting. GPs were also encouraged to raise questions and concerns with the data collection tool during the entire surveillance period. Furthermore, since data were first entered by the author of this thesis, and later taken over by a research assistant under supervision, measures were taken to ensure the continued quality and consistency of data input. Random data checks were also made by the supervisor (the author of this thesis).

Despite measures taken to reduce measurement errors, it is possible that GPs recorded patient information without directly asking patients, possibly providing inaccurate demographic information. It is also possible that variables of interest inserted at the end of the surveillance sheet were left unmarked, perhaps due to time constraints, and inaccurately assumed to be non-cases. However, the audit sheets were specifically designed to be time-efficient. In fact, many GPs were easily able to integrate them into their practice.

6 CONCLUSIONS

Through our studies and this thesis, it has been shown that GPs' prescribing decisions are seldom influenced by clinical factors alone. Indeed, antibiotic prescribing is also influenced by a range of social and cultural factors,[96,176,197,215,216] at several levels of influence.[217] Context plays a dominant role in determining appropriate antibiotic use, and improving prescribing behaviour requires a concerted effort that addresses a variety of medical, social and cultural influences, as well as broader system factors (including organisational factors), in order to be accepted and effective.[217,218]

This critically needed insight was acquired through our studies, by gaining a better understanding of GPs' views on antibiotic prescription for RTIs and perceived barriers and facilitators to change. Through the socioecological model, the complexity of antibiotic prescribing and the numerous influences on GPs' antibiotic prescribing behaviour were also illustrated. Furthermore, data on GPs antibiotic prescribing patterns for aRTCs and key drivers of antibiotic prescription were also attained. It is evident that improving their antibiotic prescribing will require change at not just the individual level, but across all levels. These findings can not only help guide antimicrobial stewardship initiatives in Malta, but also those in countries with similar sociocultural traits.

Outlined below, are the key conclusions of this thesis:

⇒ GPs' antibiotic prescribing for aRTCs in Malta is high, indicating that antibiotics are not being used appropriately.

⇒ The abundant prescription of broad-spectrum antibiotics, particulary that for the empiric treatment of aRTCs that are unlikely to require antibiotic treatment, is concerning.

⇒ GPs raised concerns that they are forced to prescribe blindly since they lack access to up-to-date and relevant local antibiotic prescribing guidelines as well as antibiotic resistance data from the community. Therefore large caveats remain in Maltese primary care, leading to further uncertainty in the treatment of aRTCs, and most likely unnecessary and inappropriate antibiotic prescription.

⇒ Rapid POCTs remain largely unavailable and are thus rarely used in Maltese primary care, with many GPs stating that even if they were to be introduced, barriers such as the lack of human resources, time and cost will hinder their uptake and use.

⇒ GPs hold widely varying perceptions on delayed antibiotic prescribing with some GPs being largely in favour of the strategy and others preferring a wait and see approach without providing a DAP. There is also some variation in the way DAP is currently being employed in Malta.

⇒ Although GPs do not always believe the information provided to them by drug reps, several appreciated receiving up-to-date information, particlarly since they have difficulty keeping themselves updated with the latest medical advancements and products.

To conclude, antibiotic resistance is a public health threat that respects no borders.[11] Despite its political prioritisation and the availability of evidence to help inform antimicrobial stewardship activities, public health action remains inadequate.[38] Given the magnitude of this global, multi-sectoral problem, it is critical for researchers, industries (pharmaceutical, agricultural, food), policy-makers, politicians and other major stakeholders to coalesce and address this escalating situation promptly. Tackling antibiotic misuse in primary care addresses only one small piece of the puzzle but is necessary since vast amounts of antibiotics are consumed in the community setting. Curbing antibiotic misuse in the community will entail the implementation of tailored multifaceted interventions that target not only medical practitioners but also patients and pharmacists. If we are to continue to successfully treat patients in need of antibiotic therapy in the future, simple but effective solutions that take local culture into consideration and that can be scaled up to become self-sustainable, must be implemented promptly in order to safeguard the 'miracle' drugs of the 20th century.

7 RECOMMENDATIONS FOR RESEARCH AND POLICY

Outlined below are recommendations for future research and policy, based on our findings.

7.1 ANTIBIOTIC PRESCRIBING SURVEILLANCE

For any antibiotic stewardship activities to succeed, continued prescribing surveillance in the outpatient setting is critical. To-date no coordinated electronic system exists in Maltese primary care to collect electronic prescribing data but also to provide prescribers with access to electronic prescribing guidelines. This also means that there is little accountability for antibiotic prescribing. Furthermore, without such a necessary resource, it is near impossible to understand antibiotic prescription patterns in the community, monitor trends and evaluate interventions.[62] Audit and feedback with peer comparison specifically, has the potential of improving GPs' prescribing habits and is recommended. Furthermore, research on prescriber concordance to guidelines is necessary and will not be possible without much needed surveillance data. To this end, a more comprehensive antibiotic prescribing surveillance system is critically needed in Malta.

7.2 NATIONAL ANTIBIOTIC GUIDELINES

So far, it appears that national antibiotic guidelines have not been widely accessible, partly due to GPs' lack of awareness of their availability. This suggests that updated national guidelines must be better disseminated among GPs in both the private and public sectors and their availability be more widely known. Making guidelines available on mobile applications could make them easier to carry around and potentially increase their usability, however this requires further investigation. Furthermore, guidelines should include other diagnostic criteria that pose dilemmas to GPs, such as what to prescribe to patients with specific antibiotic sensitivities, preferences, co-morbidities or to smokers. When it comes to DAP recommendations, guidelines should better promote DAP through diagnosis-specific suggestions that take the natural progression of illness into account.

7.3 DELAYED ANTIBIOTIC PRESCRIBING

Given the potential that DAP has to reduce antibiotic use for RTIs, formal and standardised implementation of DAP could aid curb antibiotic overuse and help the general public understand that antibiotics are not always necessary for RTIs. Prescription pads specifically designed for post-dated antibiotics could help serve this purpose. However, this must be coupled with structured patient advice and widespread dissemination of information about the purpose and benefits of this strategy among not just doctors, but patients and pharmacists too. Furthermore, since DAP has a potential influence on patient satisfaction, further investigation on patients' views on delayed antibiotic prescribing and how their expectations can be met is recommended.

7.4 RAPID POINT-OF-CARE TESTING

Introducing rapid POCTs could positively impact antibiotic prescribing if utilised correctly. With the right implementation strategy that ensures that barriers such as cost and time are addressed, the introduction of low-cost, rapid POCTs could prove valuable to support GPs' prescribing decisions in this context, more so since diagnostic uncertainty was considered a problem.

7.5 CONTINUING MEDICAL EDUCATION

Educating prescribers is important to overcome antibiotic misuse.[104] Currently however, continuing medical education, even on antibiotics, are often sponsored by the pharmaceutical industry in Malta; a serious conflict of interest.[62] Therefore unbiased, regular educational activities are needed to promote appropriate and evidence-informed antibiotic prescription practices. Although GPs with many years of experience could benefit more from continuing medical education, all GPs should be given the opportunity to participate in educational activities that help raise GPs' awareness on appropriate prescribing by indication and patient group. Educational activities should specifically target the over-prescription of broad-spectrum antibiotics and provide GPs with the latest antibiotic prescribing recommendations according to national antibiotic guidelines. GPs could also benefit from communication training to facilitate decision-making and empower doctors to decline antibiotic requests. This can be combined with the introduction of educational tools for patients that can be used during consultations and help support GPs in patient education. Developing targeted sessions, tailored toward the specific needs of a particular GP demographic, may prove even more beneficial.

7.6 ACADEMIC DETAILING

Several GPs appreciated the interaction they had with drug reps and found them informative, particularly those working in solo practices that got little opportunity to interact with other healthcare professionals. However, such information is likely to be biased as drug reps are motivated to boost sales. Similar to strategies used in drug repping, in academic detailing, doctors receive one-to-one educational visits by a trained healthcare professional in their own professional setting.[219] This method, is successful at reducing antibiotic prescription rates whilst improving guideline-concordance.[220,221] It provides GPs with an opportunity to reflect upon their own prescription practices and get informed about the latest recommendations for appropriate antibiotic treatment.[188] With enough resources, this strategy has great potential in this setting. It can be used as a means of disseminating up-to-date local antibiotic prescribing guidelines as well as data on antibiotic resistance rates in the community. It could also provide a platform for GPs to discuss specific guideline recommendations with a trained professional, particularly for those diagnoses where the benefits of an antibiotic prescription are limited (e.g. uncomplicated acute bronchitis and rhinosinusitis). This form of outreach is therefore likely to have great impact in this setting which is why academic detailing by reliable, unbiased, medical professionals is highly recommended and should be piloted to assess its effectiveness.

7.7 REVISION OF SICK LEAVE POLICIES

Currently, sick leave certification provided by a medical doctor is required from the first day of illness if one intends to claim social security benefits after the third day of illness.[222] This encourages early consultations, particularly with GPs, since they are usually the patient's first point of contact for an acute illness. Revision of this sick leave policy could help reduce unnecessary and early antibiotic prescription.

7.8 GENERAL PUBLIC KNOWLEDGE, AWARENESS AND BEHAVIOUR

More research is needed to not only better understand patients' views on antibiotics and their appropriate use, but also how they perceive various strategies to limit antibiotic use and use them more appropriately. Further investigating their attitudes towards delayed antibiotic prescribing and rapid POCTs in particular, could help support our findings and better inform their successful implementation and integration into clinical practice in Malta.

Additionally, since the general public's knowledge and awareness on correct antibiotic use remains sub-optimal, it must be improved. People need to understand the difference between viral and bacterial infections, the natural course of various infections and that viral infections do not require antibiotic treatment. They must also be encouraged to engage in self-care for simple ailments such as the common cold before visiting a doctor, in order to discourage early consultation. Nationwide campaigns that harness the power of social media could prove effective, with appropriate key messages delivered in an easy and comprehensible manner.

7.9 PHARMACIST INVOLVEMENT

To-date little is known about pharmacists' views on their role in halting the development of antibiotic resistance in Malta which calls for further research in this area. Pharmacists are a key stakeholder, not only as dispensers of antibiotics but also educational vessels to patients and close collaborators with GPs. Their involvement in this dynamic cannot be overlooked.

"There is no single solution and several, synergistic, overlapping, and complementing approaches will be needed, with a strong overarching shared goal to ensure and sustain access to effective antimicrobial therapies."

– Holmes et al. (2016)[7]

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10 APPENDICES

APPENDIX I: STUDY PROTOCOL OF THE MALTESE ANTIBIOTIC STEWARDSHIP PROGRAMME IN THE COMMUNITY (MASPIC)

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Maltese Antibiotic Stewardship Programme in the Community (MASPIC): protocol of a prospective quasiexperimental social marketing intervention

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ABSTRACT

Introduction Antibiotic misuse is a key driver of antibiotic resistance. In 2015/2016, Maltese respondents reported the highest proportions of antibiotic consumption in Europe. Since antibiotics are prescription-only medicines in Malta, research on effective strategies targeting general practitioners' (GPs) knowledge and behaviour is needed. Multifaceted behaviour change (BC) interventions are likely to be effective. Social marketing (SM) can provide the tools to promote sustained BC; however, its utilisation in Europe is limited. This paper aims to describe the design and methods of a multifaceted SM intervention aimed at changing Maltese GPs' antibiotic prescribing behaviour for patients with acute respiratory tract infections (aRTIs).

Methods and analysis This 4-year quasiexperimental intervention study will be carried out in Malta and includes three phases: preintervention, intervention and postintervention. The preintervention phase intends to gain insight into the practices and attitudes of GPs, pharmacists and parents through interviews, focus group discussions and antibiotic prescribing surveillance. A 6-month intervention targeting GPs will be implemented following assessment of their prescribing intention and readiness for BC. The intervention will likely comprise: prescribing guidelines, patient educational materials, delayed antibiotic prescriptions and GP education. Outcomes will be evaluated in the postintervention phase through questionnaires based on the theory of planned behaviour and stages-of-change theory, as well as postintervention surveillance. The primary outcome will be the antibiotic prescribing rate for all patients with aRTIs. Secondary outcomes will include the proportion of diagnosis-specific antibiotic prescription and symptomatic relief medication prescribed, and the change in GPs stage-of-change and their intention to prescribe antibiotics.

Ethics and dissemination The project received ethical approval from the University of Malta's Research Ethics Committee. Should this intervention successfully decrease antibiotic prescribing, it may be scaled up locally and transferred to similar settings.

Trial registration number NCT03218930; Pre-results.

Strengths and limitations of this study

- This study is the first in Malta that attempts to establish an ongoing community surveillance system to gather timely data on diagnosis-specific antibiotic prescribing among general practitioners (GPs) in Malta.
- This study is also the first to employ social marketing techniques to design, deliver and evaluate the effectiveness of a behaviour change intervention to improve antibiotic prescribing in Malta.
- If effective, this intervention could easily be incorporated into routine clinical practice and scaled up locally and extrapolated to similar settings, particularly in the Mediterranean region, at a very low cost.
- In the long term, this intervention could help contribute towards reducing the development of antibiotic resistance, which is an ever-growing challenge.
- Given the country's size and number of active GPs, a randomised controlled trial will not be possible; therefore, the intervention's effect may be harder to assess; it may have a smaller effect than expected. In order to allow for better detection of the intervention's effectiveness on behaviour change, a quasiexperimental design shall be employed.

BACKGROUND

Access to effective antibiotic treatment is a prerequisite in healthcare today.[1] Unfortunately, however, widespread antibiotic use has accelerated the rate of antibiotic resistance (ABR) development.[2] Although the exact magnitude of this global problem and its impact on human health is largely unknown,[2] ABR in common bacterial pathogens has reached concerning levels in many parts of the world.[2] As a result, many available treatment options are becoming ineffective,[2] forcing us to resort to more potent, toxic and

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costly drugs, often with considerable side effects.[3] Antibiotic-resistant infections pose substantial burden on patient outcomes and health expenditure, both at societal and individual levels.[2 4] They lead to significantly longer hospital stays, increased morbidity and mortality[3] among others.

ABR is complex and driven by many interrelated factors, including knowledge, attitudes, perceptions, expectations, time constraints, economic incentives, cultural factors, health system characteristics and regulations.[5–9] A recognised key driver is the use, misuse or overuse of antibiotics, as well as unregulated consumer access to antibiotics.[6 10 11] While antibiotic overuse plays a pivotal role, underuse through inadequate dosing and poor adherence also plays an important role.[6]

Although a correlation between outpatient antibiotic consumption and ABR has been shown in Europe, the association is complex.[12 13] While the highest concentrations of antibiotic prescribing is in inpatient settings,[14] the overall quantity of antibiotic prescribing is highest in the community.[15] Indeed, the highest rates of antibiotic prescription for systemic use are in primary care,[16] with respiratory tract infections (RTIs) being the most common diagnoses.[17] Studies have shown alarmingly high rates (between 50% up to almost 100%) of antibiotics prescribed for upper RTIs in outpatient settings, even though seldom required.[18–23]

In Malta, a southern European country, wholesale distribution records have shown that antibiotic consumption in primary care has increased steadily over the past decade, despite a reduction in over-the-counter sales.[24] In fact, in a 2016 European-wide study, 48% of the population reported taking antibiotics during the previous year; the highest in the European Union.[25] The top two indications were sore throat (22%; EU28 average 14%) and influenza (18%; EU28 average 16%).[25] This was accompanied by suboptimal levels of knowledge on antibiotics among the general population; only 27% of the Maltese interviewed knew that antibiotics do not kill viruses, and only 39% knew that antibiotics are ineffective against cold and influenza.[25] Although knowledge has increased slightly since the two preceding surveys,[26 27] awareness is still low compared with other European countries.

Through the European Antibiotic Awareness Day,[28] attempts to increase knowledge and awareness among the Maltese public, prescribers and pharmacists have been made and regulations enforced. Consequently, self-medication has fallen from 19% of Maltese respondents admitting taking antibiotics without a prescription in 2001 to 2% in 2016.[24 25] As doctors are considered the most trustworthy source of information on antibiotics by the Maltese,[25] they are important role models for their patients. The future challenge is to promote better antibiotic prescribing behaviour among general practitioners (GPs),[17 24 29] particularly since 97% of antibiotic consumption in Malta results from a medical prescription.[25]

Research on effective strategies targeting prescriber knowledge and behaviour are needed to promote appropriate antibiotic prescribing and consumption.[9 12 30] The local cultural context plays an important role and cannot be overlooked.[31] Hofstede's model of cultural dimensions describes how cultures vary along groups of fundamental dimensions, namely power distance, individualism, masculinity and uncertainty avoidance. Scandinavian countries show very low scores for power distance, masculinity and uncertainty avoidance; conversely, Mediterranean countries are characterised by high power distance and uncertainty avoidance, and medium to high masculinity scores.[32] Consequently, a positive association between power distance and outpatient antibiotic consumption, including self-medication, has been shown.[33] In countries with high uncertainty avoidance, antibiotic prescribing can provide the clinician with a subconscious reassurance of certainty. In such contexts, antibiotic prescribing would presumably be high and more likely prescribed 'just in case' when faced with dubious clinical presentations.[34] Since change generates uncertainty, such cultures tend to be more resistant to change making behaviour change initiatives more challenging, particularly since national culture and unspoken rules are key drivers behind inappropriate antibiotic prescribing behaviour.[34–36] Successful interventions must recognise local key drivers of prescribing and incorporate incentives to alter behaviour into stewardship programmes.[35]

While awareness campaigns and education are often recommended,[6 9 13] interventions targeted specifically at changing behaviour are more likely to be effective. Behavioural theories, such as the theory of planned behaviour[37] and the stages-of-change model,[38] and social science methods have been suggested as suitable approaches to better understand factors influencing prescribing practices.[39] These methods have thus far been underutilised in the development of interventions targeting antibiotic prescribing.[39] Other European countries have attempted to use a behaviour change approach to promote prudent antibiotic use, although most did not consider the behavioural determinants related to antibiotic use and prescribing.[39] Moreover, interventions that attempt to reduce inappropriate antibiotic prescribing tend to be more successful when they combine physician, patient and public education and when the design is multifaceted.[17 40–43] Social marketing (SM) may provide a different insight on the development of health promotion initiatives targeting the prevention of ABR.

SM is a behavioural science approach to promote social change by applying marketing theories and techniques to plan, implement and evaluate interventions to induce voluntary behaviour change.[44] It combines concepts from commercial marketing and health communication into the following principles: behavioural focus, 'customer' orientation, segmentation (ie, tailoring), competition (ie, understanding benefits and barriers), exchange (ie, emphasis on the benefits of changing one's behaviour), marketing mix (the '4Ps' of marketing: product, price, place and promotion) and long-term planning. It also

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considers context-specific issues to tailor interventions conducive to the country's particular needs, thus increasing one's chances of success.[44] When applied correctly, SM interventions can provide the necessary tools to promote sustained behaviour change among targeted populations.[30] The utilisation of SM for the prevention and control of communicable diseases in Europe has however been limited.[44] This paper aims to describe the design and methods of a multifaceted SM intervention aimed at changing Maltese GPs' antibiotic prescribing behaviour for patients with acute RTIs.

METHODS

Study design

A 4-year quasiexperimental intervention study protocol, based on SM principles, was designed to assess whether a multifaceted SM intervention is effective at influencing GPs' antibiotic prescribing practices for acute RTIs. The SM intervention was developed in a multistage process, following a BEHAVE-based marketing plan[45] (figure 1). The BEHAVE framework allows you to address simple but essential questions prior to deciding what interventions to implement, namely (1) who is the audience?, (2) what do you want them to do? and (3) what factors influence their behaviour?[45] The study will be described stage-wise according to the three different phases: preintervention, intervention and postintervention.

Study setting

The intervention will be rolled-out in Malta, a southern European country (316 km^2; 425 384 population; 2013 est.) and one of the smallest yet most densely populated countries in the world (1346 persons/km^2).[46] The nation has two official languages: Maltese and English. Malta has an integrated health services system organised at national level, primarily funded by taxation (65%) and complemented by private financing (out-of-pocket and insurance).[47] Hospital-based healthcare is predominantly public (96%) and free at point-of-care to all citizens, whereas approximately two-thirds of primary care is provided by the private sector[47] and mainly delivered by GPs. As from 2003, qualified doctors are expected to specialise as GPs; however, GPs practising prior to 2003 were granted certified specialisation through a grandfather clause, based on acquired experience.[48] All GPs are registered on the Malta Medical Council's Medical and Dental Specialists Register. Publicly financed health services in primary care are also free at point-of-delivery. Around 80% of antibiotic use in ambulatory care takes place through prescription following a paid consultation by a private GP. No reimbursement system exists, although a small proportion of the population are eligible to receive—free of charge—a restricted list of antibiotics directly from government pharmacies.

Primary care is available all day, all year round; GPs are essentially on-call 24/7, especially since most private GPs have strong family ties with their patients and often treat several generations within the same family. Most GP clinics in the public sector are walk-in clinics, and patients are not registered with any particular doctor or group practice, thereby impeding continuity of care. In the private sector, GPs work mostly in single-handed practices (group practices remain uncommon), and patients are free to choose their own GP. They often practice within retail pharmacies or private clinics,[47] although home visits are high on demand and relatively common. In this highly regulated system, antibiotics are prescription-only medicines, acquired from community pharmacies through a non-refundable personal purchase.[24 49] As of yet, pharmacies do not keep electronic records of prescriptions dispensed; therefore, prescription-level data are currently unavailable.[24] Likewise, GPs are not obliged to keep patient records, although some do so for personal use.

Formative research: the preintervention phase

One of the pediments of any successful SM intervention is an in-depth understanding of the target audience.[50] Without thoroughly understanding how the target audience view antibiotic use and resistance within their own context, there would be little chance for success in achieving behaviour change.[50] Formative research is the best way to gain insight into the practices and attitudes of potential audience members and can be achieved through focus group discussions (FGDs) and individual interviews, among others.

The preintervention phase consists of three substudies that will inform subsequent substudies and the development of the intervention strategy. During this phase, baseline data will be collected using mixed methods.

Individual face-to-face interviews with GPs (substudy I)

In order to design a tailored intervention, understanding key issues, particularly contextual factors, which influence GPs' antibiotic prescribing practices, is essential. Therefore, this substudy seeks to explore GPs' views and understanding of prudent antibiotic prescribing as well as factors that influence their antibiotic prescribing practices. It further aims to understand the variation in GPs' perceptions on delayed antibiotic prescribing (defined later). For this qualitative exploratory study, individual semistructured interviews will be held with a quota sample of 15–20 active GPs registered at the Malta Medical Council. In quota sampling, the intention is to ensure that the strata within the sample under study are proportional to those in the population being studied.[51] GPs are eligible to participate regardless of whether they work on a part-time or full-time basis or in the public and/or private sectors, the latter distinction considered advantageous. All eligible GPs registered at the Malta Medical Council, and to whom a phone number is available, will be included as possible interviewees. Once the list is finalised, GPs will be divided into strata based on the following characteristics and in the following order: (1) years of experience, (2) sex and (3) locality of residence. GPs from within each stratum will be contacted by phone

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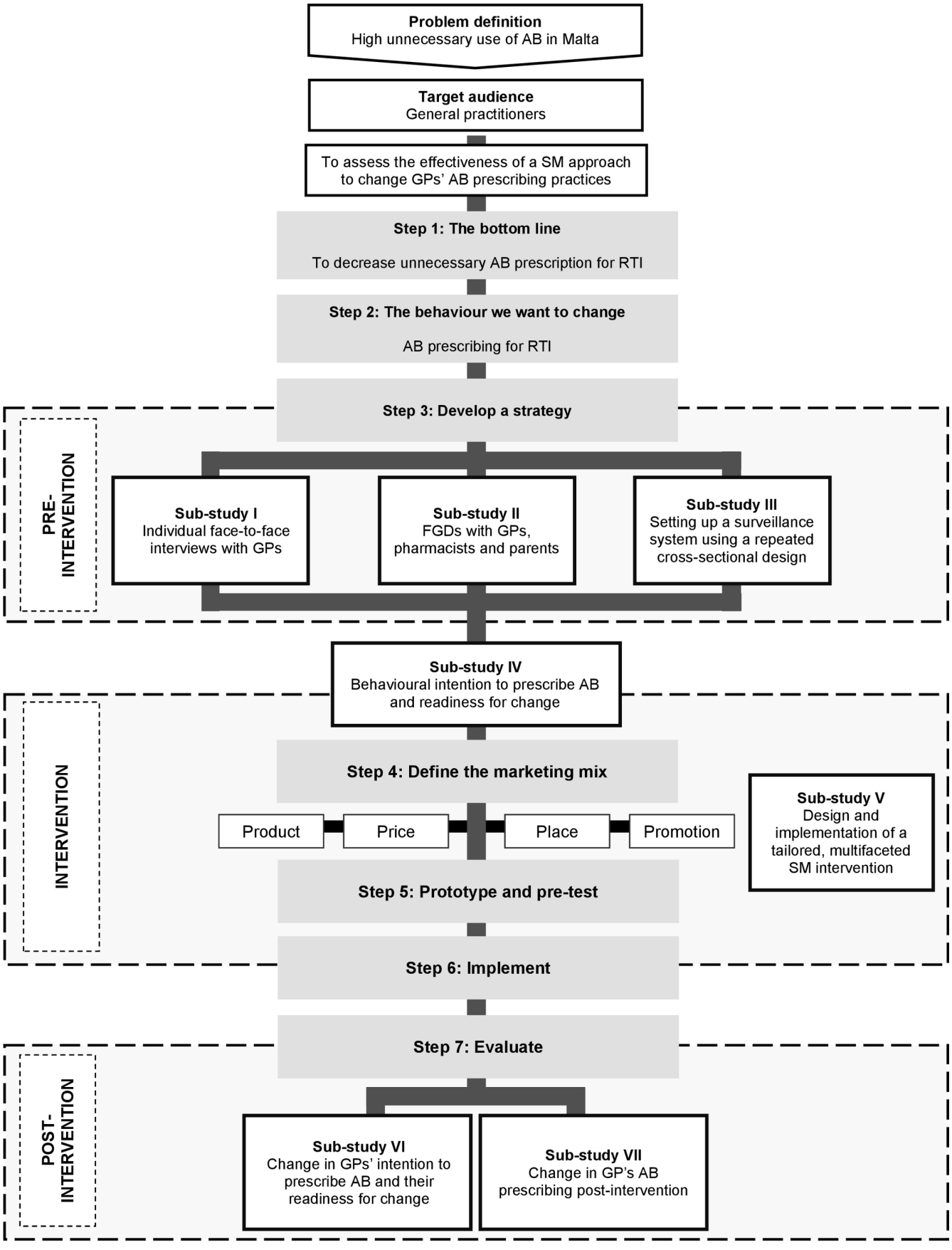

NOTE. AB – antibiotic; FGD – focus group discussion; GP – general practitioner; SM – social marketing; RTI – respiratory tract infections

Figure 1 A BEHAVE-based marketing plan for a social marketing intervention.

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in a stepwise fashion until 15–20 GPs are recruited, alternatively until data saturation is reached. These measures will ensure that the sample of interviewees is as representative of the population characteristics as possible.

A semistructured interview guide (with prompts) will be designed and developed based on a thorough literature search and adapted according to the local context. The guide will be pilot-tested with a purposive sample of up to five GPs, following which it will adjusted accordingly. Interviews will be held in English and/or Maltese by one member of the research team who is fluent in both languages and are expected to last around 45 minutes. The recorded interviews will be transcribed verbatim and translated if necessary. Data will be analysed using content analysis and phenomenography. An overview of the design of this substudy and subsequent ones can be found in table 1.

Findings will be used to identify competing behaviours as well as barriers and facilitators to behaviour change. By understanding what GPs want, they can be offered optimal conditions for exchange, that is, offering them something they consider worthwhile in exchange for them changing their behaviour. This is based on the premise that if people believe that something is of benefit to them, they will act on it; barriers stop them from acting. Therefore. the intervention should ensure that activities will maximise the benefits while reducing the barriers that are considered important to the target audience.[52]

FGDs with GPs, pharmacists and parents (substudy II)

Correct antibiotic use depends on various key stakeholders, including pharmacists, the general public and GPs, among others. In order to gain a better understanding of the antibiotic prescription–use–dispensation dynamic in Malta through these three different stakeholders, FGDs will be held. Since young children are likely to visit their GP often, parents of children under the age of 12 will be targeted. Two to three FGDs will be conducted for each individual stakeholder—parents, GPs and community pharmacists (six to nine groups in total)—each consisting of between 6 and 10 participants. The target groups will be recruited differently. GPs participating in interviews will be reinvited to participate in the group discussions. For community pharmacists and parents, snowball sampling[51] will be employed. Snowball sampling will be used in order to gain access to participants interested in discussing the topic, thus reducing the risk for non-participative interviewees. Other sampling methods would be too time-consuming to employ and may risk inviting persons who will not contribute to the discussion.

Community pharmacists will be invited to participate through local professional associations and social networks. Those interested will be asked to recommend up to three other pharmacists they believe would be interested in participating in this study. Parents will be invited through schools via school administration and staff members with whom the researchers already have contact with. Parents interested in participating will be asked to recommend up to three parents. Although this type of sampling method will allow us to gain timely access to both stakeholders, it is limited in the fact that there is a high possibility that those interested recommend their close peers thus restricting the inferences that can be made about the rest of the population. This however is not the main goal of this substudy.

Both GPs and community pharmacists must be actively working at their time of participation, while parents must be the caregiver of at least one child under 12 years of age. A discussion guide (with prompts) will be developed, and FGDs will be held in English and/or Maltese by one member of the research team who is fluent in both languages, together with an observer/note-taker. FGDs are expected to last no longer than 2 hours. The recorded FGDs will be transcribed verbatim and translated if necessary. Data will be analysed using content analysis.

Setting up a surveillance system using a repeated cross-sectional design (substudy III)

Effective surveillance is the foundation for national and international efforts to contain ABR.[6] One of the strategic objectives of the 2015 global action plan on antimicrobial resistance is to strengthen knowledge through surveillance and research.[53] There are currently large knowledge gaps on antibiotic use in many regions of the world due to the lack of adequate surveillance systems.[6] The lack of data is often greater in the community setting.[2] Such data would help assess and monitor the situation, better understand ABR trends, define optimal treatment for patients, identify key areas for interventions to contain resistance and monitor their impact and inform public health policy.[2 6]

In Malta, ABR and consumption data are routinely collected within tertiary care, and wholesale data are collected within the community setting; however, community antibiotic consumption data at prescription-level are still unavailable,[24] and as mentioned earlier, GPs are not obliged to keep patient records. Without ongoing surveillance, it is challenging, if not impossible, to devise strategies tailored towards specific needs for the local context. Furthermore, it would be difficult to measure whether any intervention in such a community would have an impact on antibiotic prescribing. In order to better understand the antibiotic prescribing patterns of GPs for respiratory tract complaints in Malta, we will set up a basic surveillance system to present the baseline 1 year diagnosis-specific antibiotic prescribing patterns for respiratory tract complaints.

All GPs registered on the Malta Medical Council's Specialists Register will be invited to participate. The invitation will also extend to GP trainees. In order to fulfil eligibility criteria, GPs must be actively practising at the time of recruitment, with no distinction made between those working on a part-time or full-time basis. In order to attract as many GPs as possible, postal invitations will be sent to all GPs registered at the Malta Medical Council and

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Table 1 Objective, study design, data collection and analysis methods for each phase of the project

Phase	Substudy	Main objective/s	Study design	Data collection and analysis methods
Preintervention	I	(1) To explore GPs' views and understanding of prudent antibiotic prescribing as well as factors which influence their antibiotic prescribing practices. (2) To understand the variation in GPs' perceptions on delayed antibiotic prescribing	Qualitative exploratory	▶ Quota sample of active registered GPs ▶ Individual semistructured interviews ▶ Content analysis and phenomenography
	II	To gain a better understanding of the antibiotic prescription–use–dispensation dynamic in Malta through three different stakeholders	Qualitative exploratory	▶ Quota sample of active registered GPs ▶ Snowball sample of parents and community pharmacists ▶ Focus group discussions ▶ Content analysis
	III	To present the baseline 1 year diagnosis-specific antibiotic prescribing patterns for respiratory tract complaints in Malta	Repeated cross-sectional surveillance	▶ Total population sampling ▶ One-year prospective surveillance ▶ Descriptive statistics and mixed effects logistic regression models
Intervention	IV	To determine GPs' behavioural intention (attitudes, subjective norms and perceived behavioural control) to prescribe antibiotics and their readiness for behaviour change	Cross-sectional	▶ Purposive sampling ▶ Self-administered questionnaire ▶ Data will be analysed using appropriate statistical methods
	V	To design, develop and implement a tailored, multifaceted SM intervention to improve antibiotic prescribing for acute respiratory tract infections among GPs	Intervention implementation	▶ Verbal feedback and feedback questionnaires ▶ Collection of delayed antibiotic prescriptions ▶ Ongoing surveillance/monitoring ▶ Logs ▶ Descriptive analysis of process indicator data
Postintervention	VI	To measure the change in GPs' intention to prescribe antibiotics and their readiness for behaviour change	Repeated cross-sectional	▶ Self-administered questionnaire ▶ Descriptive statistics and Wilcoxon signed-rank test
	VII	To evaluate the impact of an SM intervention on GPs' antibiotic prescribing for acute respiratory tract complaints in Malta	Repeated cross-sectional surveillance	▶ One-year prospective surveillance ▶ Paired, before-and-after evaluation of antibiotic prescribing ▶ Interrupted time series analysis with segmented regression

GP, general practitioner; SM, social marketing.

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to whom postal addresses are publicly available. This will be followed by one postal reminder. Other recruitment strategies will also be explored, including sending out email invitations through local professional organisations and colleges and publishing a public announcement on a local medical professionals' network (TheSynapse; www.thesynapse.eu), in an attempt to reach out to those GPs without an available postal address. Phone calls will also be made to recruit as many interested GPs as possible. GP trainees will be recruited via email invitation through the Malta College of Family Doctors, who are responsible for ensuring the quality of academic training in the GP foundation programme.

Participating GPs will be required to manually collect surveillance data for all patients seen with a respiratory tract compliant, over a predetermined 1-week period (with no substitutions), every month, for a total duration of 1 year, resulting in a total of 12 surveillance weeks. A surveillance form will be developed for this purpose following a thorough literature search. It will also be based on data collected in the previous substudies as well as previous work carried out in other European countries.[54 55] It will include data on: (1) patient characteristics such as age, comorbidities and lifestyle factors, (2) clinical characteristics such as duration of symptoms, signs and symptoms, (3) diagnostics and (4) prescription. The form will be adapted to the local context through piloting and face validity testing. GPs will also be required to provide the total number of patients seen during the surveillance week, irrespective of their compliant, using a designated tally chart.

In order to promote compliance, GPs will receive three text messages in conjunction with each surveillance week: one a day prior to the initiation of the surveillance week, another on the day and the third at the end of the surveillance week. Once the surveillance week is over, they will be requested to submit all forms filled together with a tally chart by postal mail using prepaid postal envelopes. Phone contact will be regularly maintained to provide encouragement and resolve queries. While no direct incentives will be provided to promote GP participation, GPs will be provided with certificates of participation at the end of each intervention phase that will allow them to redeem continuing medical education credits through the Malta College of Family Doctors. GPs will also receive 3 monthly feedback reports summarising the data collected during the preceding three surveillance weeks (individual and aggregated). Although a form of audit and feedback, the primary intention is not to change prescribing behaviour at this point rather to encourage GPs to continue participation by maintaining regular contact. For this reason, we opted not to actively carry out any peer comparison, although GPs could compare their personal report with the aggregate results.

Descriptive statistics will be used to describe all variables collected through the surveillance. The 1 year antibiotic prescribing patterns as well as diagnosis-specific antibiotic prescribing rates and characteristics will be reported. Should the data permit, it will be further analysed to look into factors that influence GPs' antibiotic prescribing using mixed effects logistic regression models to take into account clustering at GP level.

Intervention development, design and implementation: the intervention phase

Following the completion of substudy III, members of the research team will carry out outreach visits to all participating GPs, who will be invited to extend their participation to the intervention and postintervention phases of the project (described below). The intervention phase is expected to last 6 months.

Behavioural intention to prescribe antibiotics and readiness for change (substudy IV)

Changing prescribing behaviour is complex; however, behavioural theories can help better understand and influence it through stronger and enhanced development and delivery of tailored interventions.[52] In order to further tailor the intervention according to participating GPs' needs, this cross-sectional survey aims to determine GPs' behavioural intention (attitudes, subjective norms and perceived behavioural control) to prescribe antibiotics and their readiness for behaviour change. Two questionnaires will be developed for this purpose using the main constructs of selected behaviour change theories, namely (1) the theory of planned behaviour, which is a conceptual framework for understanding social behaviour, focusing on the intention to perform a specific behaviour[37] and (2) the stages-of-change model, which describes the behaviour change process: precontemplation, contemplation, preparation, action, maintenance and relapse.[38] Potential topics will include: current antibiotic prescribing practices, knowledge-based questions on antibiotics (focusing on RTIs), likely repercussions of antibiotic misuse, external influences to antibiotic prescribing and guideline adherence. Questionnaires will be delivered to GPs prior to the initiation of the intervention (baseline) and once the intervention is complete (substudy VI). Data will be analysed using appropriate statistical methods.

Design and implementation of a tailored, multifaceted SM intervention (substudy V)

All intervention materials will be designed following thorough formative research and consideration of local cultural factors and needs. The intervention will also be tailored according to GPs' stage of behaviour change. Furthermore, ratification of all intervention materials by the local National Antibiotic Committee will be sought prior to their dissemination. A number of strategies within primary care have been outlined in an effort to combat the development of ABR.[31] Based on findings from the previous substudies, multiple components will be developed for this intervention, each described below.

Dissemination of antibiotic prescribing guidelines

Prescribing guidelines aid clinicians in translating best evidence to practice. Although several countries

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have issued national antibiotic guidelines, there is little recent evidence that assesses its impact on prescribing behaviour.[31] It has been shown however that guideline dissemination alone is not sufficient to restrict antibiotic prescribing.[17] For this reason, hard and soft copies of the updated national guidelines shall be disseminated to every participating GP in combination with other strategies outlined below. Guidelines will be published in English.

Distribution of educational materials (including posters and booklets)

Over the past decade, the popularity of patient information leaflets in primary care has increased.[31] They can be referred to by doctors during consultations, and patients may also take them to home read later.[31] A number of studies have shown that the use of patient information booklets can help to reduce antibiotic prescribing rates[56] and provide patients with valuable information on the typical duration of illness, how to recognise signs of severe illness and increase awareness on antibiotic use.[57 58] They also lead to increased knowledge and confidence among GPs, although some report certain barriers such as lack of time and problems changing their consultation style.[57]

Should posters be developed, they will be pretested during FGDs with parents and GPs will be asked to provide input during outreach visits. Patient booklets would be developed together with a medical illustrator and could include information on viral versus bacterial infections, how to manage symptoms without antibiotics, how ABR develops and how to use antibiotics responsibly. The booklet will be distributed to a number of people from various backgrounds prior to large-scale printing in order to receive feedback on readability, attractiveness and user-friendliness and subsequently revised accordingly. Posters and booklets will be made available at all clinics of participating GPs, and booklets will be used during patient consultations.

Delayed antibiotic prescription

Delayed antibiotic prescribing refers to a scenario where a doctor prescribes an antibiotic course on the condition that they should only be taken if symptoms persist or deteriorate after a given time period (generally between 48 and 72 hours). A systematic review showed that delayed antibiotic prescribing results in marked reductions in antibiotic use and no significant differences in reconsultation or complication rates.[59] Although some national guidelines recommend delayed prescribing, its uptake in clinical practice remains low.[60 61] The motivation behind its use varies from managing diagnostic uncertainty and avoiding conflicts with patients (particularly those who tend to put pressure on doctors to prescribe), to a tool for patient education and to promote shared decision making.[61 62] Some prescribers, however, feel uncomfortable shifting clinical responsibility onto their patients.[61]

Should Maltese GPs seem receptive to this prescription method, a delayed antibiotic prescription pad will be developed and distributed to GPs for use during consultations where a delayed prescription is deemed appropriate by the GP.

Delivery of educational sessions

A recent review of interventions to improve antibiotic use for RTIs showed that educational sessions, although laborious, seem more effective than audit and feedback and distribution of written patient information.[17] Educational sessions can include: information on the core principles of prudent antibiotic use, introduction to new tools (such as guidelines), diagnostic skills training and patient communication techniques.[31] A few studies have shown that sessions incorporating these topics can lead to sustained improvements in antibiotic use that last over 2–4 years.[63 64] The extent of the impact in other studies has generally been quite modest.[58 65–68]

Educational sessions will form a core part in the planned intervention and will be delivered in accordance with GP preferences. Topics will likely include those mentioned above as well as any other topics addressing specific needs identified during the formative research phase. In order to ease attendance, sessions will be delivered face-to-face but also streamed live and recorded for those unable to attend in person. Recorded sessions and all relevant materials will be uploaded to Ping Pong, the online learning platform used at Karolinska Institutet.

Process indicators

Several process indicator data will be collected throughout the intervention period, which will also help assess compliance with the intervention protocol. Table 2 summarises a few indicators according to the intervention components previously described.

Postintervention phase: intervention evaluation

Outcome parameters

Primary outcome

The antibiotic prescribing rate for all patients with acute respiratory tract complaints, with the exception of pneumonia cases which will be excluded entirely.

Secondary outcomes

Secondary outcomes include the:

i. proportion of diagnosis-specific antibiotic prescription, specifically for the common cold, acute pharyngitis, acute sinusitis, acute bronchitis, acute tonsillitis, acute otitis media, allergy and influenza
ii. proportion of symptomatic relief medication prescribed
iii. change in GPs' stage-of-change
iv. change in GPs' behavioural intention to prescribe antibiotics.

In order to evaluate the effect of the intervention on GPs' antibiotic prescribing, their intention to prescribe

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Table 2 Process indicators collected during intervention period

Intervention components	Implementation outcomes (process indicators)	Data collection methods
Antibiotic prescribing guidelines	► No. of guidelines distributed ► Frequency of reference to guidelines ► Usefulness of guidelines in practice	► Surveillance/monitoring ► Survey (postintervention)
Posters	► No. of posters printed ► No. of posters disseminated, per GP ► No. of posters displayed in clinics ► No. of QR code log-ins	► Surveillance/monitoring ► Logs ► Survey (postintervention)
Booklets	► No. of booklets printed ► No. of booklets disseminated, per GP ► No. of QR code log-ins	► Surveillance/monitoring ► Logs ► Survey (postintervention)
Delayed antibiotic prescription pads	► No. of pads printed ► No. of pads disseminated, per GP ► No. of delayed antibiotic prescriptions issued ► No. of QR code log-ins	► Surveillance/monitoring ► Logs ► Collection of issued prescriptions ► Survey (postintervention)
Educational sessions	► No. of sessions held ► % attendance to sessions ► % attendance to sessions, by mode (face-to-face, online (live), online (recorded)) ► Satisfaction with session content and delivery	► Surveillance/monitoring ► Feedback questionnaires ► Survey (postintervention)

GP, general practitioner; QR, quick response.

antibiotics and stage-of-change, two sub-studies are planned and are described below.

Change in GPs' intention to prescribe antibiotics and their readiness for change (substudy VI)

Following the completion of the intervention phase, all participating GPs will be asked to complete the same two questionnaires outlined in substudy IV with the aim of measuring the change in their intention to prescribe antibiotics and readiness for behaviour change postintervention. Apart from descriptive and comparative statistics, the plan is to analyse paired data using Wilcoxon signed-rank test.

Change in GP's antibiotic prescribing postintervention (substudy VII)

Following participation in the intervention phase, GPs will complete another year of surveillance using identical tools and methods used in substudy III. Apart from analysing the change in diagnosis-specific antibiotic prescribing patterns for respiratory tract complaints postintervention, the impact of the SM intervention on GPs' antibiotic prescribing will also be evaluated. As before, GPs will also receive 3 monthly feedback reports (individual and aggregated). Descriptive statistics will be used to describe all variables collected through the surveillance. The 1 year antibiotic prescribing patterns as well as diagnosis-specific antibiotic prescribing rates and characteristics will also be reported. Finally, the change in antibiotic prescribing preintervention and postintervention will be evaluated using interrupted time series analysis with segmented regression. Data will be clustered at GP level.

Study status

The project was initiated in August 2014 and is ongoing. The preintervention phase ran from August 2014 to April 2016. The intervention phase has just come to completion. The project is now in the postintervention phase.

ETHICS AND DISSEMINATION

Ethical considerations

Each component of the project received ethical approval from the University of Malta's Research Ethics Committee when needed.

Several ethical issues have been considered. For all substudies, participants received verbal information about the study's purpose and their role as participants, in addition to information letters and informed consent. Participants were told that participation is voluntary and that they are free to withdraw without consequences. For the qualitative substudies, permission was requested to record the sessions. For the surveillance and intervention components, no information gathered risks compromising the patient's identity; no names and identifiable variables were collected. Nonetheless, standard data management protocols will be employed to ensure data safety. All data will be stored in a safe location and made confidential through the use of unique identifier codes kept in a separate file and accessible only to one

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team member. Moreover, no identifiable material will be published publicly.

There are no anticipated risks associated with participation apart from the time required to participate. We believe, rather, that informants could benefit from being given the opportunity to self-reflect on their own antibiotic use. In exchange for participation, GPs and pharmacists received certificates, allowing them to earn Continuing Professional Development (CPD) points from their respective colleges. Furthermore, GPs participating in surveillance received 3 monthly feedback reports (individual and overall). Overall feedback is presented in an aggregate manner and does not include any GP or patient information that may compromise their identity.

Dissemination plan

We plan to present our results at leading international and national conferences. We also plan to publish results in peer-reviewed scientific journals and disseminate them locally through local professional organisations. We intend to share our ultimate findings to the National Antibiotic Committee, which reports directly to the Superintendent of Public Health of Malta.

DISCUSSION

ABR respects no borders. It is a global problem with increasing magnitude, and it is critical that this escalating situation is addressed promptly. Although not a simple task, especially due to underlying cultural dimensions,[32 36] strategic behaviour change initiatives to promote prudent antibiotic use and prescribing are urgently required[30] and are attainable, as shown by other European countries.[32] There is a need to propose simple solutions that consider local cultures and can be scaled up to become self-sustainable.[35]

To our knowledge, this community intervention is unique in Malta. It is the first to establish a community surveillance system and employ SM techniques to design, deliver and evaluate the effectiveness of a behaviour change intervention to improve antibiotic prescribing. As mentioned earlier, although SM techniques are promising to promote sustained behaviour change among selected groups,[30] its utilisation for the prevention and control of communicable diseases in Europe has thus far been limited.[44]

Changing antibiotic prescribing behaviour is complex and requires multifaceted interventions.[5] This study uses various approaches in an attempt to change GPs' prescribing behaviour, generating evidence towards the effectiveness of tailored, multifaceted SM interventions in this field. It will allow us to gain insight into GPs' diagnosis-specific antibiotic prescribing practices over time which, in Malta, has been hard to achieve so far. Should this intervention successfully decrease antibiotic prescribing rates, it may be scaled up locally and transferred to similar settings at a very low cost.

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Contributors All authors were all involved in the conception, planning and design of this study as well as the development of all data collection instruments. EAS-G managed the project; she recruited all participants, led data collection and analysis, designed educational materials and coordinated their printing, delivered an educational session and liaised with the various stakeholders involved. EAS-G wrote the first draft of this manuscript and made all necessary amendments after review. MAB delivered one educational session. MAB, SR-K, AN and CSL were involved in manuscript review and critique, and all authors contributed to the final approval of the manuscript. All authors are in agreement that they are accountable for all aspects of the work and that all questions related to its accuracy have been appropriately investigated and resolved.

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Competing interests None declared.

Ethics approval The University of Malta's Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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APPENDIX II: IMPLEMENTATION OF THE MALTESE ANTIBIOTIC STEWARDSHIP PROGRAMME IN THE COMMUNITY (MASPIC)

As mentioned in Chapter 3, the formative studies included in this thesis informed the design, development and implementation of a multi-faceted SM intervention targeting GPs' specific needs. Described below is a short summary of the components delivered during the six-month intervention that ran between October 2016 and March 2017.

Waiting room posters

Four waiting room posters (Appendix III) were developed and pre-tested before implementation. During the six-month intervention, GPs were requested to put up all the four posters in patient waiting areas to serve as an educational tool.

Patient booklets

Patient booklets were developed in collaboration with a medical illustrator to drive across important messages on the correct use of antibiotics and to impart knowledge about the differences between bacteria and viruses as well as self-care. These booklets were handed out to patients during one-to-one consultations with GPs by the GPs themselves. GPs were also encouraged to use the booklets as an educational tool. The booklets were double-sided to include both an English and a Maltese version. The English version can be found in Appendix IV.

Delayed antibiotic prescription pads

Standardised DAP pads (Appendix V) were first developed by the Maltese National Antibiotic Committee and then adapted based on our pre-intervention findings. Patient information regarding the purpose of the DAP, what symptoms to look out for, and how to engage in self-care were also added to the reverse side of the prescription.

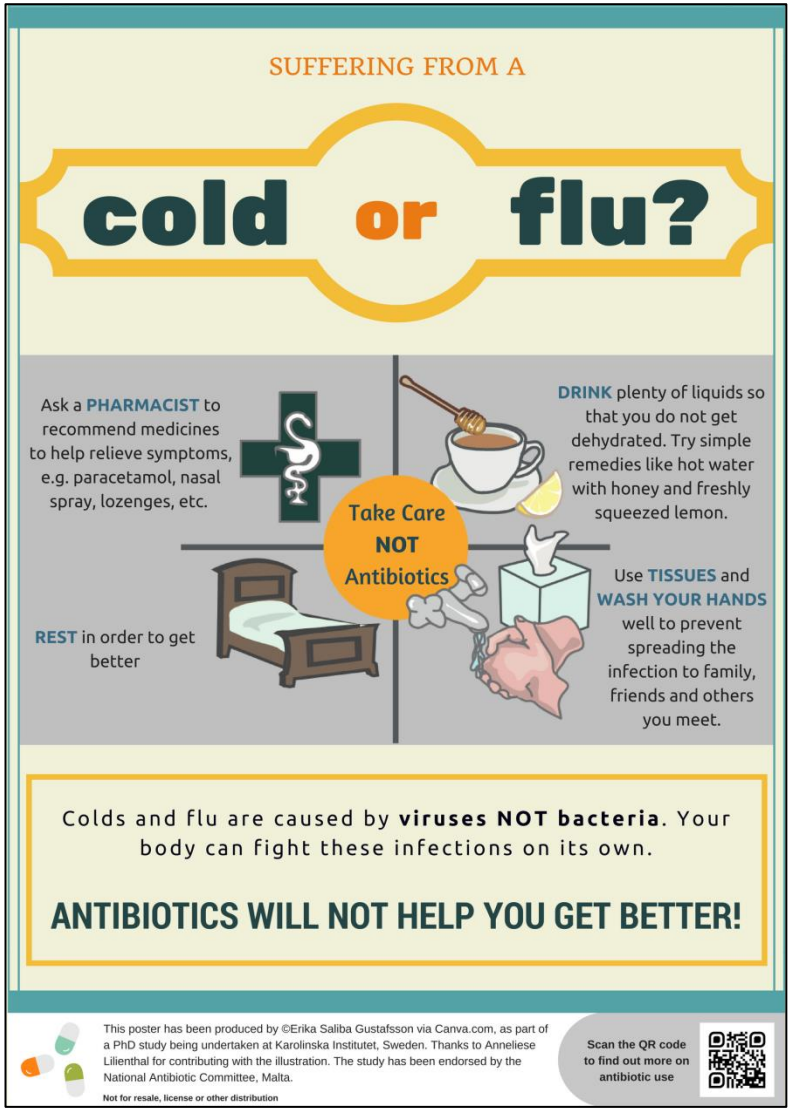
Updated national antibiotic guidelines

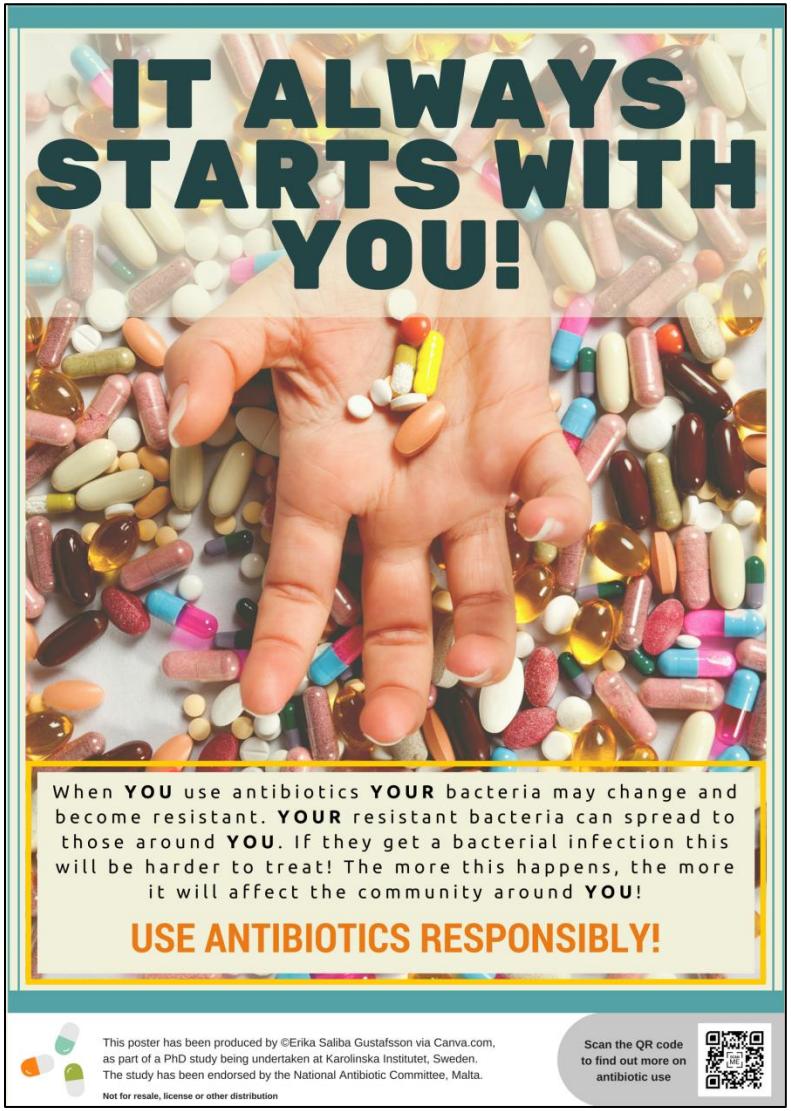
Hard and soft copies of the updated national antibiotic guidelines were provided to all participating GPs for their reference. This was combined with an educational session (*see below*) delivered to GPs as part of a series of educational sessions.

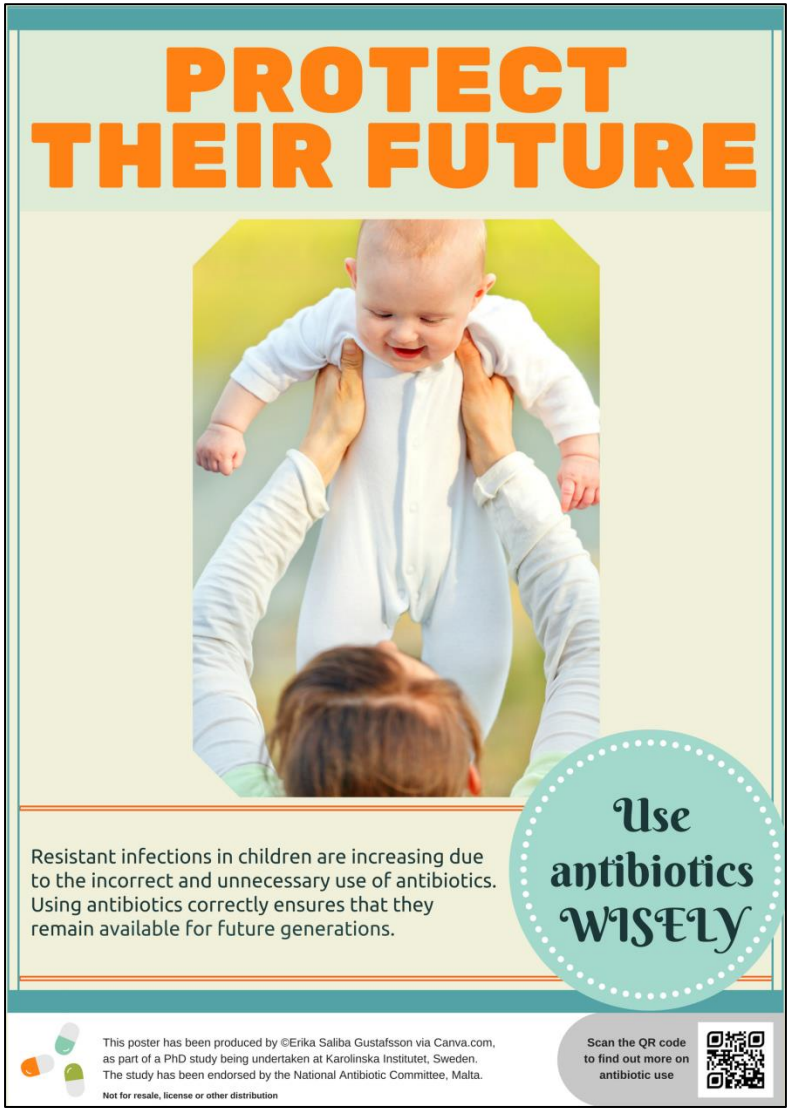
Educational package

Four interactive evening sessions were delivered to GPs over the six-month intervention period. The modules were delivered by four different lecturers and GPs were able to attend both in person and virtually through an online education platform specifically designed for the intervention. Sessions were also recorded to allow for later viewing if GPs were unavailable to attend in person on the day of the lecture. Topics included: (i) Antibiotic use and resistance from a global and local perspective – options for action, (ii) Introduction to the latest national antibiotic prescribing guidelines, (iii) The core principles of prudent antibiotic prescribing – appropriate antibiotic indications, dosages, choice and duration, and (iv) Effective patient communication – communication skills training and shared decision-making.

APPENDIX III: INTERVENTION MATERIALS – WAITING ROOM POSTERS




IT ALWAYS STARTS WITH YOU!
When YOU use antibiotics YOUR bacteria may change and become resistant. YOUR resistant bacteria can spread to those around YOU. If they get a bacterial infection this will be harder to treat! The more this happens, the more it will affect the community around YOU!
USE ANTIBIOTICS RESPONSIBLY!
This poster has been produced by ©Erika Saliba Gustafsson via Canva.com, as part of a PhD study being undertaken at Karolinska Institutet, Sweden. The study has been endorsed by the National Antibiotic Committee, Malta.
Not for resale, license or other distribution
Scan the QR code to find out more on antibiotic use


PROTECT THEIR FUTURE
Resistant infections in children are increasing due to the incorrect and unnecessary use of antibiotics. Using antibiotics correctly ensures that they remain available for future generations.
Use antibiotics WISELY
This poster has been produced by ©Erika Saliba Gustafsson via Canva.com, as part of a PhD study being undertaken at Karolinska Institutet, Sweden. The study has been endorsed by the National Antibiotic Committee, Malta.
Not for resale, license or other distribution
Scan the QR code to find out more on antibiotic use

APPENDIX IV: INTERVENTION MATERIALS – PATIENT BOOKLET (ENGLISH VERSION)

TOGETHER WE CAN KEEP ANTIBIOTICS EFFECTIVE

How to manage your respiratory tract infection

This booklet has been endorsed by the National Antibiotic Committee, Malta, and has been produced as part of a PhD study being undertaken by Erika Saliba Gustafsson at Karolinska Institutet, Sweden. Thanks to Anneliese Lilienthal for contributing to its design.

Notes:

Scan the QR code with your mobile phone to find out more on antibiotic use.

Malta, September 2016
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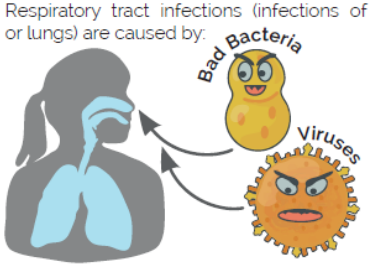
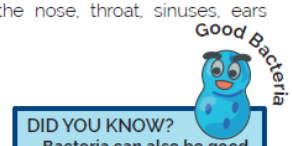
ALL ABOUT RESPIRATORY TRACT INFECTIONS

Respiratory tract infections (infections of the nose, throat, sinuses, ears or lungs) are caused by:





- Common colds, influenza (flu), and most respiratory tract infections are caused by viruses **NOT** bacteria
- Common colds, influenza (flu), most coughs, sinusitis, ear infections, sore throats and other similar infections most often get better without antibiotics – **your body can fight these infections on its own**

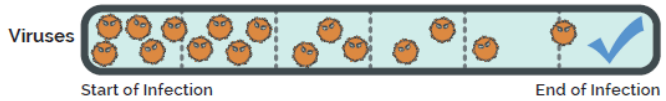
How long do respiratory tract infections usually last?*

THE INFECTION	CAUSE	USUALLY LASTS	DO ANTIBIOTICS HELP?
Otitis media (infection in one or both ears)	Mainly viral, Sometimes bacterial	4 days	No, however children under two with infection in both ears and any child with an ear infection that is draining, are likely to benefit from antibiotics
Sore throat	Mainly viral, Occasionally bacterial	7 days	No, unless symptoms get worse or last longer than 1 week
Common cold	Always viral	10 days	No, the common cold is caused by viruses
Influenza (flu)	Always viral	up to 14 days	No, influenza (flu) is caused by viruses
Sinusitis	Mainly viral, Sometimes bacterial	18 days	No, however if symptoms persist or worsen, antibiotics may be needed
Bronchitis	Always viral	3 weeks	No, taking antibiotics will not help you get better faster
Pneumonia	Usually bacterial	10 days or more	Most likely, consult your doctor

*Adapted from the Royal College of General Practitioners' TARGET antibiotic toolkit (2015)

ANTIBIOTICS – ALL I NEED TO KNOW

Antibiotics are precious medicines used to treat infections caused by bacteria. Antibiotics do not work against infections caused by viruses, such as the common cold; they will not help you get better faster, neither will they prevent you from spreading the infection.



No antibiotics needed! Your viral infection will get better on its own WITHOUT antibiotics.

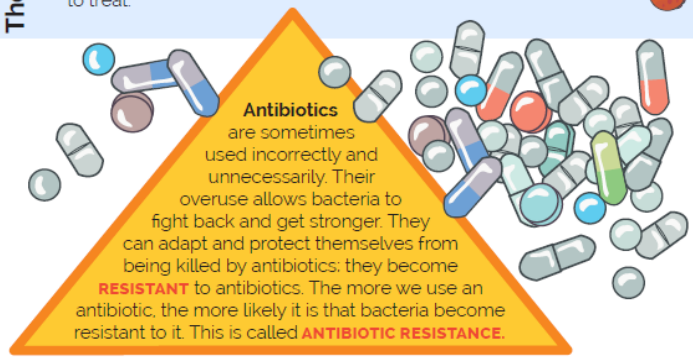
Taking antibiotics for a viral infection will NOT prevent you from getting a secondary bacterial infection.

The effect of antibiotics on our body

Most antibiotics cause side effects so use them with caution. Side effects can include diarrhoea, rashes, vomiting, etc.

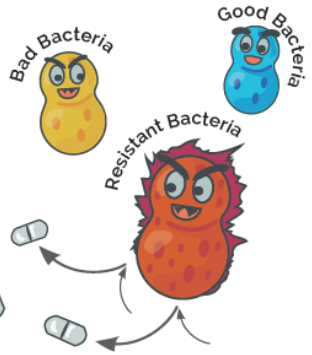
Be aware that antibiotics also kill good bacteria in our body that normally keep us healthy. This can result in other infections such as vaginal thrush (vaginal itching). Studies also show that high antibiotic use in children can increase their risk of asthma and obesity.

Using antibiotics can make your own bacteria resistant. This means that if you get another bacterial infection, it may be more difficult to treat.



ANTIBIOTIC RESISTANCE

If **YOU** use antibiotics incorrectly and unnecessarily it will lead to the development of resistant bacteria that cannot be killed by the most commonly used antibiotics. This leaves us with very few treatment options.



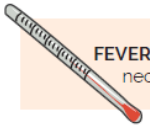
It always starts with YOU!

YOUR antibiotic use may cause **YOUR** bacteria to change and become resistant.

YOUR resistant bacteria can spread to those around **YOU**. If they get a bacterial infection this will be harder to treat!

The more this happens, the more it will affect the community around **YOU**!

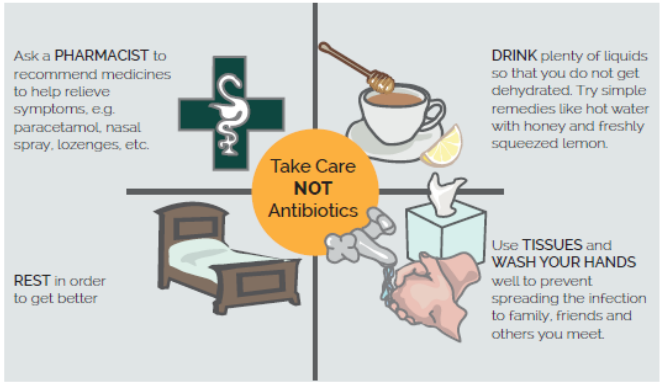
Antibiotic resistance is a threat and it affects **EVERYONE**.
If **YOU** use antibiotics responsibly **YOU** can help slow down the spread of antibiotic resistance. This will **keep antibiotics effective** now and for future generations.



FEVER is a sign that your body is fighting the infection: it does not necessarily mean that you need antibiotics!

SO WHAT SHOULD I DO?

If you feel that you are getting a cold or the flu:



HOW DO I TAKE ANTIBIOTICS RESPONSIBLY?

- ☑ **Only** take antibiotics **when necessary.**
- ☑ **Never pressure** doctors or pharmacists to give you antibiotics.
- ☑ **Follow your doctor's advice** on how and when to take the antibiotic.
- ☑ **Do not skip doses** and **always complete the entire course**; even if you feel better.
- ☑ **Avoid saving antibiotics**, instead **ask your pharmacist** for advice on how to dispose of any remaining antibiotics correctly.
- ☑ **Do not use any leftover antibiotics** and **never give antibiotics** to others.

Only take antibiotics if prescribed by a doctor

APPENDIX V: INTERVENTION MATERIALS – DELAYED ANTIBIOTIC PRESCRIPTION PAD

Rx

Doctor's name: .....

Doctor's mobile number: ..... Reg. no.: .....

(or doctor's rubberstamp)

DELAYED ANTIBIOTIC PRESCRIPTION

Patient's name: .....

Age: ..... **Sex:** ..... **Locality:** .....

Diagnosis:

- ❑ Common cold
- ❑ Acute sore throat
- ❑ Acute tonsillitis
- ❑ Acute laryngitis
- ❑ Acute cough / acute bronchitis
- ❑ Influenza (flu)
- ❑ Acute pharyngitis
- ❑ Acute otitis media
- ❑ Acute tracheitis
- ❑ Acute rhinosinusitis
- ❑ Other: .....

Date of prescription: ...../ ...../ 20.....

Antibiotic name & dose: .....

Frequency & duration: .....

This prescription is valid until: ...../ ...../ 20.....
(maximum 4 days after the prescription date)

Antibiotic should only be dispensed if upper respiratory tract infection symptoms persist and/or get worse **at least 2 days after the prescription date** (especially in the presence of fever).

*L-antibijotiku għandu jingħata biss, jekk is-sintomi tal-infezzjoni fil-pajp tan-nifs jippersistu u/jew imorru għall-agħar **imqar jumejn wara d-data ta' din ir-riċetta** (speċjalment jekk jitla' d-deni).*

Doctor's signature: .....

This delayed prescription pad has been produced as part of a PhD study being undertaken by Erika Saliba Gustafsson at Karolinska Institutet, Sweden. The study has been endorsed by the National Antibiotic Committee.

The majority of upper respiratory tract infections (of the nose, throat, sinuses, ears or upper part of the lungs) are caused by viruses. Your body can fight these viral infections on its own within a few days, with just some rest and by drinking plenty of water and warm fluids (e.g. warm water with honey and lemon, tea, etc.). **Antibiotics are not effective against viruses.** Taking antibiotics for viral infections will only expose you to unnecessary side effects and risk your body's bacteria becoming resistant to the antibiotic. As a consequence the antibiotic will likely be less effective in the future, if you or your family may need it for a serious bacterial infection. If this were to happen, the infection would be much harder to cure.

However, if you start feeling worse or fever develops/persists at least two days after having been seen by the doctor, this could indicate a bacterial infection. In this case, you should take this prescription to a pharmacist who will dispense the antibiotic prescribed. If necessary, contact your doctor again.

Il-biċċa l-kbira tal-infezzjonijiet fil-pajp tan-nifs (fl-imnieħer, fil-griżmejn, fis-'sinuses', fil-widnejn jew fil-pajp tan-nifs) huma kkawżati minn 'viruses'. Il-ġisem huwa kapaċi jfejjaq lilu nnifsu minn dawn l-infezzjonijiet ikkawżati minn 'viruses' fi ftit jiem, b'naqra mistrieħ u billi wieħed jixrob ħafna ilma u likwidi oħra (bħal mishun bl-għasel u bil-lumi, te, eċċ.). ***L-antibijotiċi ma jaħdmux fuq 'viruses'.*** *Jekk tieħu l-antibijotiċi għal infezzjonijiet ikkawżati minn 'viruses', tkun qed tesponi lilek innifsek għal 'side effects' bla bżonn, kif ukoll tirriskja li l-'bacteria' li jinsabu f'ġismek isiru reżistenti għal dak l-antibijotiku. B'hekk, hemm iċ-ċans li l-antibijotiku jsir anqas effettiv fil-futur, jekk inti jew il-familja tiegħek jkollkom bżonnu għal xi infezzjoni serja kkawżata minn 'bacteria'. Jekk jiġri dan, l-infezzjoni tkun ferm aktar diffiċli biex tikkuraha.*

Madanakollu, jekk taqleb għall-agħar jew jitlagħlek/jżidlek id-deni u jkunu għaddew imqar jumejn wara li jkun rak it-tabib, dan jista' jindika li jkun hemm infezzjoni kkawżata minn 'bacteria'. F'dan il-każ, ħu din ir-riċetta għand spiżjar sabiex jagħtik l-antibijotiku. Jekk tħoss il-bżonn, erġa' kellem lit-tabib tiegħek.

Scan the QR code to find out more on antibiotic use.
Għal aktar informazzjoni dwar l-użu tal-antibijotiċi, skanja l-'QR code'.

APPENDIX VI: INTERVIEW GUIDE [PAPERS I & II]

1) May you briefly tell me something about your work as a general practitioner?
2) How do you look upon the role of antibiotics in medicine?
3) How do you look upon antibiotic use and resistance in Malta (from a local and national level)?
    a. What factors do you think are contributing to this resistance in Malta?
4) What do you understand by the term 'unnecessary antibiotic prescribing'?
5) Have you heard about 'delayed antibiotic prescribing'?
    a. What do you understand by 'delayed antibiotic prescribing'?
    b. What are your views on 'delayed antibiotic prescribing'?
6) What are your general thoughts on the antibiotic prescribing practices of other Maltese GPs?
7) What are your views on the 'drug rep culture' in Malta?

So now I would like you to reflect upon the last time you prescribed antibiotics and another time when you did not prescribe antibiotics for a respiratory tract infection. I would like you to respond to some related questions, keeping those scenarios in mind.

8) What are your views on antibiotic prescribing for respiratory tract infections?
    a. Please describe your experience with antibiotic prescribing for respiratory tract infections.
    b. Please give me some examples of specific situations in which you prescribed or did not prescribe antibiotics for respiratory tract infections.
    c. How do you select which antibiotic to prescribe?
9) What kind of information do you provide your patients who present with a respiratory tract infection?
    a. How do you look upon your role as an educator?
10) Which factors do you think influence the way you prescribe antibiotics?
11) How do you feel your patients impact your antibiotic prescribing?
12) How do you feel the pharmaceutical industry/medical reps impact your antibiotic prescribing?
13) What are your thoughts on near-patient testing to aid in identifying infections?
    a. Do you make use of near-patient tests yourself?
14) What do you do if someone in your own family/a close relative has a respiratory tract infection?
15) What do you think are your specific needs in terms of antibiotic prescribing for respiratory tract infections?
16) Is there anything else that you would like to add?

Thank you for your time and valuable insight into this topic!

APPENDIX VII: GP DEMOGRAPHICS SHEET [PAPERS I-IV]

GP code: *[for office use only]*:

Date: _____

GP demographics

1) Date of birth:			
2) Sex:	□ Male □ Female		
3) Country of birth:			
4) Home address:			
5) E-mail address:			
6a) Telephone no.:		**6b) Mobile no.:**	
7) Country where you obtained your medical undergraduate degree:			
8) Years of practice as a doctor *(in total)***:**			
9a) Year of specialisation in family medicine *(if specialised)***:**			
9b) Did you full under the 'grandfather clause'?		□ Yes □ No	
9c) Are you currently a trainee?		□ Yes □ No	
10) Years of practice as a GP:			
11) How much do you currently work?		□ Part-time □ Full-time	
12) Approximately how many patients do you meet daily?			

13) Health sector of practice *(please tick all relevant options)***:**

Type of Sector	Location
□ Public sector	□ Healthcare centre □ Home visits
□ Solo practice	□ Private clinic □ Pharmacy clinic □ Home visits
□ Group practice	□ Private clinic □ Pharmacy clinic □ Home visits
□ Company doctor	

14) Areas within which you conduct home visits *(if applicable)***:**

15) Please write the addresses of your practice/s and tick your main clinic of practice:
(N.B. If you work in a pharmacy, please include the name of that pharmacy)

Address	Main clinic of practice *(please tick)*
	□
	□
	□

Thank you for your input!

APPENDIX VIII: SURVEILLANCE DATA COLLECTION FORM [PAPERS III & IV]

GP code: *[for office use only]*

Date of visit: _____ **Time of visit:** _____

Consultation provided: ☐ **at patient's home** ☐ **at GP clinic** ☐ **over-the-phone**

Patient form for respiratory tract complaints

1. Patient demographics *(please tick all items)*

Age	____ years	
Sex	☐ male	☐ female
Current smoker	☐ yes	☐ no
Other underlying co-morbidities/conditions (E.g. DM, COPD, CHF, immunodeficiency, etc.)	☐ yes	☐ no
	If yes: _____	
Patient took antibiotics (past 2 weeks)	☐ yes	☐ no
***If yes** (antibiotic taken for):*	☐ same complaint	☐ other complaint

2. Educational level *(tick only 1 option – highest achieved)*

☐ pre-school/kinder ☐ primary ☐ secondary ☐ upper secondary ☐ tertiary
☐ none of the above

3. Total number of people presently living in the household: _____

4. Regular (daily/several times a week) contact with children <5 years of age

☐ yes ☐ no

5. Total number of symptomatic days *(tick only 1 option)*

☐ <1 ☐ 1-3 ☐ 4-7 ☐ 8-14 ☐ >14

6. Signs and symptoms *(tick at least 1 option)*

☐ fever (>38.5°C) ☐ productive cough ☐ non-productive cough
☐ sore throat (no exudate) ☐ rhinorrhoea ☐ otalgia
☐ purulent otorrhoea ☐ tonsillar exudate ☐ odynophagia
☐ tender cervical nodes ☐ hyperpnoea ☐ dyspnoea
☐ sibilant rhonchi ☐ purulent sputum
☐ other: _____
☐ none of the above

7. Diagnostic tests *(tick at least 1 option)*

Rapid Strep A test		☐ positive	☐ negative		
CRP (mg/L)	☐ <10	☐ 10-24	☐ 25-49	☐ 50-99	☐ >100
Thoracic X-ray		☐ positive	☐ negative		

Other: _____
☐ none of the above

8. Aetiology *(tick only 1 option)*

☐ suspected viral infection ☐ suspected bacterial infection
☐ suspected mixed aetiology

9. Primary clinical diagnosis *(tick only 1 option)*

☐ common cold ☐ acute otitis media ☐ acute sinusitis
☐ acute pharyngitis ☐ acute tonsillitis ☐ acute bronchitis
☐ pneumonia ☐ influenza ☐ allergy
☐ acute exacerbation of chronic bronchitis/COPD/ asthma
☐ suspected TB ☐ other respiratory tract infection: _____

10. Antibiotic therapy *(fill in accordingly)*

Generic name			
Dose/Frequency		Duration	days
Route			

☐ delayed antibiotic prescription ☐ no antibiotics prescribed

11. Symptomatic treatment *(tick at least 1 option)*

☐ analgesic ☐ nasal spray ☐ expectorant ☐ antitussive
☐ decongestant ☐ anti-pyretic ☐ herbal remedy ☐ corticosteroids
☐ anti-histamine ☐ other: _____
☐ none of the above

12. Others *(if applicable)*

☐ allergy to penicillin
☐ referred to specialist/hospital
☐ patient/accompanying person asked for antibiotics
☐ sick leave certificate: ____ days
☐ patient is a regular client in my practice
☐ patient is not a Maltese resident
Nationality *(if known)*: _____