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EXPLORING BARRIERS AND ENABLERS TO THE IMPLEMENTATION OF FEASIBLE INTERVENTIONS THAT ADDRESS ANTIBIOTIC RESISTANCE IN ROMANIA

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Identification of feasible interventions to combat antibiotic resistance and associated implementation barriers and enablers for these interventions in Romania
Thesis for Doctoral Degree (Ph.D.)

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Preface

The COVID-19 pandemic has greatly impacted this PhD research, making this period even more memorable due to the constraints it introduced as well as the points of reflection it prompted.

A key learning for me, which was also captured in one of the many reports evaluating the pandemic, is that we are much better at responding to an acute crisis than a protracted one. The loss of urgency to act at national level on anthropogenic risks, such as antimicrobial resistance or climate change is paradoxical, despite the recognition of their longer-term existential effects. This ambiguous risk perception should trigger public health professionals, to reframe these longer-term 'quiet' challenges, into acute problems and actionable strategies. In Romania, despite some recognition of antimicrobial resistance as a major concern, action to contain it remains timid. This PhD is a small endeavor to shed further light on the intricacies of the phenomenon and offer resource-efficient solutions that could be explored. Beyond my growth and learning as a researcher, for me, this journey has been marked by hope, as I have witnessed the immense human capital resources that can be harnessed when a problem is brought to the forefront and people are asked to contribute.

As my PhD comes to an end, it coincides with a potentially transformative shift in human behavior with the emergence of Artificial Intelligence (AI). This presents new challenges and opportunities for behavior change interventions, creation and diffusion of knowledge, and decision-making. Policymakers will undoubtedly face significant challenges and opportunities in this regard. A fundamental step is to develop a profound understanding of societal patterns, agency, and structural considerations and think through creatively on how AI would impact these. Amidst this transformation, our humanity and capacity to collaborate should remain sources of strength. This PhD has provided numerous insights, primarily related to the complexities surrounding antibiotic use, but also encompassing broader aspects of agency and structural determinants of healthcare providers' behavior and their interactions with patients and communities. It is crucial to build upon such findings and establish pathways to foster and strengthen trustful bonds that enable layers of collective action, to effectively address challenges such as antimicrobial resistance.

Abstract

Background: Antimicrobial resistance (AMR) is a major global public threat to human and animal health and sustainable development with significant economic and societal implications. The key drivers of AMR are numerous with one key one being non-prudent use (whether misuse or overuse) of antibiotics. Non-prudent use practices are: inappropriate prescribing, self-medication and antibiotic use without prescription, non-adherence to appropriate or recommended treatment. These may result from deficient patient-doctor interactions, treatment characteristics, access to treatment, storing of antibiotics at home, limited access to healthcare, and from intentions to self-medicate. A significant number of these factors are directly associated with human behavior and occur in a community setting. The Behavior Change Wheel (BCW), which proposes the identification of capabilities, opportunities and motivations that may dictate or change a certain behavior, is a useful framework to further understand different stakeholders' behaviors that drive antibiotic consumption (ABC) and AMR as well as related interventions. Furthermore, while antibiotics are extensively used in the community, most interventions implemented thus far are set in health facilities and are delivered or are targeting healthcare professionals. This approach misses other community spaces and engagement opportunities. Romania has the highest total ABC for systemic use in the European Union (EU). Data on public knowledge on antibiotics in this country, shows a decline in knowledge compared to previous years. All these suggests that the Romanian setting would benefit from addressing related ABC and AMR issues through community-based interventions. Furthermore, the Romanian health and social systems are confronted with challenges that parallel or will be encountered by other countries.

Aim: The overall aim of the project was to construct an evidence base for developing and implementing community-based interventions to combat AMR and inform relevant policy documents, in view of combating AMR in Romania.

Methods: Two studies (study I and III) relied on qualitative methodology (content analysis), using semi-structured interviews to understand pharmacists and family doctors' perceptions on related roles as well as ABC and AMR in Romania. Study I captured data from 18 interviews with pharmacists whereas study III from 12 family doctors' interviews. Study III represented a quantitative and qualitative synthesis of evidence on the value of community-based educational interventions to improve antibiotic use. Seventy-three papers were included, ranging from quantitative, qualitative and mixed-methods studies. Study IV used a quantitative methodology to capture perceptions of future Romanian health professionals about antibiotic use. A total of 479 participants completed the study IV survey- 233 medical students from seven faculties and 246 pharmacy students from four faculties.

Key findings: Study I articulated three sub-themes that would describe pharmacists' perceptions. The first one referred to their difficulties in 'maintaining equilibrium between ethics, law and economy'. The second sub-theme characterized 'antibiotic resistance problem as rooted in a low social capital environment'. This reflected the deep causes of antibiotic resistance that go beyond strictly antibiotic management. Lastly pharmacists were found to be 'wanting to fulfil their educational role', which is how they felt they could best contribute. The overarching theme

'Undervalued medicines' professionals struggling with agency related and structural barriers to meet their deontological duties'- reflects the way pharmacists perceive their current societal standing as well as how their roles are challenged by several barriers that impact their decision-making processes. **Study II** revealed advantages of community-based behavior change interventions in improving antibiotic use. Multifaceted interventions were found to provide the greatest benefits. Particularly, interventions that combined educational components with persuasion had a better impact across most outcomes (knowledge, attitudes, and beliefs; antibiotic adherence; antibiotic use) compared to interventions focused solely on education. The review also identified challenges in evaluating this type of research and emphasized the necessity for standardized approaches in study design and outcome measurements. While there is some emerging evidence on the cost-effectiveness of these interventions, it remains limited in scope. **Study III** identified the perceived factors affecting ABC and antibiotic prescribing by family doctors. Some factors pertained to the perceived behavior of family doctors or patients, others were associated with different systems, local contexts, and the COVID-19 pandemic. An overarching theme was articulated: 'family doctors in Romania see their role differently when it comes to antibiotic resistance and perceive the lack of patient education or awareness as one of the major drivers of ABC'. All these perceived factors spanned the capability, opportunity, and motivational domains of the BCW and could be addressed through a mix of interventions. **Study IV** found that most students responded they felt prepared in at least 14 areas (covered by 14 questions) (out of 22 areas/questions for medical students, and 19 for pharmacy students). In terms of willingness to engage, a similar trend was observed among both medical and pharmacy students, with scores of 2 out of 4 (4 being the maximum score showing the maximum engagement willingness, considering there are 4 areas of engagement) and 3 out of 4, respectively. A significant proportion, approximately 53.5% (n=254), confirmed that they received sufficient training to ensure the appropriate use of antibiotics in their professional fields. Students who scored low on preparedness expressed a desire for additional education. Regarding their estimation on how antibiotic use will evolve in Romania, the highest number of responses from medical and pharmacy students (n=159, 33.5%), highlighted the view that the situation would worsen. Regarding the survey design, the factor structure identified through Exploratory Factor Analysis (EFA) could not be validated through Confirmatory Factor Analysis (CFA), indicating that further adjustments are required for the model and/or questionnaire.

Conclusions: Promising evidence supports the benefits of community-based interventions in enhancing antibiotic use, particularly multifaceted approaches. Considering the impact of the COVID-19 pandemic, policymakers should consider these interventions alongside clinical-based approaches to rebuild trust. Inclusive participation in community-based interventions fosters public ownership and utilization of community channels. Romanian healthcare professionals hold diverse perceptions of AMR. Factors influencing appropriate antibiotic use and AMR in Romania include the behaviors of pharmacists, family doctors, patients, the health system, local contexts, and the pandemic's impact. Findings also have important implications for the education and training of future Romanian healthcare professionals, necessitating further research to establish standardized methods for monitoring and evaluating progress in preparedness, engagement willingness, and teaching preferences regarding antibiotic use.

List of scientific papers

I. **Ghiga, I.**, Stålsby Lundborg, C. **'Struggling to be a defender of health' –a qualitative study on the pharmacists' perceptions of their role in antibiotic consumption and antibiotic resistance in Romania**. *J of Pharm Policy and Pract* **9**, 10 (2016).

II. **Ghiga I**, Sidorchuk A, Pitchforth E, Stålsby Lundborg C, Machowska A. **'If you want to go far, go together'-community-based behaviour change interventions to improve antibiotic use: a systematic review of quantitative and qualitative evidence.** *J Antimicrob Chemother.* 2023 May 6

III. **Ghiga I**, Pitchforth E, Stålsby Lundborg C, Machowska A. **Family doctors' roles and perceptions on antibiotic consumption and antibiotic resistance in Romania: a qualitative study.** *BMC Prim Care.* 2023 Apr 10;24(1):93.

IV. **Ghiga I**, Pitchforth E, Popescu GA, Fulop I, Stålsby Lundborg C, Machowska A. **How do future Romanian health professionals feel about antibiotic use? Results from a cross-sectional survey in Romanian Universities of Medicine and Pharmacy** (manuscript)

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

Contents

List of abbreviations

AMR	Antimicrobial resistance
ABC	Antibiotic consumption
APEASE	Behavior Change Wheel criteria to assess interventions appropriateness: Acceptability, Practicability, Effectiveness, Affordability, Side-effects, and Equity
AWaRe	Classification system which categorizes antibiotics into three groups (Access, Watch, and Reserve) considering their impact on antimicrobial resistance.
BCW	Behavior Change Wheel
CFA	Confirmatory Factor Analysis
COM-B	Framework based on three key components: Capability, Opportunity, and Motivation (COM), which are interconnected and influence behavior (B)
COREQ	COnsolidated criteria for REporting Qualitative research Checklist
COVID-19	Coronavirus disease 2019 caused by the virus severe acute respiratory syndrome coronavirus 2
DALY	Disability-adjusted life years
DDD	Defined daily dose
ECDC	European Centre for Disease Prevention and Control
EFA	Exploratory Factor Analysis
EU	European Union
EEA	European Economic Area
FAO	Food and Agriculture Organization
GDP	Gross domestic product
MeSH	Medical Subject Headings
MRSA	Methicillin-resistant *Staphylococcus aureus*
PICOS	A method to define a researchable question through a systematic review. The structure for the research question uses a PICOS structure, which specifies the: population, intervention, comparison, outcome, and study(ies) design, that are of interest.
PoC diagnostics	Point-of-care diagnostics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

ToC	Theory of Change
WHO	World Health Organization
WOAH	World Organization for Animal Health
UN	United Nations
UNEP	United Nations Environment Programme

1 Background

1.1 Global outlook on antimicrobial resistance

1.1.1 AMR an imminent global challenge demanding immediate and concerted action.

Antimicrobial resistance (AMR) is a major global public threat to human and animal health and sustainable development with significant economic and societal implications[1–3]. It is a pervasive phenomenon as it not only affects individuals who are taking antibiotics themselves, but also other individuals whose health can be impacted by the collective use of antibiotics within a population[4]. While efforts to quantify the impact of AMR are challenged by various difficulties, conservative results in this respect paint a worrying picture. Difficulties in measuring AMR burden of disease spring from: complexities of registering AMR related features (e.g., deciding which drug resistant infection to track, what protocol to use for their identification; the fact that infections with one bacteria can lead to a series of clinical syndromes, and difficulties in measuring sepsis); lack of good quality microbiological data and difficulties in linking these to clinical-related outcomes; limited laboratory capacities, different methodological approaches to performing measurements and minimal integration with other one-health fields such as animal, husbandry and environmental sectors among others [5]. However, even with these various limitations, conservative estimates from 2019, would indicate that at a global level, 4.95 million deaths could be linked to AMR[6], ranking as the third most common cause of death globally[6]. Furthermore, a study conducted in the European Union (EU) and European Economic Area (EEA), measuring the health burden of five types of antibiotic-resistant infection caused by eight bacteria, found an overall related DALY rate of 170 per 100000 population, which is similar to the combined burden of HIV, influenza, and tuberculosis for the measured period in the same setting[7]. These 2015 results show an uprising trend, representing a double burden compared to the 2007 status [7,8]. Within the EU, it is approximated that AMR is connected to an annual toll of 33,000 deaths and a financial burden of €1.5 billion each year, attributed to expenses related to healthcare and decreased productivity[9].

In recognition of the urgency of the situation, globally in the past decade, several initiatives have been developed and are being implemented to curb AMR. Some of these developments are: the Global Action Plan[10], the 2016 political declaration at the United Nation High Level Meeting on AMR[11] (UN, 2016), the work of the Interagency Coordination Group on AMR including its 2019 report (IACG, 2019), new global structures such as the quadripartite joint secretariat (first established in 2019 as a tripartite secretariat and becoming quadripartite in 2022, representing a cooperation between World Health Organization (WHO), Food and Agriculture Organization (FAO), United Nations Environment Programme (UNEP) and World Organization for Animal Health (WOAH))[12], Global Leaders Group on AMR[13], the Independent Panel on Evidence for Action against AMR[14], the Multi-Stakeholder Partnership Platform and AMR Multi-Partner Trust Fund[15]. All these have raised the urgency of addressing AMR in a comprehensive manner and have also unlocked resources available for countries to strengthen their capacities and capabilities, although funding is still limited.

However, their success depends on operationalization and last-mile implementation of proposed recommendations. These later efforts can be facilitated by a greater understanding of the key drivers of AMR, the effectiveness of various interventions to tackle them, identifying required resources – both human and financial, as well as galvanizing a series of enabling factors such as sustained local

political will, consistent and continuous implementation of programmes, nurturing valuable partnerships and cross-sectorial collaboration.

1.1.2   In Europe, the fight against AMR remains a fluctuating endeavor, marked by varying degrees of success.

In the EU, several policy instruments were developed to control the AMR phenomenon[9,16]. However, there is wide variation in policy outcomes -such as antibiotic consumption (ABC) and resistance rates, across the European member states[17,18]. This is to be expected as member states have different social and health system organization and capacities, different economic status, priorities, and cultural and behavioral characteristics.

While noting this large variability among countries, a trend that has been maintaining for several years, shows higher percentages of AMR in the eastern and southern regions of Europe compared to the northern and western parts[19]. This trend seems to be most consistent for resistance to third-generation cephalosporin and carbapenems in *Klebsiella pneumoniae*, and carbapenem resistance in *Acinetobacter* spp[20]. The observed pattern is a cause for concern as it indicates difficulties in managing healthcare-associated infections and is believed to be linked to the increased strain on intensive care units due to the impact of COVID-19. However, overall, between 2016 and 2020, the most significant disease burden was attributed to infections caused by third-generation cephalosporin-resistant *Escherichia coli*, with *Methicillin- resistant Staphylococcus aureus* (MRSA) and third-generation cephalosporin-resistant *Klebsiella pneumoniae*[20(p20)]. Data from 2021, shows progress compared to past years, regarding the number of laboratories that are now providing data to the European surveillance networks but not all use a standardized approach. When it comes to development of national action plans on AMR (as advised by the 2015 Global Action Plan on AMR), 44 out of the 52 countries covered by 2021 data, reported they had developed such a plan. In the EU/EEA countries group, 68% of countries (19 of the 28) met the WHO target for countries regarding the consumption of antibiotics[20] (the target is for 60% of total antibacterial consumption in a country to come from the category called "Access" in the WHO's Access, Watch, Reserve (AWaRe) classification list)[21]. Remaining antibiotics are in the 'Watch' and 'Reserve' category meaning they are recommended as first-choice for severe clinical presentations or resistant pathogens to the antibiotics on the 'Access' list ('Watch'), or as last-resort antibiotics for multidrug-resistant infections ('Reserve').

The most recent European Commission Eurobarometer survey results on public knowledge, attitudes and practices regarding AMR and antibiotics, seem to indicate improvements at EU level, with 2021 data suggesting that 23% of Europeans took antibiotics in oral form, the lowest figure in more than ten years[19]. Approximately 8% of antibiotics were taken without a prescription. A continuous concern is that only half of the respondents indicated that antibiotics are ineffective against viruses, a similar trend that reported in the previous 2018 Eurobarometer when 66% of participants reported that antibiotics are not efficient to treat colds and 43% reported antibiotics do not work against viruses[22]. In 2021, the main reasons for taking antibiotics were for treating urinary tract infection (15%), a sore throat (13%), bronchitis (12%), a cold (11%), flu (10%), fever (10%) or COVID-19 (9%) while in the 2018 data, approximately 20% of antibiotics were taken to treat flu or cold. Therefore, while some changes can be noticed when it comes to reasons for taking antibiotics, some aspects are

still similar between 2018 and 2021 – (e.g. knowledge on antibiotics efficiency in treating viral diseases).

1.2   Multiple factors contribute to the consumption of antibiotics and the emergence of resistance

The key drivers of AMR are numerous and span: non-prudent use (misuse or overuse) of antibiotics, antivirals, antiparasitic or antifungal medicine [23,24,25], lack of access to clean water and inadequate sanitation [24,26], poor infection prevention and control practices [24], increase in healthcare interventions [24,27], impeded access to quality medical products such as therapeutics, vaccines or diagnostics [24], challenges in implementing legislation and a general lack of awareness and understanding regarding the factors driving and the consequences of AMR [24]. These drivers are further exacerbated by the lack of development of new classes of medicines such as antibiotics and increased global interconnectivity which facilitates rapid spread and development of AMR [27,28]. Adding to the complexity, the COVID-19 pandemic is believed to have exacerbated the AMR problem [29–32,33] as a result of prescribing of broad-spectrum antibiotics, particularly in the beginning of the pandemic [34], unnecessary over-prescription of antibiotics [35,36] and self-medication with antibiotics in an attempt to prevent viral infection [36,37].

These AMR factors require specific and targeted interventions. In the case of non-prudent use of antibiotics, the following practices contribute to the emergence of drug-resistant bacteria: inappropriate prescribing, self-medication and antibiotic use without prescription [38], non-adherence to appropriate or recommended treatment[39,40] . These may result from deficient patient-doctor interactions (usually a consequence of these being time-constrained)[41], treatment characteristics[41], access to treatment[41,42], storing of antibiotics at home[43], limited access to healthcare[43], and from intentions to self-medicate[43]. A significant number of these factors are directly associated with human behavior, emphasizing the necessity to understand which interventions are effective to address non-prudent use of antibiotics and which are appropriate within diverse contexts, which may have varying behavioral norms and encounter different social and economic limitations.

Systematic reviews highlight effective interventions, including parent education, combined patient/clinician education, and electronic decision support systems, aimed at reducing inappropriate antibiotic prescribing for acute respiratory tract infections[44]. Additionally, interventions centered around public-targeted communication shown positive effects in improving antibiotics use[45]. Other research aimed to map government policy interventions[46] and interventions aimed at improving antibiotics prescribing by general practitioners[47]. A recent systematic review examined the effectiveness and cost-effectiveness of behavior change interventions aimed at improving the prescription and utilization of antibiotics in low-income and middle-income countries[48]. The findings of this review revealed that while antibiotics are extensively used in the community, interventions implemented thus far were set in public health facilities, targeting doctors, nurses, and other medical staff. The most prevalent type of intervention was providers' education[48].

1.3   Behavior change theoretical considerations and related interventions

Factors affecting the misuse of antimicrobial products, are often dictated by the interaction between the individual and their environment[49,50]. Moreover, prescribing, dispensing, or using antibiotics involve processes of decision-making. However, the predominant design of available interventions, rely on a simplified assumption that by obtaining knowledge and creating more awareness around the problem would translate into a better health outcome, meaning that the decision-making process of using antibiotics would be conditioned by appropriate knowledge. But there is now widespread recognition that personal decisions are impacted by several individual, structural and social factors. Furthermore, social influences and expectations need to be understood, at all levels. In addition, attitudes are not purely informed by reason, but are the result of a culmination of emotional, intuitive, cognitive biases which make perceptions as important as reality. All these signals to the need to use behavior theories to enhance the understanding of the AMR problem, as well as inform the design and evaluation of interventions and policies. A 2011 review of different behavioral frameworks, discussed drawbacks of traditional models or theories such as Theory of Planned Behavior or the Health Belief Model which do not capture the impact of impulsivity, habit and self-control among others[51,52], and proposed a more all-encompassing framework to meet these gaps. This approach is structured in the form of a Behavior Change Wheel (BCW), anchored in an understanding of the different capabilities, opportunities and motivations that may dictate or change a certain behavior.

> ➢ Capabilities refer to physical capabilities in the form of skills, abilities that may be acquired through practice and to psychological capabilities such as knowledge, memory attention, decision processes and behavioural regulation.
> ➢ Opportunities pertain to physical and social factors, such as the environmental context or resources and the social influences, pressures, norms and comparisons.
> ➢ Lastly motivation is structured into automatic motivation that may consist of reinforcements (carrots and sticks) and reflective motivation that refer to beliefs about capabilities, roles, identities, goals.

These are further complimented by a set of nine intervention functions and seven enabling policy categories[51]. The nine interventions consist of education, persuasion, incentivization, coercion, training, enablement, modelling, environmental restructuring, and restrictions. Policies categories consist of guidelines, communication/marketing, fiscal measures, regulation, legislation, service provision and environmental/ social planning[51]. While apparently complex, the BCW has become more and more used including in the realm on antimicrobial related research[48].

In addition to this framework, several other concepts and theories may be pertinent to advance understanding the context and suggesting a way forward for designing appropriate interventions.

Agency and structure are fundamental concepts in sociological theory. Germov[53] defines *agency* as "the ability of people, individually and collectively, to influence their own lives and the society in which they live", in other words the belief that one can perform an action that would lead to a certain result successfully[54]. On the other hand, *structure* is conceptualized as "the recurring patterns of social interaction through which people are related to each other, such as social institutions and

social groups"[53]. There are different views, which led to the emergence of various theories, on the dominance of agency vs structure and vice-versa. Thus, within the context of our research these concepts are worth considering, to enhance the understanding of perceptions of whether enhancing agency and control of beneficiaries of the interventions could bolster the ownership and investment in these activities– for example by offering a selection of choices on the type of interventions that could be implemented or providing opportunities to contribute to the design of interventions. However, crucial questions remain of how much agency could motor change if structural barriers remain in place.

Social capital is another concept that would help explore the topic of this research. Rostila[55] proposes the following definition of social capital: "*the social resources that evolve in accessible social networks or social structures characterized by mutual trust*". Drilling into the effect on health, it is proposed that social capital can have a *compositional effect* on health through the direct influence of trust on individual health, but also a *contextual effect* due to the impact that social trust has on the socio-political determinants of health - the political and social environment, the welfare regime[56]. Social capital can be classified using the concepts of *bonding, bridging and linking capital*. Bonding capital pertains to relationships and trust formed within close-knit groups of affiliation, whereas bridging capital encompasses a broader spectrum by occurring between individuals who acknowledge their socio-demographic differences[57,58] . Linking capital refers to the connections among individuals that involve a formal or institutionalized authority within society[59].

Social capital is intricately linked to the concept of trust. However, trust is a complex multifaceted societal concept, with several sociological theories endeavoring to elucidate and explore its intricacies. Social exchange theory (more correctly theories) is one of the most highly influential theories in the social sciences, with far-reaching implications spanning multiple disciplines. The original theory stems from the 1920s' and has undergone many transformations and adaptations within different fields[60–64]. However, at its core, it postulates the notion that individuals have a sense of expectation of reciprocity and return of benefits. Meeting these expectations over time can sustain trust. Social identity theory suggests that group membership plays an important part in trust building, being enhanced when individuals feel a sense of shared identity with others. Other areas of research focused on identifying traits that would promote trustworthiness. These are attributes such as ability, benevolence, and integrity which a trustor expects from a trustee[65]. Overall, trust relies on a mix of cognitive evaluations and emotional experiences, and develops through sustained interactions, consistent behavior, and the meeting of expectations.

Lastly another key important area connected to values and behavior change pertains to cultural specificities. A useful framework used in past research to understand various cultural specificities is Hofstede's model of cultural dimensions, which proposes six cultural dimensions to explore how culture may influence society including its norms, communication aspects, organizational structures,

leadership styles[66]. These dimensions are individualism vs. collectivism[a], uncertainty avoidance[b], power distance[c], masculinity vs femininity[d], long-term vs short term orientation[e], and indulgence vs restraint[f]. The use of this anthropological model may explain some of the differences between countries and help contextualize further the findings from this thesis.

1.4 AMR represents a significant and inadequately researched issue in Romania, demanding increased attention and investigation

1.4.1 Elevated levels of antibiotic consumption and resistance prevail, presenting a significant concern in Romania

According to the latest 2021 data reported to ECDC, Romania has the highest total ABC (community and hospital sector) for systemic use, registering 25.7 Defined Daily Dose (DDD)/1000 inhabitants / day. This is more than triple the rate of the Netherlands, which had the lowest ABC at 8.3 DDD/1000 inhabitants/day[18]. Similarly to 2020, in 2021 the mean total consumption (community and hospital sectors combined) of antibacterials for systemic use in the EU/EEA was 16.4 DDD per 1 000 inhabitants per day[18].

Penicillins are the most utilized antibiotics in Romania[17]. Furthermore, there is a persistent tendency of higher ABC in community settings as opposed to hospital settings. This is an inversed trend compared to other EU countries[17,18.]

Regarding resistance patterns, similarly to other EU countries, in Romania there has been a statistically significant increase in resistance to several classes of antibiotics for *Klebsiella pneumoniae* and *Acinetobacter* spp[20].

1.4.2 There is limited knowledge among the Romanian public on antibiotic use

Most of the data on public knowledge on antibiotics in Romania is captured through the EC Eurobarometer survey. In comparison to other EU countries, for the respondents from Romania there was a decline in knowledge compared to previous years. The survey results also revealed that doctors are perceived as the primary source of information on antibiotics, followed by pharmacists[19].

Contrary to the findings of the Eurobarometer survey, a separate study carried out in 2019 within a specific county in Romania (Mures) revealed that the majority of participants demonstrated a high

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[a] Indicating the extent to which individuals prioritize their own interest over those of groups. A collectivist society places greater emphasis on group harmony and success.

[b] Indicating the willingness of individuals to tolerate uncertainty, ambiguity and embrace change.

[c] Reflects the degree to which individuals in a less privileged position within society accept and anticipate an unequal distribution of power.

[d] Masculine societies value competition, and emphasize assertiveness, material rewards and praise achievements. Feminine societies praise cooperation, modesty, quality of life and tend to be more consensus oriented.

[e] Indicating the degree to which a society prioritize maintaining traditions and norms over more pragmatic shorter-term results.

[f] Indicating the extent to which a society values gratification and places greater value on satisfying basic human desires as opposed to exercising restraint with stricter social norms and controls.

level of understanding regarding antibiotic usage and the potential dangers associated with self-medication using antibiotics[67].

1.4.3 The Romanian context exhibits distinct characteristics that should be noted when seeking to comprehend the broader landscape.

1.4.3.1 Key socio-economic data

Key socio-economic data on Romania[17–20,68–75,76] as well as other details that are discussed in 1.4.3 is summarized in Figure 1.

Romania is now a parliamentary republic which emerged from an over 40 years communism regime in 1989 and joined the EU in 2007. Romania has had a decreasing population trend for the past thirty years. International indexes reflect conservatory progress around inequalities and human development: GINI[g] - was 35.8 in 2018 (Romanian GNI maximum value of 39.6 in 2006 and minimum of 23.3 in 1989)[73] (WB, 2020b) and Human Development Index[h] was 0.828 (in 2019) ranking 49 out of the 187 UN-recognized countries and territories (a progress since the 0.7 value 1990)[74].

Life expectancy in Romania is 76 and under-5 mortality rate per 1000 live births is 7.3[74]; both these indicators place the country behind the EU averages. Romania also has a high tuberculosis incidence[i] compared to other European countries.

The country is administratively structured into counties, cities, towns, communes, and villages. There are 41 counties plus the Bucharest region, which is the capital of Romania.

Figure 1 lists the key data from the Romanian setting on antibiotics, its health system, socio-cultural profile and relevant general country characteristics.

All these data suggest a country that has gone through a gradual transition, which is on its way to graduate into a higher income classification country. However, Romania is still prone to high inequality and a delayed reflection of its overall increased income status into population's health status. A future challenge for the country is the increasing shift in the population pyramid, with an alarming natality decrease. In addition, it can be inferred that as the life expectancy will continue to maintain a growing trend, this will pose a greater demand in terms of populations accessing hospital care in their second half of their life. Tuberculosis continues to remain a challenge when it comes to infectious diseases.

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[g] measures income inequality on a scale from 0 – perfect equality to 100- perfect inequality
[h] indicates long-term progress across three of human development: a long and healthy life, access to knowledge and a decent standard of living
[i] 68 per 100, 000 people

Antibiotics	• Antibiotics cannot be sold without a medical prescription unless in cases of medical emergencies and cannot be bought online[79] • Consistent above average resistance to key antibiotics[17,18] • The highest antibiotics consumptions rates in the EU[17,18] • Public knowledge on correct use of antibiotics is low[19, 22, 68] • The National Action Plan on Antimicrobial Resistance is under development
Health system	• Decentralized and pluralistic mandatory social health insurance system (key institutions: Ministry of Health, National Health Insurance House, National Agency for Medicines and Medical Devices)[78] • Contributions to the healthcare system are through directly payment by employees, however while designed as an approach that should ensure national coverage, it is estimated that 11% of the population is not insured, with most of these people being in the rural setting[71] • Financing of the healthcare system is low compared to other EU countries[71] • Brain-drain of healthcare workforce towards other EU countries[71, 72] • Number of family medicine practices and pharmacies have been slightly decreasing and rural areas are underserved[76]
Socio-cultural profile	• High potential for the underdeveloped areas of cognitive and emotional intelligence, creativity and learning • Defensive stance, prone to pessimist traits such as skepticism and cynicism • Competitiveness in the work field, with work as a social affirming tool • Family and religion very important • Lack of trust in people, except for family members • Very adaptable and adjustable • See themselves as warm, friendly, intelligent, funny, patriotic people *(data synthesized from findings of David[75])*
General country characteristics	• Upper-middle income country, with a per capita GDP of 14, 643.2 USD [73] • Population of 19.1 million people [74] • Overall deaths increased by 14% compared to 2019 [76] • Life expectancy is 76 – with decreasing natality [76]

Figure 1 Key data on Romania

1.4.3.2   Romanians' socio-cultural profile

Using the previously mentioned Hofstede's model as a framework, Romanians exhibit the following cultural characteristics:

- **High power distance** indicating an acceptance of hierarchy more likely due to fear, which oftern leads to frustrations and an aversion towards authority[77]. Research also found that there is a propensity for negativity and non-obedience for norms and rules, likely stemming from the communist past[75]. Regarding work, Romanians have a strong desire for

competence and in favorable socio-cultural conditions, this translates into high performance. This is evident in the behavior of Romanian diaspora and those employed in multinational companies as compared to those that work mostly in state structures[75].

- **Collectivism** rather than individualism, signaling less self-assertion with the needs and goals of the group tending to be prioritized over those of the individuals[75,77]. This has implications on work environments where individual performance may not be rewarded similarly to western societies. Romanians value greatly family, compared to other social groups[75].

- **High uncertainty avoidance**, indicating a higher resistance to change, innovation and general tendency to align with overall decisions as a safety mechanism[77]. This also stems from the communist past and impacts current Romanian leadership styles that tend to punish mistakes – even from high-performers, rather than focus on identifying strengths and incentivize individual performance. Therefore, risk-taking behavior is low. For Romanians, avoidance also leads to defensiveness, which further translates into inferiority or superiority complexes[75].

- An **intermediate stance between long-term and short-term orientation**, as Romania is not a past-oriented society but nor is it one that is fully characterized by present-day pragmatism[77]. National decisions do not seem to consider fully and in a consistent manner the impact on future generations – the clearest examples being the economic actions taken after the 1989 revolution where short-terms gains for few prevailed over long-term economic growth. Reserch found that tradition and security score at a medium level[75]. In particular the moderate assessment on security, is attributed to Romania having adhered to NATO and EU, which improved the population's security outlook[75].

- **Relative femininity** with Romania having a consensus-oriented society, however reaching consensus is sometimes impeded by the negative outlook (cynism and skepticism)[75]. Some of the patterns in Romanian society are thought to stem from the long term impact of the communist's regime, which promoted a doctrine of egalitarianism and determined behaviors that avoided drawing attention to oneself[77].

- **Restraint**, rather than indulgence, as in line with other past communist countries, it is marked by a focus on day-to-day needs (also linked to the difficult economic situation in Romania) which impedes a focus on individual happiness[77]. Romanians seem to maintain a highly critical spirit with predominant low self-esteem[75].

Most recent large-scale research undertaken in Romania, found that Romanians indicate a high potential for cognitive and emotional intelligence as well as creativity and learning, a potential that is not capitalized on[75]. Romanians prioritize three fundamental aspects: work, which serves as a means of social affirmation; family, seen as the primary safety net; and religiosity, offering a sense of purpose and meaning in life. A major feature of Romanians is a lack of trust. This transcends all persons and institutions, except family. Romanians scored low when it comes to universalism (concern for the overall good), benevolence (preoccupation for the good of people they know), hedonism, stimulation (looking for new) and self-determination (autonomy/ independence). Romanians tend to score higher in achievement, which reflects their wishes for competence, as well as in power, indicating their desire to attain social status[75]. Additionally, they show a higher inclination towards conformism. While believing in science, religion remains highly important to

Romanians, with the data from 2015 showing that in a clash between science and religion, 50.2% would choose religion[75]. However, religion is perceived as balanced among Romanians, encompassing not only normative and ceremonious aspects but also serving the purpose of doing good and providing meaning to their present life, not solely focused on the afterlife. Romanians see themselves as warm, hospitable, and friendly persons[75]. The trait of 'honesty' was considered significant and self-assessed as important in 1988 and 1993[78]. However, it showed a decline in importance in subsequent years, such as in 2005 and 2007[79]. This trend has continued, as observed in the 2014/2015 analysis conducted by David[75]. Discipline and conscientiousness rank on the lower end in terms of importance[75].

1.4.3.3 Romanian healthcare system

The Romanian health care system consists of a decentralized and pluralistic mandatory social health insurance system. The Ministry of Health is responsible for the overall governance function of the healthcare system. The National Health Insurance House is the other important government institution which has a main function of administering and stewarding the National Health Insurance Fund. Both the Ministry and the House are represented at district level through local institutions[80]. The services of healthcare providers (e.g., family doctors, laboratories, hospitals) are bought by the local district health insurance funds and also, through special programmes (such as infectious disease control, mental health, maternal and child health) by the Ministry of Health. Contributions to the Fund are directly paid by employees; some populations (e.g., unemployed, persons under 18, pensioners) are exempt from paying them. However, while designed as an approach that should ensure national coverage, it is estimated that 11% of the population is not insured, with the majority of these people being located in the rural setting[71]. This is due to the reliance on employees' contribution which do not manage to cover all the population needs and the limited public expenditure on healthcare which amounted to 5.7% of the country's GDP in 2019, the second lowest among EU member states[71]. The national health programmes cover certain conditions and medicines for specific populations. Patients are however required to contribute to a proportion of the costs for outpatient medicines[j] [71]. The situation is further complicated by a perceived lack of transparency and a lack of evidence-based strategy to address the health system's needs with unclear criteria to allocate resources and no mechanism to evaluate health impact. Most of the funds go into paying of salaries of healthcare professionals with little left for purchasing medicines and consumables (patients are forced to buy themselves the basic medical products), for investment in enhancing the infrastructure (funds missing even for basic repairs) or for research to improve quality of care. The House usually allocates less than 10% of the overall Fund to support the primary care sector, below the EU average. The primary system is further challenged by antiquated infrastructure, a lack of an adequate interoperable digitalized system and an overall behavior of patients to go straight to the emergency practices rather than respecting the family doctors' gatekeeping roles[81].

When it comes to the legislation on medicines, the National Agency for Medicines and Medical Devices, subordinated to the Ministry of Health, is the main responsible national institution. Its roles

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[j] 10% for lower-priced generic products, 50% for more expensive generics and medicines under patent, and 80% for medicines that are deemed to have a low cost-effectiveness.

include ensuring medicinal product quality control, activities such as pharmaceutical inspections and establishing relevant regulations.

Regarding the healthcare workforce, while Romania's educational system educates a satisfactory number of professionals, the country has experienced a brain-drain phenomenon since its adherence to the EU in 2007[71].

Recent data indicates a slight decrease in the availability of family medicine practices and pharmacies in the context of healthcare system services (please see Table 1). The data also shows a stark discrepancy between the number of services provided in an urban vs a rural setting. In 2020, it was observed that 98 villages lacked access to a family doctor, and overall, the rural sector had six times the number of patients assigned to a family doctor compared to the urban setting[76].

Table 1 Overview of family medicine practices and pharmacies in 2019 and 2020 (data extracted from NIS,2021 p.10 [76])

Type of medical units	2019	2020		
	Total	Total	Urban	Rural
Independent family medicines practices	10866	10652	6385	4267
Independent general medicine practices	728	746	648	98
Medical practices in schools or universities	2040	2064	2048	16
Pharmacies and related units	9904	9828	6075	3753
Laboratories	6618	6580	6310	270

1.4.3.4   Legal framework on antibiotic use in Romania

The antibiotic legal framework in Romania prohibits antibiotic sales without a medical prescription[82]. Doctors (including dentists) are the only healthcare professionals allowed to prescribe antibiotics. Pharmacists dispense antibiotics based on doctors' prescriptions. However, when pharmacists consider it is appropriate – they judge there is an emergency situation and the patients cannot see a doctor, they can dispense antibiotics – usually a small amount that would allow the start of treatment, until the patients are able to see a doctor. Antibiotics cannot be sold over the internet.

1.4.3.5   Doctors and pharmacists' educational considerations

Romanian higher education system is aligned with the Bologna process, with the medical program duration of study being six years (360 ECTS credits) and the pharmacy program lasting five years (300 ECTS credits)[83,84]. After graduation, the students obtain an internationally accredited diploma and license to practice in all EU/EEA countries. The universities of medical and pharmacy are traditionally state owned with a few newer private institutions which emerged during the post-communist

regime (after 1990). All universities should be non-for-profit, apolitical and of public utility. Universities are autonomous and decide the curricula, in accordance with the national strategies and the national academic standards. While the main subjects where antibiotics are discussed are either part of microbiology and pharmacology courses (both medical and pharmacy faculties have these courses), there are other courses that further solidify and advance capabilities future health professionals need to have for the correct use of antibiotics (e.g., direct medical/ pharmacy practice, communication related courses, clinical pharmacy, infectious disease courses).

1.4.3.6   AMR-related challenges that are recognized in Romania

A recent Romanian report evaluating the existing legislation in key areas necessary for the control of AMR and healthcare-associated infections described several challenges such as the absence of qualified or insufficient proportion of existing human resources, in relation to the number of beds, limited diagnostic capabilities, inadequate availability of antibiotics, lack of an integrated information system for antibiotic control, suboptimal surveillance of resistance and healthcare-associated infections, and inadequate monitoring of ABC[82]. Furthermore, the report highlighted the lack of intersectoral coordination, standardized information systems, and dedicated human resources, as well as insufficient funding and a need for a culture shift in the population towards rational antibiotic use[82].

Overall, the high antibiotic related rates, the low level of general knowledge from the public on antibiotic use, suggests that the Romanian setting would benefit from addressing related issues. Furthermore, the Romanian health and social systems are confronted with challenges that parallel or will be encountered by other countries such as the insufficient funding, a decreasing healthcare workforce, a high urban-rural divide and difficulty in understanding the integration of social and healthcare that have bearings on ABC and AMR rates in this country. Therefore, given the specificities of the Romanian context, the approaches to tackle ABC and AMR, may benefit other nations that will experience a similar trajectory, of transitioning from certain socio-economic status and having similar healthcare systems' arrangements.

2   Research aims

2.1   Aim

The overall aim of the project was to construct an evidence base for developing and implementing community-based interventions to combat AMR and inform relevant policy documents, in view of combating AMR in Romania.

The guiding overall research question was: 'What types of community interventions to combat AMR are perceived as feasible and promising by various stakeholders, to be adopted in Romania and what are the main enablers and barriers in view of their implementation?'

2.2   Objectives

To reach the aim several objectives were pursued:

1. Synthesize the evidence on the value of community-based behaviour change interventions to improve antibiotic use. This included an identification, summarization, analysis and critical appraisal of the relevant literature on the various types of interventions, their effectiveness and/ or cost-effectiveness and their potential implementation challenges.
2. Gather an in-depth understanding of the perceptions of key health professionals -family doctors and pharmacists on their roles in respect to ABC and AMR, as well as their views on related drivers and ways to tackle these phenomenons (e.g. understanding barriers and enablers for introducing community based interventions in a Romanian setting).
3. Explore the perceptions of future Romanian health professionals about antibiotic use, including their related self-assessed technical preparedness, engagement willingness, expectations, teaching preferences, received training in the area of antibiotics as well as their assessment of the evolution of antibiotic use in Romania.

To reach these objectives, four studies guided by specific research questions were performed as shown in Figure 2.
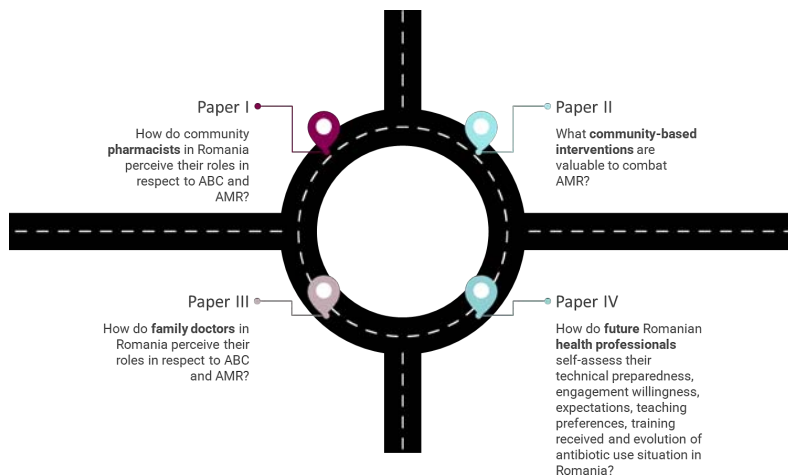
Figure 2 Overview of research questions addressed throughout the PhD thesis

3 Methods

3.1 Methodological overview of studied included in this thesis

To attain the overall aim of the thesis, a combination of methods was employed. Table 2 provides a summary of these methods.

Table 2 Overview of methodological approach to the studies included in the thesis

Study	Main topic	Study design	Data collection	Data analysis
I	Pharmacists' roles and perceptions on antibiotic consumption and resistance	Qualitative	Individual semi-structured interviews *(data collection: February and March 2015)*	Manifest and latent content analysis
II	Quantitative and qualitative synthesis of evidence on the value of community-based educational interventions to improve antibiotic use	Systematic review of both quantitative and qualitative studies	Systematic search of literature *(literature search: May 2020 and October 2021)*	Analytical synthesis of quantitative and qualitative results
III	Family doctors'roles and perceptions on antibiotic consumption and antibiotic resistance	Qualitative	Individual semi-structured interviews *(data collection: September – October 2021*	Manifest and latent content analysis
IV	Perceptions of future Romanian health professionals about antibiotic use	Quantitative – cross-sectional	Survey *(data collection: November 2022)*	Descriptive statistics, exploratory and confirmatory factor analysis, content analysis
Thesis analysis	Theory of change (ToC) articulation	ToC development	Data synthesis and amalgamation from studies I-IV *(data synthesis: April 2023)*	Analysis based on ToC domains

3.1.1 Study setting and participants selection

Studies I, III and IV have been set in Romania. The Background section provides data to explain the rational for selecting this setting as well as details on the country's organization, healthcare system, national policies and recent developments related to antibiotics as well as a Romanian cultural context. This and the following sections offer methodological considerations; further related

reflections are offered in section 5.4. Methodological considerations in the section 5. Discussion. COREQ Checklist[85] has been used to verify reporting of methodological considerations for qualitative studies throughout these sections.

Studies were conducted at different timepoints which bring additional specificities that might have impacted perceptions captured in these studies. The COVID-19 pandemic represented an important point of inflection. These considerations are analyzed in the section 5. Discussion section. Studies I, III and IV gathered participation from different regions in Romania as shown in Figure 3.
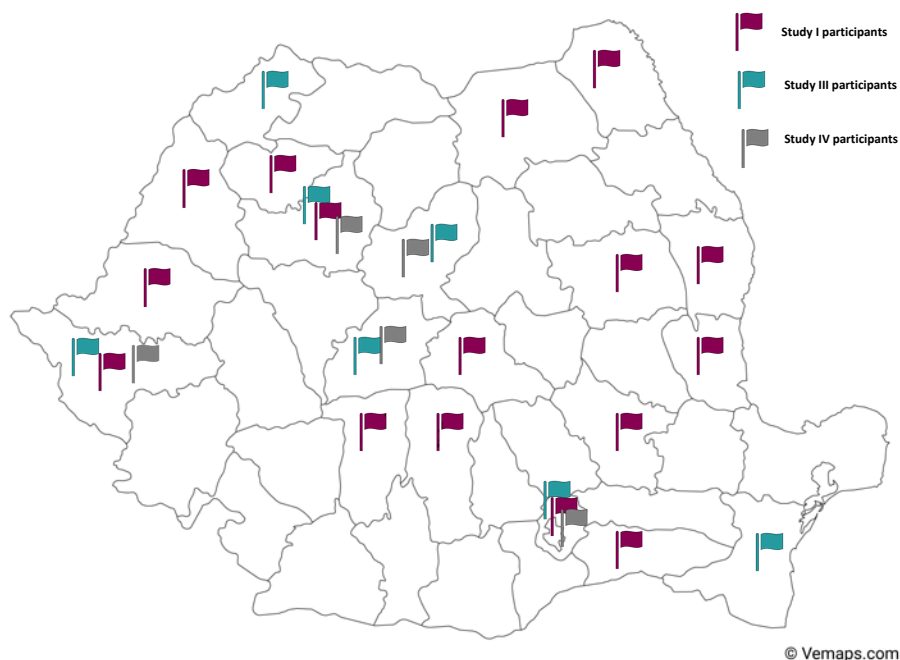
Figure 3 Overview of participants geographical setting in studies, 1,3 and 4

Both studies I and III aimed to achieve maximum variation in terms of participants' professional experience, geographical location, gender distribution, and urban/rural work settings. This was accomplished by actively engaging a diverse pool of potential participants. For both studies, purposing sampling was employed by initially disseminating information regarding the study and obtaining informed consent from individuals employed in the relevant field, as well as from the College of Pharmacists and Physicians, and through postings made on relevant social media platforms.

For study I, the process of informing potential participants and soliciting their participation was also conducted directly in pharmacies. For the in-person data collection efforts, there was a high refusal to participate, with the most common reason being lack of time with many pharmacists mentioning that they would be happy to fill in a survey but don't have time for an interview. Most of participants preferred to have a phone conversation, usually after working hours. Some pharmacists who were

contacted referred other pharmacists to the study, again via phone. For this type of outreach effort there were only two refusals and similarly the refusal motive was lack of time.

For study III, in person outreach was challenged by the ongoing COVID-19 pandemic but doctors were contacted by phone through the publicly available contact data posted on the Romanian national insurance registry. However, recruitment for study III was particularly difficult, with the most cited reason for non-participation being the lack of time, with some attributing this to the heavier workload due to COVID-19. In some instances, participants deemed themselves unsuitable for the study, believing that an infectious disease specialist would be better equipped to engage in an AMR research project. Although doctors were contacted from all geographical regions, with similar efforts (contacting at least five doctors in each county), no participation was secured from doctors from the East and South-East region of Romania. Around 200 family doctors were contacted directly via telephone with only 12 agreeing to participate.

For study I, a total of 19 pharmacists signed the informed consent form, and 18 interviews were ultimately included in the analysis. Study I participants' age ranged from 24 to 60 years, with only two being male, representing 11% of the sample. This sex distribution is consistent with that of students at faculties of pharmacy, where the number of male students is significantly lower than that of female students. All participants graduated from state-owned institutions. One participant included in the analysis worked in a rural setting, while the rest worked in urban areas. One participant had experience working in chain pharmacies, while the remainder worked in independent pharmacies (with one person owning one or two pharmacies). In study III, a total of 12 participants were recruited, with ages between 35 and 71, of which 42% were female. Only one participant worked in the rural setting. Family doctors had direct contractual agreement with the National Insurance House in Romania and did not provide services through private clinics.

Saturation was considered achieved for both studies, as there was data repetition in the interviews with no new insights emerging [86]. Based on this consideration, in study I, saturation was attained after the 16th interview. Nevertheless, two more interviews were conducted to verify this observation. In Study III, saturation was achieved following the 11th interview, and one additional interview was conducted to confirm this assessment. For study III participants also consistently flagged a lack of time and any attempts to prolong the discussions did not yield further informational richness. This, combined with the PhD author's judgement that further data was unlikely to yield significant new insights, determined her not to pursue further interviews.

For study IV all final-year medical and pharmacy degree students from Romanian universities were eligible to participate. The web-based link for the survey was disseminated via social media platforms such as Facebook and LinkedIn, as well as through students' associations. Out of the 13 universities in Romania, 12 have both medical and pharmacy faculties, while one has only a medical faculty. The PhD author collected data by visiting eight faculties, comprising four medicine and four pharmacy faculties located in proximity to each other. Ultimately study IV captured data from a total of 479 participants: 233 medical students from seven universities and 246 pharmacy students from four universities. From the in-person collection approach, all persons that were handed a questionnaire, filled it in.

3.1.2 Study designs and data collection instruments

3.1.2.1 Qualitative studies

Qualitative research methodologies were deemed appropriate for studies I and III, as the aim was to gather empirical and conceptual knowledge to gain insight into the participants' subjective reality and how they articulate meaning from different situations and experiences[87].

Individual interviews were used to achieve a more thorough comprehension of the participants' attitudes and perceptions regarding ABC and AMR. This approach was also thought to be best suited, considering the potentially sensitive nature of some of the topics discussed (e.g. dispensing antibiotics without a prescription, prescribing antibiotics excessively, opinions about the authorities' performance).

To support data collection for studies I and III, a semi-structured interview guide was developed and followed for each study (the annex section contains both guides). Their development relied on key concepts identified through literature review aiming to gather views on status of ABC and AMR in Romania and the role of respective healthcare providers in this area, drivers that would lead to unnecessary solicitations and/or prescribing/dispensing of antibiotics, potential interventions to ensure optimal antibiotic use and related considerations for their operationalization and impact monitoring. For study I the questions were structured in relation to the different stakeholders that pharmacists interact with, while for the second study the domains were grouped according to the theory of change categories. This approach was taken as by the time study III was conducted, the potential interventions in focus had become more crystallized (as study II was conducted). The interview guides were developed in English and then translated in Romanian. All interviews were audio recorded.

For study I, one pilot interview was conducted with the purpose to assess the clarity and comprehension of the questions in the interview guide. The results were not included in the analysis due to the familiarity between the investigator and this participant which could have impacted the interpretation of the results. Other than this interviewee, the PhD author had no prior relationship with any of the other participants in both study I and III. All questions were deemed appropriate and small changes in phrasing were made to ensure better comprehension. For study III, testing was also performed on one participant. While the study guide was not amended, the pilot interview showed less meaningful inputs on questions pertaining to resource needs and potential impacts, a trend that continued throughout subsequent interviews.

For both studies interviews began with collecting demographic data and information on the participants employment. Questions were then posed according to the interview guide, however depending on how the discussion unfolded, questions were rephrased or skipped, and new ones were asked to understand more fully participants' experiences[86].

For study I, three interviews were conducted face-to-face and the remaining 15 were performed over the phone. For the face-to-face interviews the informants were asked to indicate a place where they would feel comfortable, thus the interview setting varied from cafés to pharmacies. The average length of time for an interview was around 35 minutes – with the shortest being 20 minutes,

and some of the longest approximately 70 minutes. For study III, all interviews with one exception were performed over the phone. The one face to face interview took place in the clinic where the respective doctor was working. For study III, the length of time for interviews varied between 15 and 90 minutes, with an average time per interview of 30 minutes. All interviews for both studies were performed in Romanian by the PhD author. No reimbursement was offered for participation in any of the studies. No repeat interviews were attempted as in the opinion of the PhD author, the participants covered the topics addressed and did not signal any desire to add more considerations when asked at the end of the interview if there are other things to be explored (to be added).

The PhD author has a thorough understanding of contextual specificities encompassing social and health systems, cultural, economic, policies, and the political environment and is a Romanian native speaker. She is also a graduate of one of the pharmacy faculties in Romania (she graduated in 2009). However, she has never worked post-graduation in a pharmacy and at the time of the research she did not have any employment in the Romanian setting. As part of her role as the sole data collector and performing the first steps of the analysis, she reflected on how her background, biases and experiences might impact data collection and analysis. The PhD author acknowledged her prior knowledge and personal experiences in relation to the pharmacist and medicine professions. Her main preconceived notions might have been more from her university years, which might have influenced her initial understanding of the research topics. She considered how her own background as a graduate of pharmacy might make her more sympathetic throughout the interactions with the participants from study I. She considered power dynamics in both studies, specifically focusing on whether older participants might feel judged or undermined by assertive probing questions from a younger researcher, in particular for study III. Regarding biases, the PhD author considered her assumptions about pharmacy and medical practices, specifically the situations where she might know of various practices (e.g. prescribing or dispensing antibiotics unnecessarily).

Mindful of this, she engaged in various reflective processes. She recorded notes during and after each interview and engaged in reflective commentary consistent with the emergent design approach[88,89]. The intent was to document her biases and assumptions, by critically examining her positionality towards the various topics, which might have influenced the data collection and analysis. Another reason for this approach, was to enhance subsequent interviews and analysis by documenting the investigator's initial observations of emerging themes. In particular for the first study, as she advanced more with the interviews, she has decided to use silence more often rather than prompts, to minimize the potential 'leading' of responses as well as avoid situations where she might be perceived as intrusive. For study III, silence was used less due to the reminders from the participants that they had limited time for the interview. The PhD author gained greater qualitative data collection experience through unrelated research endeavors between study I and study III. For both studies, she tried to bracket her beliefs and assumptions, and even when she recognized certain information from previous interviews, she used deliberate naivety not to prejudge potential responses. She tried to avoid any situations where participants might feel uncomfortable or threatened and aimed to establish rapport, actively listening and exhibiting genuine interest and openness to learn the participants' perspectives.

3.1.2.2   Systematic review

The study protocol was preregistered with the PROSPERO database (CRD42020184157). The review adhered to the Preferred Reporting Items for Systematic Reviews (PRISMA 2020 statement)[90]. Pre-specified PICOS criteria (population, intervention, comparison, outcome, and study design) were followed to identify interventions or innovations in community settings that promote correct antibiotic use among the general public. The review included all age groups, sexes, and levels of literacy. Interventions delivered outside community or ambulatory care settings were excluded. The review included both quantitative or qualitative studies, published in English, French, Spanish, Italian, Polish, or Romanian from 2001 onwards. Studies without a comparison group and those without community responsibility or engagement were excluded.

Two professional librarians from Karolinska Institute searched the MEDLINE (OVID), Embase (embase.com), and Web of Science (Clarivate Analytics) databases twice (May 2020 and October 2021) to identify relevant studies. The search strategy included Medical Subject Headings (MeSH) terms and keywords, and additional studies were identified through hand-searching reference lists of relevant reviews and included studies. Two researchers independently screened titles and abstracts for eligibility based on pre-defined PICOS criteria and assessed full-text articles for eligibility. Consensus was reached among researchers for the final list of included studies. The search strategy yielded 14319 articles that were screened. Out of these, 73 papers met the inclusion criteria.

Customized tables were created and used for data extraction, which included participant characteristics, intervention and comparator details, study design, and outcomes of interest. Data from both quantitative and qualitative studies were extracted, with a focus on outcomes related to the pre-defined PICOS criteria. One author performed the main extraction, which was checked by another author.

3.1.2.3   Quantitative study

In study IV, data was collected throughout the span of one month, using a questionnaire distributed either electronically through REDCap or in paper format, which was later transferred to REDCap[91].

The survey questionnaire combined several types of questions aimed to achieve the study objectives grouped in the following domains: demographics, technical preparedness, engagement willingness, expectations, teaching preferences, training received and evolution of antibiotic related situation in Romania. The preparedness, teaching preferences and training received related questions were built on from those used in a previous 2015 medical student study conducted by the European Society of Clinical Microbiology and Infectious Diseases Study Group for Antimicrobial Stewardship[92]. This consisted of a multi-country study among medical students. The questions used in this questionnaire were assessed, adjusted and complimented with questions specific to Romanian medical and pharmacy curricula related to antibiotics. The original questionnaire had seven preparedness domains, which were condensed to five for the current study. Out of the initial 27 preparedness questions, 25 were retained in a similar or combined format, resulting in 22 questions. However, two questions were excluded due to their lack of relevance to the specific training practices in Romanian universities. These questions pertained to the practice of administering point-of-care tests and measuring/auditing antibiotic use in a clinical setting. The new questionnaire enclosed additional

questions exploring the students' engagement willingness as well as capturing their recommendations around antibiotics for their university (teaching recommendations) and governmental structures (polices and activities). The domain that aimed to capture teaching preferences, maintained all the previous existing questions but rephrased them to match the Romanian context specificities (e.g. renaming 'placements' to 'internship') and added two more potential preferences (internships in public health directions and in pharmaceutical companies). The initial questionnaire had two overall questions - one on receiving adequate training and one on whether medical examinations contained questions on antibiotic treatment. The transformed questionnaire maintained the first question on receipt of sufficient training and replaced the last question with one capturing perceptions on the evolution of antibiotics use in Romania. Overall, the questions were structured also with a view that they are appropriate for each type of student category (medicine and pharmacy). The main differences in this respect were in some of the preparedness related questions.

The PhD author developed the questionnaire, which was reviewed by all co-authors, translated into Romanian, pilot-tested on two graduates who suggested changes to aid comprehension, back-translated and then deployed. Overall, 41 and 38 questions were asked to medical and pharmacy students respectively.

3.1.3   Data management and analysis

3.1.3.1   Qualitative methods

In both studies, the data was analyzed using the manifest and latent qualitative content analysis method described by Graneheim and Lundman[93]. Content analysis was chosen as the research questions and objectives sought to capture both the obvious or explicit meaning as well as the underlying or hidden associations. The studies did not aim to develop theories (therefore grounded theory was not taken into consideration). The studies were resource bound and study III was impacted by the pandemic public health and social measures (that limited engagements or attempts of direct prolonged observations), therefore longer periods of data collection or deep immersion in certain clinical settings would have been challenging. For study III, the possibility of using a different methodology such as thematic analysis was considered. However, given the exploratory nature and reduced sample size of the research, it was determined that this approach may lead to issues regarding the accuracy of interpretation of hidden meaning[94]. Thematic analysis, which requires a higher level of abstraction and interpretation, was therefore deemed unsuitable.

In terms of analysis process, content analysis implies using codes to establish categories that are internally consistent and mutually exclusive at the manifest level. The categories are then interpreted to uncover the underlying meaning reflected in the emergent themes at the latent level. For both studies, the same approach was undertaken. The first step to facilitate data analysis, was to transcribe and translate the interviews into English. The transcription was done by the PhD author and was verbatim, capturing every word and sound as it was spoken in the audio recording. She listened to the audio recording several times and there were no situations where the discussion was unclear and might have solicited a recheck with participants. Throughout the transcription effort the PhD author aimed to capture a detailed representation of the conversation. The PhD author read the

transcripts as a whole several times. The interviews were then considered as units of analysis, and sections of the text that were connected through content and context were identified as meaning units[93]. The meaning units were not condensed, as they were clear enough for coding without further simplification. The meaning units' content was coded, and subsequently grouped into sub-categories and then into categories. Emerging sub-themes were identified from the categories, which represented a higher level of abstraction and interpretation of the text. Ultimately, a comprehensive theme was developed to the best extent possible, aiming to encompass the interpretation of most of the text. Microsoft Excel was used to facilitate data analysis. A sample of the analytic coding process from manifest to latent content level is presented in the annex section.

Throughout the data analysis the PhD author engaged in peer debriefings with one of her supervisors that allowed the PhD author to test her assumptions and interpretations. As the codes and categories were formed, she continuously compared and contrasted the data maintaining an iterative process to categories and themes formation. Negative cases - instances when emergent data deviated from the emerging patterns of categories or themes, were analyzed. The PhD author reflected on the reasons behind such situations, whether they relate to singular particularities of individuals or their circumstances. In all such instances, the approach was to revisit the emerging categories and themes to account for new nuances and accommodate a more comprehensive data interpretation. Finally, analysis results and themes were reviewed and queried by co-authors, which provided additional opportunities for reflection and analysis refinement. One member-check of data interpretation was undertaken for study I, with positive feedback that the emergent themes captured the respondent's opinions.

For both studies there were several categories and subcategories that emerged which would indicate the richness and complexity of data. The intent was to capture a wide range of nuances. The small but numerous categories can also be interpreted as indicative that saturation was reached. When interviews provided data that only confirmed existing categories rather than leading to new ones, it was considered that it is unlikely new distinctions would emerge and saturation was reached. The numerous categories might indicate a more descriptive level of analysis. However, a higher level of abstraction, by articulating themes was attempted. Overall, the approach taken was meant to ensure that the analysis offers a comprehensive understanding and provides meaningful insights from data.

3.1.3.2   Systematic review

In study II, quantitative and qualitative studies were assessed separately. Due to a diversity in definitions of exposure and types of outcomes, harvest plots were used to visualize the associations between different behavior change components and outcomes instead of performing an exploratory meta-analysis. The reported exposures fell into 12 categories, and the reported outcomes were combined in eight categories. For qualitative studies, a description of findings without further grouping in exposure-outcome categories was provided.

Bias in quantitative studies was evaluated using the Effective Public Health Practice Project[95] quality assessment tool, which assesses study quality based on selection bias, study design, confounders, blinding, data collection method, and withdrawals and dropouts. The tool assigns an overall study

quality rating of strong, moderate, or weak. Qualitative studies were evaluated using the Critical Appraisal Skills Programme[96] qualitative research assessment checklist, which considers various questions to ensure trustworthiness in qualitative research and also assigns an overall study quality rating. The PhD author conducted the initial assessment, which was then checked by another researcher. Any discrepancies were resolved through discussion, and a final assessment was agreed upon.

3.1.3.3   Quantitative methods

In study IV, descriptive statistics were used to summarize participants' characteristics and answers. Categorical variables were presented as frequencies and percentages, while continuous variables were reported using means, standard deviations, and ranges. University names were encoded to prevent bias. Preparedness, engagement willingness, and teaching method preference scores were calculated and analyzed using mean, standard deviation, range, and correlation coefficients. Exploratory factor analysis (EFA) was conducted to identify underlying factors and assess the suitability of the data for factor analysis. Confirmatory factor analysis (CFA) was used to confirm the factor structure identified in EFA. Content analysis was used to analyze free text responses, and codes were compiled into categories. R version 4.2.1 software was used for all statistical analyses.

Elements of the BCW were used to structure findings and analysis across all studies. This approach was considered suitable to facilitate future comparative analysis and assist in further research on the development, implementation, and evaluation of behavioral change interventions.

3.2   Theoretical underpinnings

There are several theoretical underpinnings throughout the entire PhD research as shown in Figure 4. These concepts are discussed in the Background section. The COM-B model has been used to anchor this PhD research starting from the design to the interpretation of findings. However, as the findings grew beyond individual-level considerations, other frameworks were helpful to explore their implications.
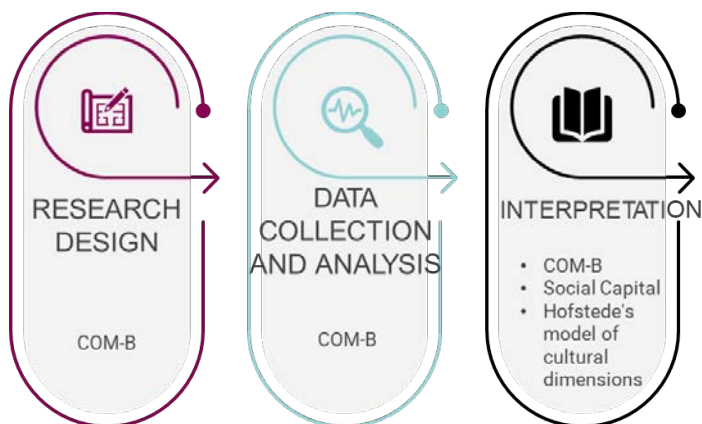

Figure 4 Theoretical underpinning of throughout the PhD research

3.3   Ethical considerations

The Romanian National Bioethics Committee of Medicine and Medical Devices (NBCMMD), the mandated national committee responsible for the review of non-interventional studies in Romania, was informed about all studies conducted within this PhD research - studies I-IV, including subsequent changes to study IV. Study I was deemed exempt from NBCMMD approval through an official letter dated 08.01.2015. Studies II-IV were reviewed and approved by the NBCMMD, with approval number 3SNI issued on 17.02.2020. Due to modifications in the design of study IV, the new approach was presented to the NBCMMD, who issued an official letter on 28.10.2022 advising that the study could be conducted without additional official approval, given the proposed methodology.

Studies I and III utilized interviews as a data collection methodology and were audio recorded and are stored on a password protected computer. An informed consent form was provided and was signed by all the participants prior to their interview in Romanian language.

Study II did not involve collection of any primary, personal, or confidential data.

Study IV utilized a survey prefaced by an informed consent information form. The survey was administered in an anonymous manner. As per the guidance provided by NBCMMD, considering this particular characteristic, it was deemed acceptable to include the information form stating that the act of completing the survey would serve as an expression of consent for data usage, thereby obviating the need for obtaining a signed informed consent form that may have included personally identifying information such as the participant's name and contact details, including email address. Institutions names were masked during the analysis step.

The informed consent form in all studies (I, III and IV) listed the confidentiality and data protection provisions, the use of the data as well as the rights of participants in this type of research.

Several ethical considerations have been reflected upon:

Respect for persons: all conducted studies respected the choices of autonomous people – participants being health professionals that are active in their field or future health professionals in the last stages of training, all able to make their own decisions. Participation was voluntary and obtained after information was provided on the research itself and all participants' questions were answered by the researcher. An informed consent was available and signed by participants who received a copy – apart from study IV participants (please see above reasoning). Participants were also advised that they could refuse to answer any question or terminate the interview at any moment. Confidentiality was maintained and there is no identification of the participants personal identifying data, in the reporting of studies' results. The informed consent forms and the recordings of the interviews are kept in a place with restricted access, these being the only sources of data which may allow identification of participants. The PhD author assigned numerical codes to the transcripts and recordings to ensure anonymity, with no personal information appearing in any report. The PhD author was the sole person to have access to the code sheet and the only researcher that performed the transcription.

Beneficence: studies were conducted with researchers' underlying concern to do no harm and promote the good of participants. The studies did not involve any physical procedures. Close

attention was paid not to influence participants' responses or place any pressure in divulging information they may not want to share. The studies' findings aim to support the medical activity in general and advance better health outcomes. Nonetheless, participants were informed that the research was conducted as part of the investigator's thesis project and that the investigator had no affiliation with any state institutions in Romania, indicating that there was no guarantee that the decision-makers would take note of or consider this research.

Justice: all participants were treated in the same way. The nature of the research does not expose participants to harm. Given that all conversations were performed telephonically or at the place of work of the participants, no cost was inferred on these.

Respect for communities: the research may have implications on how certain professional communities view themselves. An effort was made to ensure that the research is brought to the attention of the relevant professional communities – respectively the Romanian Colleges of Pharmacists and Physicians. The researcher explained the aims of the activities and sought a partnership relationship in reaching out to potential participants.

4 Results

4.1 Drivers of antibiotic consumption and resistance in Romania

Studies I, II and IV supported the identification of several perceived drivers of ABC and AMR in Romania. These findings together with the results from the literature review informed the articulation of a problem tree, which lists the causes/drivers and the impacts/ symptoms of the high consumption of antibiotics and consequently the high rates of AMR in Romania. These are shown in Figure 5.
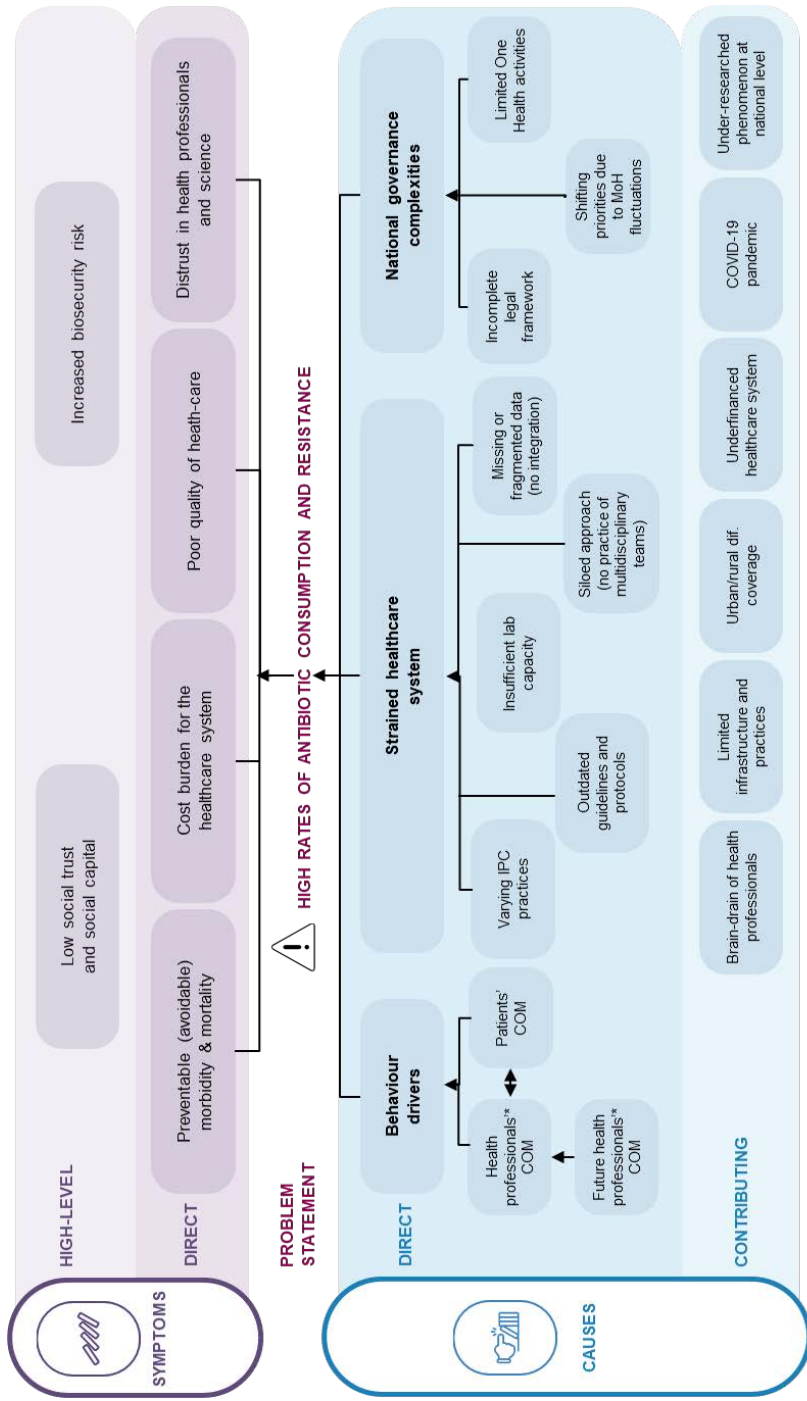
The problem of high ABC and consequently worrying AMR trends in Romania has several direct and contributing causes. One category is represented by the behavior of key stakeholders such as health professionals –pharmacists (study I) and family doctors (study III), whose behavior is shaped in their formative years at university (study IV). Both study I and III identified constraints due to laboratory capacity (limited antibiogram practices), siloed approach to delivering care, as well as challenges that pertain to data (its absence, its unreliability - although unclear at which levels, as well as an overall fragmentation). Studies I and III also signaled constrains that refer to governance arrangements such as shifting priorities, incomplete legal framework – in particular with limited enforcement mechanisms, and while only mentioned by very few respondents (in study I), limited one health activities[k]. Other underlying contributing factors refer to a continuous brain-drain of healthcare professionals, limited infrastructure which also relates to a more limited availability of medical services in the rural areas. COVID-19 strained healthcare system delivery and brought about a higher consumption of azithromycin in Romania. AMR in general seems to be an under-researched phenomenon and from results in study IV, there is little appetite of current students in specialized universities to explore this, despite the worry that the situation will worsen in Romania.

These sparks considerations related to the consequences of high ABC and AMR. An exploratory analysis, positioning these more as hypothesis to be further tested, reveals direct consequences such as preventable morbidity and mortality, additional cost burden for the healthcare system, poor quality of healthcare and distrust in health professionals and science. These are themes that emerged throughout studies I, III and IV. Ultimately this will lead also to increased biosecurity risk. The latent meaning of the data –from studies I and III, unveiled a socio-cultural dimension that connects to this type of phenomenon. While ABC and AMR do not necessarily cause the low social trust and social capital, they might be a symptom or a perpetuating factor of these existing phenomenon.

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[k] One health activities pertain to interdisciplinary endeavors that recognize the interconnectedness of health of humas, that of animals and the environment in which they live.

SYMPTOMS

HIGH-LEVEL
- Low social trust and social capital
- Increased biosecurity risk

DIRECT
- Preventable (avoidable) morbidity & mortality
- Cost burden for the healthcare system
- Poor quality of heath-care
- Distrust in health professionals and science

PROBLEM STATEMENT

⚠ **HIGH RATES OF ANTIBIOTIC CONSUMPTION AND RESISTANCE**

CAUSES

DIRECT

Behaviour drivers
- Health professionals'* COM
- Patients' COM
- Future health professionals'* COM

Strained healthcare system
- Varying IPC practices
- Outdated guidelines and protocols
- Insufficient lab capacity
- Siloed approach (no practice of multidisciplinary teams)
- Missing or fragmented data (no integration)

National governance complexities
- Incomplete legal framework
- Shifting priorities due to MoH fluctuations
- Limited One Health activities

CONTRIBUTING
- Brain-drain of health professionals
- Limited infrastructure and practices
- Urban/rural dif. coverage
- Underfinanced healthcare system
- COVID-19 pandemic
- Under-researched phenomenon at national level

COM: capabilities, opportunities and motivations
* Key professionals: doctors (with various specialities), pharmacists, veterinarians

Figure 5 Problem tree detailing the drivers and consequences of antibiotic consumption and antimicrobial resistance in Romania

4.2 Behavioral drivers of current and future healthcare professionals in Romania in relation to the appropriate use of antibiotics

The drivers of future and current healthcare professionals' behavior related to appropriate dispensing, prescribing and use of antibiotics were explored through the lens of the COM-B model, and are detailed in subsequent sub-sections. This supported the identification of individual enablers and barriers to drive behavior change and engage in implementation of community-based interventions.

4.2.1 Driving capabilities

Capabilities comprise of the individual abilities – whether they are psychological or physical to participate or conduct an activity. Understanding these capabilities involves understanding stakeholders' awareness of their behavior, their understanding of the desired type of action as well as the costs and consequences of following it or not. Furthermore, capabilities encompass stakeholders' confidence level on whether they can perform certain activities – including status of certain skills such as cognitive, perceptual, or psychomotor as well as physical strength and stamina (depending on the activities). Some of these aspects (such as behavior awareness) are very closely linked to 'Motivation' which proposes to capture beliefs about capabilities. However, in this thesis these are presented as 'capabilities' findings and were a mix of beliefs about individual capabilities as well as those of others that impact antibiotic use.

As far as it concerns the awareness of their behavior most pharmacists and doctors recognized the importance of the ABC problem. However, a common nuance was that it was mostly the fault of 'others'. This meant that pharmacists working in independent pharmacies considered it was a problem more prevalent in chain pharmacies, family doctors considered that fellows from other specialties were the ones contributing to the problem, and generally, both type of professionals also considered the others were to blame for the phenomenon.

> *I noticed that in the big pharmacy chains they no longer give out antibiotics, but in the small ones they still do, and they no longer come to the family doctor, and they say that the 'pharmacy doctor' gave them the antibiotics. (Study III –Family doctor- Interviewee 1)*

Regarding the *knowledge* needed to perform their tasks, while not pointing to particular shortcomings – both pharmacists and doctors expressed the need to have additional educational resources available to them such as dedicated courses (as part of continuous professional development). Pharmacists expressed reservations on the standard that certain private universities in Romania may have. Doctors stressed the interpretability of guidelines and related limitations, while emphasizing the importance of reliance on experience and treatment personalization.

> *But it would be very good and highly recommended for these courses, that are taken to get professional points, to be on antibiotic themes, because the great majority now are about pharmacy marketing, how to associate various products –OTCs, para-pharmaceuticals, etc. Meaning a lot of companies and producers, even generics, are looking to make courses pertaining to marketing and sales. (Study I –Pharmacist - Interviewee 8)*

A lot of medical education, two folds – once with the doctors, a re-evaluation of the indications and ways of prescribing, and secondly patients' education, because many times, these antibiotics are prescribed at the request of the patient. (Study III – Family doctor - Interviewee 2)

Students reflected on their technical preparedness across several domains. Figure 6 shows self-assessed levels of preparedness across different universities and faculties and reveals most students self-assessing as medium-prepared (study IV). Both medical and pharmacy, felt prepared in assessing the need for antibiotics, understanding antibiotic resistance as well as communication and engagement on the topic of antibiotic use. However most medical students did not feel ready to prescribe a combination of antibiotics with other medicines, nor setting the appropriate timing and duration of antibiotic administration or deciding on treatment without the use of guidelines. Both medical and pharmacy students felt less prepared to monitor antibiotic therapy and assess emerging evidence, and similarly to participate as a researcher in clinical or epidemiological research.

Regarding *skills*, in particular the interviews with pharmacists showed that there were situations when patients posed pressure and insisted on obtaining antibiotics. While this does not necessarily indicate a lack of doctors' or pharmacists' skills it does imply a certain degree of resilience that needs to be sustained through *communication* skills, implying also a certain degree of assertiveness.

Sometimes they become aggressive, but we try to take them in another way. So not for them to receive a negative answer without getting an explanation… so going around it so that we can prove that the antibiotic can be harmful in certain situations […] We must always know to manage the situation [...] to develop trust in the pharmacy and the respective pharmacist (Study I –Pharmacist- Interviewee 13)

[...] they say for them it only passes with antibiotics and they insist, I am not a proponent of antibiotics but […] still in our country, in a pharmacy, if the person insists, they are dispensed an antibiotic without a medical prescription even if now it's more regulated, they still can get it, if not, they borrow from their neighbors .. (Study III –Family Doctor- Interviewee 7)

Future healthcare professionals reported they feel overall ready to discuss in lay-man's terms appropriate antibiotic use with patients, especially in situations when these may not be necessary. Overall, they provided a range of recommendations on how they could be supported to increase their knowledge spanning enhanced curriculum design and content including integration and emphasis on resistance and optimization into the curriculum, more frequent practical experience, improved teaching methods including more interactive learning approaches and support in scientific research participation.

The lack of diagnostics capacities was expressed by family doctors, for whom ordering antibiograms may be less of a common practice.

Oh dear, but you are asking a family doctor, you should be asking a specialist, me as a family doctor what can I tell you.. I don't know what to tell you.. I am not working with antibiograms .. more like this, from my medical knowledge. This is a topic for an infectious disease specialist (Study III –Family doctor- Interviewee 5)

If all of us would try to educate the patients and not dispense antibiotics without prescription but also when the patient goes to the doctor, not to be… I mean to have the possibility of, I don't know...an antibiogram … of a proper diagnosis and to be able to receive exactly the right antibiotic, you know what I mean? Not to try and then to change (Study I –Pharmacist- Interviewee 6)

This also was reflected in the students' feedback, which suggested healthcare provision optimization needs such as mandatory imposition of antibiograms.

When considering the potential of data to serve as a feedback loop and enhance the knowledge and decision-making process, both pharmacists and doctors expressed some reservations. These stemmed from either doubt on data accuracy or the fact that data alone would not comprehensively provide the full picture of whether antibiotics are correctly prescribed or dispensed.

> *They come and take data from me, and they send it further, but it doesn't seem right at all. If this is how it's done for the antibiotic consumption it doesn't seem fair… My impression is that these data are not always reliable … And the fact that we are not correctly informed. I would really like to see at the end of the season, really how many patients were diagnosed, and if there was an epidemic or not… (Study I –Pharmacist-Interviewee 14)*

> *A simple monthly doctors' prescriptions report won't say whether the antibiotics were necessary or not, it won't express seriousness. (Study III –Family doctor- Interviewee 12)*

On the other hand, students stressed the importance of monitoring and collecting data and individualized patient registries that would capture resistance and antibiotic use related data, and a greater integration and monitoring of electronic prescriptions data.

A joint capability across professions should be the ability to collaborate. Across all studies, findings suggest a deficit when it comes to *collaboration and teamwork* between professions. For pharmacists there also seemed to be a concern with the pharmacist assistants' taking on duties that are not in their remit – such as dispensing antibiotics without a prescription.

> *There are a lot of pharmacies where the dispensing is being done by the pharmacist's assistant. The assistant doesn't have the knowledge. Probably to an assistant to whom the owner says „you need to reach the target" he will also dispense antibiotic without prescription. (Study I – Pharmacist- Interviewee 17)*

> *There is a complicity from the part of pharmacies […] it has changed only partially because we still are living with this tendency from the pharmacist to compete with the doctor's profession, this is my opinion. (Study III –Family doctor- Interviewee 11)*

> *I wish to see the day when the pharmacist will be the one who is asked in the hospital what antibiotic should be used, not which one is the cheapest one, who owns the license… (Study I –Pharmacist- Interviewee 14)*

Most medical and pharmacy students reported they feel ready to work in a multidisciplinary team in a clinical setting with wider variation among pharmacy students. In their recommendations, both groups, stressed the importance of collaboration between healthcare providers. However, for medical students, the suggested collaboration was predominantly intra (between school doctors and family doctors) rather inter-professional (between doctors and pharmacists).
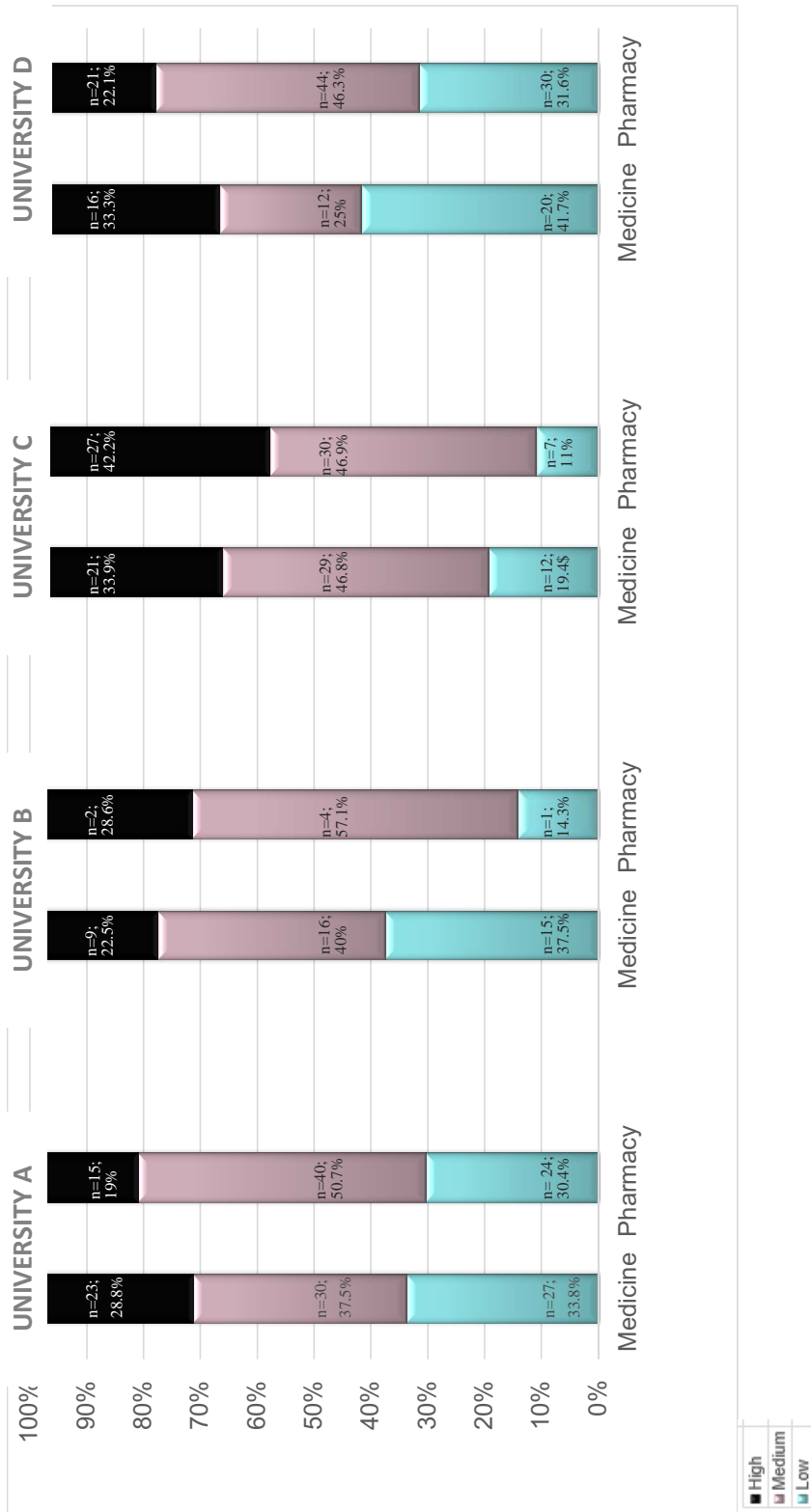
Figure 6 Self-assessed levels of preparedness across different universities and faculties (the two universities that had only one respondent were excluded from the analysis)

4.2.2 Driving opportunities

Opportunities pertain to the external (contextual) factors that make the performance of that activity possible. This encloses the formal rules that dictate a certain type of behavior, the support social networks may convey, access to resources that may facilitate or enable the desired actions – including the time and structural environments.

The studies unfortunately uncovered mostly factors that constrain the performance of optimal prescribing or dispensing. Therefore, while these are not opportunities, they are driving factors that if addressed, may be transformed into supportive environments.

Both doctors and pharmacists expressed their concern with difficulties in *accessing or continuity of care in rural settings*, which might determine a behavior that would favor prescription or dispensing of antibiotics.

> *The majority are from the rural area, and don't have access to a doctor or they don't have a pharmacy in the countryside, in their village […] Now it's truly hard the accessibility to the family doctor, very difficult. (Study I –Pharmacist - Interviewee 9)*

> *It's one thing to treat someone in town, 300m from the practice and it's something different to treat someone who lives 20 km in the woods somewhere. That's why I'm saying that treatment individualization needs to be very well thought through. (Study III –Family doctor- Interviewee 10)*

Another health system factor pertains to the perception that AMR *occurs mostly due to hospital acquired infections* which from a social perspective, would flag that the change pressure and efforts should be mostly concentrated in that sector.

The *COVID pandemic brought higher ABC.* While this may be a temporal effect, it does highlight the potential challenge with diffusion of accurate scientific advice. This is not something limited to the Romanian setting; however, it will require tailored solutions in line with social and cultural specificities.

> *There needs to be an educational campaign, but now it's not possible as another campaign should be taking place…I never understood though why we were asked to prescribe azithromycin for COVID-19.. honestly, nobody explained. (Study III –Family doctor- Interviewee 2)*

Another hindrance is that *patients may see antibiotics as preventive treatment and obtain medical advice from their social network rather than medical professionals*.

Leveraging the power of local communities to enable action to tackle ABC was highlighted. For pharmacists this was also linked to the social influence and the standing healthcare professionals may have which could also be interpreted as a driving motivation.

> *I don't think this is necessarily a system thing more about local actions […] local initiatives are very good because they account for specificities and someone that actually works locally, is invested personally and is known, they should be involved to see this through. (Study III –Family doctor- Interviewee 12)*

> *It's up to you how you make it and then your role in society, how you get out of your flat, home or wherever, if someone can lift your hat in front of you or you can be neglected and nobody to recognize you, it is up to you how you act in that community... If the world knows you, "oh look it's our pharmacist, we went and he took care of us" [...] there are people around you that appreciate what you do... But it is only up to you how you are in the public eye, not someone else; how you can be a defender of health in that small slice you have... (Study I –Pharmacist - Interviewee 10)*

However, particularly pharmacists, expressed disappointment that the professional reputation has diminished which also points to social comparisons between what the profession used to be compared to present day.

> *I would like to say, you ask me strictly about the connection with antibiotics, in general at this hour, the patients see the pharmacist as a medicine salesperson because this is what the profession has been reduced to. (Study I –Pharmacist- Interviewee 18)*

Medical and pharmacy students provided a range of recommendations to advance policies or activities aimed to ensure the responsible use antibiotics use in Romania.

4.2.3   Driving motivations

Motivations represent the cognitive (internal) processes that influence or determine the behavior. These concern the value stakeholders place on the behavior change, how much satisfaction they could expect as a result of this change, whether there is a fit or rather a clash with their self-identity and how pressing the need to change is or whether there are other priorities that would take precedence.

One key driving motivation is patient welfare. Both pharmacists and doctors exhibited empathy when considering the difficulties patients may face to access healthcare and therefore benefit from antibiotics. While this could be explored through an external factor lens (see Driving Opportunities), this speaks to the core of a healthcare professional's ethos, their guiding principles, values, and beliefs that inform their professional conduct and decision-making.

> *There is a category that are not insured, which are a lot in the Roma areas, and you know that they are uninsured and with those there is nothing you can do. You can't leave them to die, because anyway no doctor will consult them if they are uninsured, and then it's a social problem throughout the country. (Study I –Pharmacist- Interviewee 7)*

> *There are some patients that go abroad you know. There, they really don't have access to the doctor. These patients ask for antibiotics, to have it there for the worst. At least in XXX, there are a lot that are away, so there is also this situation. (Study I –Pharmacist - Interviewee 9)*

However, while wanting to uphold professional and ethical standards, healthcare professionals stressed the pressures and perceptions on easiness for patients to start treatment elsewhere and the uneven applicability of the law. This pointed to a problematic motivational impact of the legal and regulatory framework, with concerns about its insufficient enforcement.

> *But not to find ourselves that someone goes, and they don't receive, and makes a complaint until the upper level and then you are told that still for 3 days treatment, weekend, in certain situations… the legislation is not that well set up, leaves room for interpretation and from here a lot of things derive…(Study I –Pharmacist- Interviewee 7)*

The influence of family doctors is very small, because me for example as a family doctor I am against abusive use of antibiotics, but the patient will just go to another doctor. (Study III –Family doctor- Interviewee 6)

All healthcare professionals saw themselves as educators which indicated a strong reflexive motivation. Almost all held the belief that patients lack knowledge on risks of taking antibiotics inappropriately, and sometimes exhibit an inability to adhere to treatment.

So, the pharmacy, yes, you know it's the first door and the most accessible one for the patient who, in order to save time or, I don't know, fear, or the fact that he doesn't have money, comes to the pharmacy and we have an important educational role ...The role of the pharmacist is an educational one and it's a very important one. (Study I – Pharmacist- Interviewee 6)

From a public health standpoint, there was a demotivating perspective that prevention is an under-invested area and the recent campaigns linked to the COVID-19 pandemic, while in the beginning had positive results in the area of hand hygiene, were less successful when it came to vaccination.

Sanitary education programmes should be organized by the Ministry of Health like there are in all the countries. Or to be developed by all these NGOs, we have nothing around here. [(Study I –Pharmacist - Interviewee 16)

I think it's an inefficient campaign [about the COVID-19 vaccine], without much planning.. mostly it's disinformation. (Study III –Family doctor - Interviewee 5)

4.3   The value of community-based interventions

The systematic review (Study II) analyzed community-based interventions from 73 papers and found overall positive emerging evidence on the benefits of such interventions on improvement of antibiotic use.

To facilitate analysis, interventions were categorized according to the BCW framework nine intervention functions domains: education, persuasion, incentivization, coercion, training, enablement, modelling, environmental restructuring, restrictions. Table 3 presents interpretation of the intervention functions in accordance with Michie et al[51] and Cuevas et al[48].

Table 3 Categorization of interventions in accordance with the Behavior Change Wheel functions

Intervention category	Description of interventions (adapted from [51] and [48])
Education	They aim to increase recipients' knowledge and understanding and could consist of direct face-to-face education sessions, advice via phone or other mediums, seminars, workshops and use of educational materials.
Training	They aim to impart skills, and therefore could consist of sessions that would lead to acquiring new skills and enhancing capabilities. This includes train-the-trainers' approaches.
Modelling	These interventions imply offering an example for recipients to aspire to or emulate. Such interventions consist of peer-to-peer learning, tutoring and mentoring activities.

Intervention category	Description of interventions (adapted from [51] and [48])
Enablement	They aim to foster support and reducing of obstacles so that capabilities and opportunities are enhanced and more easily accessed. Such interventions consist of providing feedback in various forms including through auditing, reminders and other type of support (e.g. to increase adherence).
Persuasion or coercion	They aim to stimulate positive or negative feelings to enable action. These interventions could be the use of communication materials (leaflets, brochures, radio/TV/online spots, posters) which impart also a positive or negative message aimed to stimulate a reaction from the receiver.
Incentivization	These interventions are anchored into creating an expectation of a reward, be it monetary or non-monetary, following a type of behavior change.
Restriction	These interventions are mediated by rules (legislation, guidelines, policies) aimed to limit or enhance opportunities to engage in a certain type of behavior.

Figure 7 presents the combination of harvest plots that pair the behavior change components and the type of outcomes. Knowledge, attitude and beliefs were the most measured outcomes. These improved for interventions with the following combinations: i) education as a single behavioral component, ii) education and persuasion or coercion, iii) education, training and persuasion or coercion, iv) education, training, persuasion or coercion and modelling. Regarding interventions that combined education and training, an equal number of studies demonstrated both no change and improvements, but the "no-change" category had larger sample sizes. On the other end, cost appears to be one of the least monitored outcomes. However, in studies that reported it, there seems to be an improvement following interventions with the following combinations: i) education and persuasion or coercion and ii) education, training, persuasion or coercion and modelling. The combination of interventions consisting of education, training, persuasion or coercion, and modeling appeared to solely result in improvements, with no reports of worsening or no change.

Multifaceted interventions demonstrated a greater improvement in reported outcomes, and the most successful community-based interventions involved combining activities like peer-education workshops, providing educational materials such as booklets, videos, newsletters, posters, and poster contests, engaging in conversations and quizzes, organizing theatre performances, and offering targeted educational materials and sessions (e.g., aimed at schoolteachers).
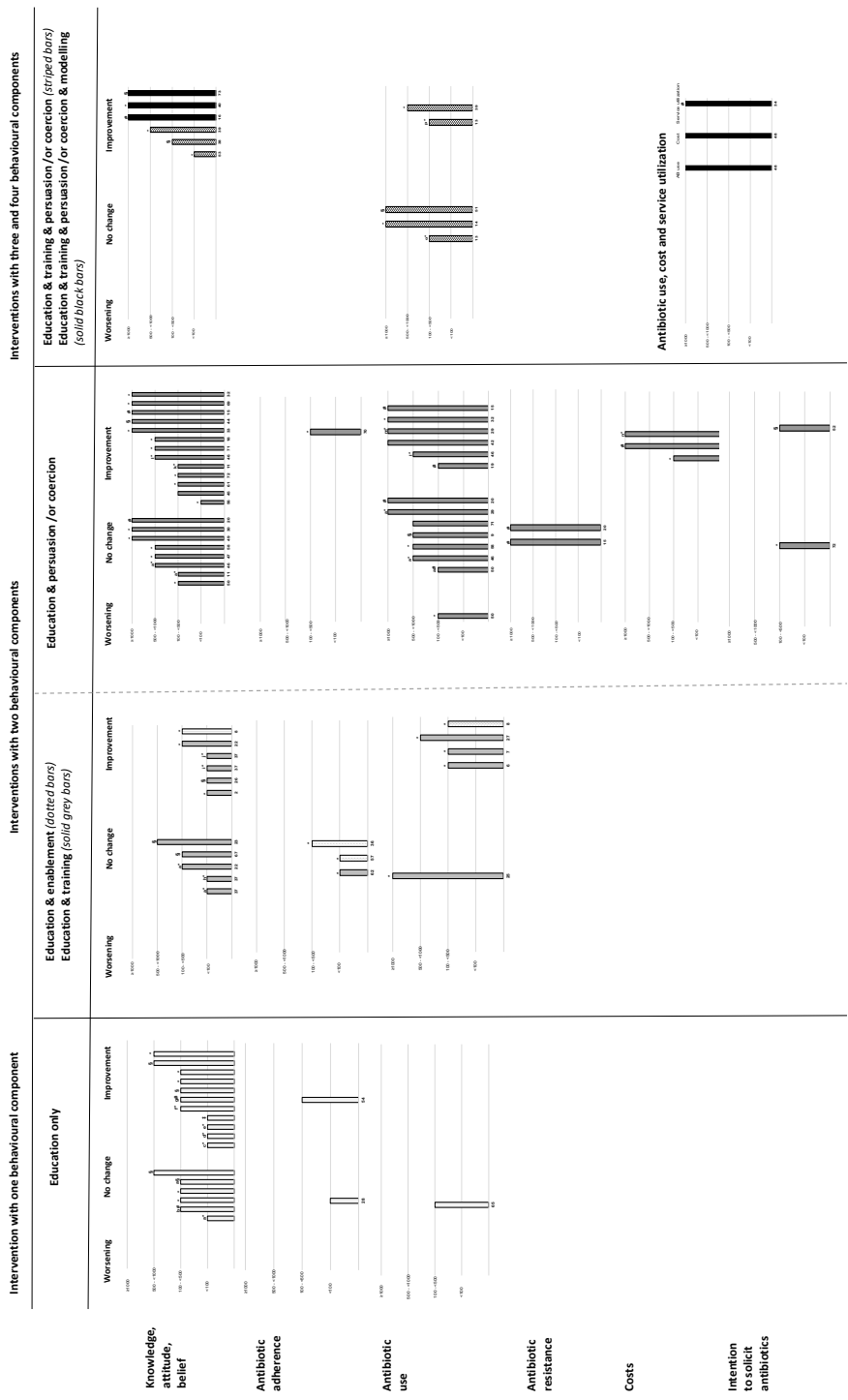
Figure 7 Supermatrix reflecting a combination of harvest plots and reported outcomes identified through the systematic review (for footnote explanation please see appendix section - study II)

4.4 Promising community-based interventions in Romania

An exploratory list of promising community-based interventions in Romania is presented in Table 4, considering the results from the systematic review (study II) which suggest that interventions that combine initiatives with the following behavioral components: education, training, persuasion or coercion and modelling, and the findings from studies I, III and IV. Community-based interventions refer to audiences that are not primarily healthcare professionals.

In its original design, the PhD should have explored the prioritization and related barriers and enablers of these interventions through a Delphi exercise with key policymakers in Romania. However due to challenges brought about by the pandemic, study IV design was changed.

Therefore, considering the lack of data from this Delphi exercise, in this section an exploratory analysis effort is presented, which offers a long list of potential interventions to be explored in a future Delphi study with experts in Romania, based on available data from the studies I-IV.

Reflecting on generic emerging obstacles in implementing these activities, considering the Romanian context, these may revolve around the complexities of modifying school curricula, increased demands on the time of specific healthcare professionals requiring financial compensation, and the potential for a significant attrition rate among trainees who are still students. For some there might be a need for an increased level of monitoring to ensure the quality of the delivered intervention and also safeguard the wellbeing of both those receiving and delivering the interventions. However, these were not able to be validated through this PhD, in absence of the Delphi study.

Similarly, to the above, there are potential important enablers to the implementation of these interventions. Most of them would have low resource requirements, easiness in access, they bring benefits for both the recipients as well as the persons delivering the interventions. In particular when it comes to the Romanian students, study IV found that most of them expressed a willingness to offer community interventions such as workshops for high school students (or younger university students) on appropriate antibiotic use in their spare time as well as to participate in national awareness campaigns regarding the use of antibiotics by disseminating materials provided by the public health departments.

When it comes to the reach of these interventions – as shown by data from study II, this would vary – some have the potential for wide national audiences whereas others may be more limited with local applicability.

Different policy campaign packages could be designed by combining interventions with different behavioral components - education, training, persuasion or coercion and modelling. Another consideration when designing such packages of interventions related to the desired reach of each of these – whether local, regional or national. Another planning consideration should pertain to financial resources needed – not solely for the design and implementation of the interventions, but also for the monitoring and evaluation programme that should be in place. However, key to designing and implementing these packages of interventions is a concern with their sustainability and periodicity. Evidence stressed the importance of ensuring these are not one-time off events, which would lose their impact after a few months.

Table 4 Exploratory list of appropriate community-based interventions in Romania

Intervention	Behavioral component the combination explores	Target audience	Persons delivering the intervention
Introducing hygiene lessons in schools that could have a module on bacteria and viruses	Education	School / high-school children	Teachers
Seminars and education sessions on health-related aspects (could be framed as 'wellbeing' classes)	Education	Students	Healthcare professionals
Workshops in kindergartens or schools	Education	Parents	Healthcare professionals
Dedicated website that could provide education sessions	Education	Members of the public	Healthcare professionals
'Train-the-trainers' type of training where students could gather new skills and enhance their capacities to further impart knowledge	Training	Students	Healthcare professionals
Cartoons and games (type eBug)	Persuasion or coercion	School / high-school children	
Communication materials such as leaflets, brochures, newsletters, radio/TV/online spots, posters	Persuasion or coercion	Students Parents Members of the public	Messages should be tailored for each of these audience health care professionals should be part of the team developing them

Theatre performances (could be performed by children to parents' groups, or by students to children & parents audiences; could be performed in community spaces or as street shows)	Persuasion or coercion	School / High-school children Students Parents Members of the public	School / High-school children Students
Contests (e.g., poster contest and quizzes)	Persuasion or coercion	School / High-school children	(Steered by teachers)
Peer-to-peer learning and tutoring activities such as students delivering specialized projects (microbiology workshops)	Modelling	School / High-school children	Students
Mentoring (however this would be applicable mostly to specialized universities and would target future healthcare professionals)	Modelling	Students	Healthcare professionals

4.5 Exploring a 'Theory of Change' for community-based interventions in Romania

The PhD aimed to articulate a Theory of Change (ToC) that would inform policymakers in introducing the promising community-based interventions. Due to limitations brought about by the change in study IV, this chapter will attempt an emerging ToC which draws on the findings from all constituent papers.

A ToC in this case would aim to comprehensively describe how community-based interventions would lead to a reduction in ABC as a result of optimization of antibiotic use, in Romania. ToC would aid planning, implementation and evaluation of such programmes and flesh out the corresponding linkages between the resources, activities and outcomes of the interventions.

A ToC is a comprehensive and dynamic description of how and why a desired change is expected to happen in a particular context[97]. It is a tool used in program planning, implementation, and evaluation to help organizations and individuals understand and articulate the linkages between the activities, resources, and outcomes of a program or initiative.

Assumptions

The ToC approach relies on identifying and monitoring certain assumptions that aid the understanding of why and how interventions are expected to work. They are represented by the beliefs, values, and contextual factors that inform the program or initiative, and represent the causal pathways from inputs to impacts. However, they are dynamic elements that may change over time as the intervention and other external factors lead to changes, therefore the assumptions should be monitored, and the ToC should be adjusted so that it remains valid and fit for purpose.

Inappropriate antibiotic use is driven by suboptimal prescribing or dispensing. However suboptimal prescribing or dispensing needs to be approached from multiple perspectives. There is emerging evidence from other fields[98–100], as well as this one[101–103], that a participatory approach would lead to better health outcomes, which enlarges the stakeholders' engagement pool beyond healthcare providers, patients and policymakers, to the wider public that would transform activities from a mitigation approach to a prevention approach. Furthermore, by focusing on communities, not solely individual patients, there is greater potential for community ownership and transfer of certain efforts in promoting appropriate antibiotic use. The Romanian context seems to be less resource prone for prevention activities, which oriented the assumption that these types of community-based interventions may be a less cost intensive approach. However, in particular for resource constrained settings it is important to explore interventions that show effectiveness (rather than emphasize trialing completely new approaches). In particular for achieving a sustained behavior change it is important to take a longer-term programmatic view and not restrict the approach to pilot testing. Still there should be an organic growth of implementations, despite the potential scalability of interventions.

Key assumptions relate to the Romanian social norms and cultural beliefs that shape the provider and recipient's behaviors. While Romanian society is characterized by high-power distance, it was also found that the acceptance of hierarchy is accompanied by frustrations, therefore a community-

based approach where interventions are delivered in a less government-mediated way could be better accepted. The collectivist nature of the Romanian society would also favor interventions that require group collaboration towards achieving wider benefits. However as previously shown, Romania's particularity is that the collectivism does not necessarily extend to groups beyond family. Therefore, interventions that would place parents at their center, to benefit their children, may be more successful in a Romanian setting. The high uncertainty avoidance trait would point to reticence to change and innovative practices. However, a way to overcome this, is to provide reassurances that negative results would not necessarily be the responsibility of the providers. Furthermore, it may be beneficial to implement interventions that have already an emerging evidence base on their effectiveness. The intermediate stance between long-and short- term trait combined with that of restraint, may favor the acceptance of these type of interventions, as not all the results from these interventions would be available immediately. However, some improvements might be reflected in Eurobarometer survey results (depending on the scale of the interventions). Further considering the restraint characteristic, it will be important to continue to reinforce the message that antibiotics are not a 'quick-fix' to mitigate potential tendencies of instant gratification. The femininity trait of the Romanian society, in particular the consensus decision-making, is a strength towards the implementation of these type of interventions, that would benefit from a participatory and consensus-oriented design and implementation. Other individual traits of Romanians such as the desire to be competent would support the involvement of healthcare professionals, who, while not primarily delivering the intervention would be consulted (and recognized) as experts in the design, monitoring and evaluation of these interventions. Lastly, in a Romanian setting, it may be beneficial to involve religious figures, especially as champions/ promotors of such initiatives. All these socio-cultural considerations should be explored in relation to each specific intervention type and from the perspective of both beneficiaries and implementers. Please also see section 5.3.1.

Inputs

Considering the necessary inputs such initiatives require, these could be grouped into: i) human resources, ii) financial resources, iii) materials, equipment and information management systems. When considering human resources these can be categorized in the human resources that would directly deliver the interventions, as well as those that would be responsible for the 'programmatic' aspects, the project team. The persons delivering the interventions could broadly fall into two main categories: healthcare professionals and lay persons such as teachers, students, parents, community health workers or other trained groups. The major cost drivers would be for the personnel, training and materials, as well as programmatic costs that would support the community engagement and exchange efforts and information flow.

Activities

The types of interventions are described in the previous subchapter.

However, from a programmatic point of view the type of activities the campaigns would entail could consist of a i) planning phase that would encompass a situational analysis, defining the target audience for the interventions, establish SMART (specific, measurable, achievable, relevant, and time-bound) objectives, mapping key stakeholders that should be involved in the development and

implementation of the intervention; ii) developing the package of interventions that would consist of co-creating the packages of interventions, preferably involving as much as possible representatives from the target audiences, providers of the intervention and key representatives of local communities - an associated timeline and budget should also be developed; iii) pilot-testing the package and make iterative transformations based on emergent learning; iv) develop and follow a monitoring and evaluation plan; v) ensure sustainability: communicate successes and look for opportunities to embed successful elements into long term activities (e.g., linking it to school curriculum) and funding mechanisms.

Outputs

The traditional outputs being followed consist of changes in knowledge, attitudes and practices among healthcare providers and the general public on the use of antibiotics, improved antibiotic prescribing practices among healthcare providers, lower ABC rates. However, as our research uncovered there are difficulties in measuring these types of outputs, which triggers a need to create standardized instruments to this effect.

To ascertain the most suitable intervention functions, policy categories, behavior change techniques, and modes of delivery for a given context, with a higher likelihood of implementation and impact policymakers could consider APEASE criteria[i] linked to BCW[104]. These look at whether the intervention is affordable, practical, effective, acceptable, whether there are any potential side-effects and equity considerations[105].

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[i] Affordability, Practicability, Effectiveness and cost-effectiveness, Acceptability, Side-effects and safety, Equity

5 Discussion

The purpose of this overall body of work was to articulate an evidence-informed approach to the potential implementation of community-based interventions to combat AMR. By assessing the existing evidence on the value of these interventions, the scope was narrowed to a closer examination of their potential introduction in Romania, with a particular view of exploring their implementation and the wider ABC and AMR phenomenon through the lenses of current and future healthcare professionals.

Main findings show that doctors, pharmacists, and students from related fields generally share consistent views, although there is some variation among professions. Furthermore community-based interventions show significant variability, but there are indications of certain combinations of these that are more effective than others. The research has identified various broader systemic barriers and enablers that need to be addressed comprehensively to tackle issues related to ABC and AMR. Lastly the findings from this research trigger several theoretical and methodological implications. In this discussion section implications of these findings are explored.

5.1 Divergences and commonalities of healthcare providers perceptions on antibiotic use, their roles and related challenges and opportunities

5.1.1 Capabilities considerations

The findings section lists several capabilities, as perceived by future and current healthcare providers. These span awareness on their and other's roles and how this may affect behavior, how they would collaborate between themselves (intra and inter-professionally), knowledge and skills to correctly perform their duties, access to data and other supportive tools (e.g., diagnostics).

The mixed awareness regarding whose behavior is contributing most to emergence of AMR, combined with the findings on collaboration and teamwork, prompts reflections on the general collaboration between doctors and pharmacists. A recent review that also considered the COVID-19 experience, suggest that this crisis has played a significant role in accentuating the responsibilities and capabilities of pharmacists, while simultaneously fostering a greater sense of teamwork, demanded by the prevailing circumstances[106]. However, in general, the level of interprofessional collaboration varies considerably and is contingent upon numerous influencing factors, including shared values, interpersonal relationships, clarity of roles, mutual communication and trust[107–111]. The more prevalent strains seem to result from different understanding of the roles of pharmacists, no division of competences and little time to allow for such cooperation activities[106,112,113]. Current views on roles, are informed by practices of some doctors who advise patients to engage in discussions with pharmacists on acquiring medications, as these are considered more accessible and have more time compared to doctors. This would signal those doctors would see an educational role for the pharmacists especially around safe use of medicine[114]. The role of pharmacists in delivering patient education came through chiefly in study I, which found that the pharmacists can, and want, to play this educational role. These results are also in line with previous research which also found positive impacts of such approaches[115–119]. However, it is important to consider that for pharmacists to fulfill this role, it would require a shift in the current reimbursement model. Presently, pharmacies

are primarily reimbursed for the sale of products rather than the provision of services, which poses a barrier to fully embrace their potential in offering expanded healthcare services [120]. On the issue of doctors' time (which seem to determine some doctors in other settings to direct patients towards pharmacists), interestingly, study III interviews, did not uncover specific concerns regarding the amount of time doctors can allocate to patient consultations. This is at odds with the significant emigration of Romanian doctors to other European countries, and the worry that this exodus is expected to create constraints in delivering primary healthcare services[72]. However, it is important to interpret the absence of this finding cautiously, due to the restricted time of the interviews which in turn points to the doctors' limited availability.

When considering wider research, another area where physicians seem to recognize the importance of pharmacists, is in conducting reviews of patients' medications to identify potential interactions. This collaborative approach lead to enhanced effectiveness of pharmacotherapy and improved adherence among patients[108,121]. Certain physicians also viewed the idea of pharmacies dispensing extended supplies of regularly taken medications positively[122]. Furthermore, in some countries pharmacists can conduct seasonal vaccination campaigns[123] and perform diagnostic tests for COVID-19[124,125]. However, some doctors do not deem pharmacists knowledgeable to diagnose patients[122,126]. All these are not current practices in Romania and the results from study III would not necessarily support expansion of pharmacists' responsibilities. It was eluded there is this perception that the pharmacists would compete with the medical profession and be a 'pharmacy doctor'. When it comes to enablers of cooperation emerging evidence suggests that facilitators include increased data exchange and communication facilitated by integrated software for information sharing [127]. Another enabler of cooperation, that also came out in study I was the pre-existing personal or shared work environment connection between doctors and pharmacists. This converges with findings identified in the wider literature, from the doctors' perspective, which show that those with established relationships with some pharmacists value the role of those specific pharmacists, but not necessarily others. Doctors without prior interprofessional interactions are less enthusiastic and unlikely to deepen these relationships[128]. Cooperation and teamwork can be fostered ever since the university years. Findings from study IV shed light on the commonalities and differences in preparedness levels between medical and pharmacy students. This finding sparks reflections on the potential for integrated teaching to address common needs and start fostering teamwork. While acknowledging the different roles of these professions, an area where more in-depth and joint training might be explored in Romania, is in relation to monitoring antibiotic therapy and assessing emerging evidence in particular in engaging in research activities – whether these are clinical or public health. This is because both pharmacy and medicine students in study IV felt unprepared and these subjects would equip all students with relevant knowledge to engage and critically assess research which is relevant for both professions. Overall, it is important to note that collaboration between doctors and pharmacists strengthens patient care, ensuring safe and effective medication use, improved adherence, and better health outcomes. This cooperation is particularly crucial given the increasing number of medications and potential interactions, leading to long-term cost savings in healthcare expenditure[129]. Certain interventions targeted at enhancing trust could be investigated by implementing inter-professional collaborations, such as roundtables, trainings, and seminars. Additionally, the dissemination of periodic data on antibiotic prescriptions and sales through pharmacies could also be explored as a strategy.

Regarding the knowledge and skills to perform their duties, doctors (study III) highlighted the importance of interpretability of guidelines and acknowledged their limitations while emphasized the value of relying on experience and tailoring treatments to individual patients. This resonates with the findings from a recent review that examined the global landscape of publicly available antibiotic prescription guidelines published in English which found considerable variability when it comes to their structure, content, and recommendations [130]. Thus, for a doctor with limited time, it can be difficult to workout which recommendation would be best. Greater guideline consistency and clarity, with particular applicability to the Romanian context, periodically updated and based on national regulations and emerging patters of resistance in Romania would be needed. Apart from updating guidelines, various interventions implemented in different settings aimed to enhance relevant healthcare professionals' capabilities. These interventions include providing job aids, prescription pads, and infographics, which facilitate the quick identification of pertinent information[45,48].

Family doctors in Romania have identified challenges associated with a lack of diagnostic capacities as a crucial capability needed. This aligns with previous research emphasizing the necessity for rapid tests that can enable point-of-care (POC) diagnostics and complement empirical prescribing practices[131,132]. There are promising developments to address this concern with increasing evidence on the POC tests value in reducing antibiotic prescribing[133–137]. For example, a recent Swiss study sought to address the challenge of distinguishing between bacterial and viral infections for lower respiratory tract infections, by utilizing a combination of lung ultrasound and procalcitonin test, with the integration of results through an algorithm. The study revealed a notable one-third reduction in antibiotic prescriptions as a result of this approach. Furthermore, the use of the procalcitonin test alone proved sufficient to achieve this significant reduction[138,139]. However, there are also studies that question the value of association between POC and antibiotic prescribing[140]. In general, POC testing is not introduced widely and there is considerable variation across countries. Findings from a recent perspective audit in 18 European countries, found that in Romania, the practices of POC testing (to identify strep A throat infections, and to use the biomarker CRP to inform antibiotic prescribing for acute cough) or performing blood cell differential counting are practically absent[141]. On the whole the analysis from this study found that POC testing was not associated with antibiotic prescribing. The differences in prescribing, being explained by individual illness severity and country-level factors – such as previous antibiotic prescribing levels in that country, existing guidelines and stewardship programmes for antibiotics, culturally related GP and patient factors.

Another layer that was less explored but could be linked to both capabilities and motivations, pertains to the high consumption of broad-spectrum antibiotics in Romania. Past studies found that exercising greater pressure on family doctors results in an increase in the prescription of broad-spectrum antibiotics[142]. Specifically in Romania, research found that compared with other countries in the analysis, Romanian had high rates of prescribing broad-spectrum penicillins, macrolides and antivirals[141]. This pattern is cause for concern since broad-spectrum antibiotics contribute more significantly to the development of AMR compared to narrow-spectrum antibiotics[143]. Furthermore such prescribing practices are often linked to lack of knowledge or limited implementation of latest AMR related best practices[144]. Nevertheless, knowledge may not be the sole determinant of this practice. Limited resources for conducting antibiograms and POC testing, can pose a challenge for family doctors to prescribe narrow-spectrum antibiotics that precisely target the causative pathogen,

considering both the medical risk assessment as well as cultural factors associated with the doctor-patient relationship.

Regarding students' knowledge and skills, study IV indicated that both medical and pharmacy students felt prepared in assessing the need for antibiotics, understanding antibiotic resistance as well as communication and engagement on the topic of antibiotic use. The findings on sufficient knowledge for assessing the need for antibiotics – such as identifying early signs of infection are consistent with previous research across several EU countries, including Romania[92], and convergent with some of the findings of a systematic review of 22 studies which found that students considered themselves prepared to identify signs of infection and making a clinical decision[145]. However the Romanian students' self-assessment seem to be somewhat divergent with findings from the same systematic review which found students felt less preparedness when it comes to interpretation of results [145,146,147,148]. Most medical students did not feel ready in three out of the seven areas when it comes to making decisions to initiate antibiotic treatment. In particular they did not feel ready to prescribe a combination of antibiotics with other medicines, setting the appropriate timing and duration of antibiotic administration, and deciding on treatment without the use of guidelines. The students' recommendations regarding the incorporation and prioritization of resistance and optimization in the curriculum underscore the importance of improving readiness in these areas. Our findings are also consistent with a systematic review assessment of 72 studies which found that final year medical students have insufficient capabilities to prescribe antibiotics safely and effectively [149]. When it comes to pharmacy students, in our study, most felt prepared to initiate antibiotic treatment. Due to the dominant focus of existing studies on pharmacy students' knowledge, attitudes, and practices regarding antibiotic use for viral infections and the effectiveness of antibiotics, it is challenging to directly compare our findings with those of other studies. However, most findings in the existing literature consistently suggest a deficiency in the level of knowledge of pharmacy students [118,150,151,152,153, 154] .

Students also expressed a lack of readiness concerning monitoring antibiotic therapy and evaluating emerging evidence. Both medical and pharmacy students did not feel prepared to interpret scientific study findings or engage in clinical or epidemiological research as researchers. This is not surprising, taking into account the relatively limited number of research publications produced in Romania[155].

Overall, the readiness patterns observed among the participating universities exhibited similarities. In both medical and pharmacy faculties, students generally reported a moderate level of preparedness. However, one medical faculty stood out, as most students there expressed a low level of preparedness. The next level of preparedness scores displayed greater variability, with a split assessment: half of the students reported a high level of preparedness, while the other half reported a low level of preparedness. Among the universities, two displayed consistent patterns among both medical and pharmacy students, while the remaining two exhibited variability. The reasons behind these differences are challenging to ascertain but could potentially stem from factors such as available resources, teaching methodologies employed at specific times in different universities, or cultural distinctions, considering the similarity in curricula across Romanian universities.

Students provided various suggestions to enhance their knowledge. These span enhancements in curriculum design and content, particularly through integrating and emphasizing topics related to

AMR and optimization of antibiotic use. In addition, they highlighted the importance of increased practical experience, usage of interactive teaching methods, and facilitation of participation in scientific research. These insights aim to foster their development and augment their comprehension of antibiotic use.

Studies I and III, revealed the perceptions that patients exerted pressure and demanded antibiotics. This is a recognized factor that seems to be strongly associated with the doctors' decision to prescribe antibiotic[156–162] and the pharmacists' to dispense antibiotics without a prescription[163–166]. Although our findings do not necessarily indicate a lack of skills among doctors or pharmacists, it does highlight the need for resilience in managing such situations through effective communication and assertiveness. This has important bearings when viewing this finding through a cultural lens – further discussed in Section 5.3.1. As far as the future healthcare professionals' feedback, they would not have been yet exposed to such situations except during their internships, however many recommended the need to conduct wide educational community-targeted campaigns. Still, students expressed confidence in their ability to discuss appropriate antibiotic use with patients in a layman's language, particularly in situations where antibiotics may not be necessary.

When discussing the potential of data to act as a feedback loop and improve knowledge and decision-making, both pharmacists and doctors expressed certain reservations. These concerns were based either on doubts about data accuracy or the realization that data alone may not offer a complete picture of whether antibiotics are being prescribed or dispensed appropriately. In contrast, students emphasized the significance of monitoring and collecting data, including the establishment of individualized patient registries to capture information on resistance and antibiotic use. They also highlighted the need for greater integration and monitoring of electronic prescription data as a valuable resource for improving antibiotic-related practices. Findings from other studies showcased mixed results with some indications of positive impact of feedback loops[167] while others led to inconclusive or no-change results[168,169,166].

5.1.2   Opportunities considerations

Regarding the opportunity domain, participants in studies I and III primarily highlighted negative factors associated with physical opportunities that could influence behavior. These factors included issues like limited access or continuity of care in rural settings, the adverse effects of the COVID-19 pandemic, the seriousness of hospital-acquired infections, as well as the empowering role of communities. Interventions aimed at addressing these factors would necessitate system-based approaches, such as establishing infrastructure to bridge gaps in continuity of care. A potential solution could involve implementing mobile clinics or pharmacy services, along with the deployment of eHealth solutions to enhance monitoring and follow-up processes. In Romania, however, such initiatives are currently limited to sporadic occurrences.

Another opportunity could be in respect to enhancing surveillance networks. This opportunity is connected to two findings that showed perceptions that AMR is mostly due to hospital acquired infections and ABC has been exacerbated by the COVID-19 pandemic. Notably, the initial COVID-19 treatment recommendations exhibited some ambiguity on the use of azithromycin, leading to its prescription in early 2020. Despite the guidelines issued in November 2020, which explicitly

discouraged the use of azithromycin, the most recent ECDC report indicate that Romania has attained the highest position within the EU in terms of total consumption of antibiotics for systemic use[17,18]. This setback indicates a regression to the levels the country had ten years ago. Determining the precise factors behind this increase is challenging; nevertheless, it is anticipated that the COVID-19 pandemic has played a significant role. This trend has the potential to contribute to the emergence of antibiotic resistance for this medication and possibly lead to cross-resistance with other antibiotics. All these underscores the importance of heightened surveillance to detect any emerging patterns. This need was also identified by the students in study IV. Limiting hospital acquired infections, necessitates the implementation of a comprehensive antibiotic stewardship program. The perceptions expressed by family doctors regarding the importance of combating AMR in hospitals are supported by data and previous incidents reported within the Romanian context. In addition to the previously mentioned data from the ECDC report[18], there have been notable cases highlighted in the media in recent years concerning the use of substandard disinfectants in hospitals [170].

Communities have been recognized as facilitators for interventions against AMR. Their early engagement is beneficial in the design, customizing and piloting of public campaigns. However, to facilitate this, it is necessary to identify levers for enabling participatory community processes. This starts with a common understanding of the problem, identification of community needs and resources relevant to the problem, as well as reaching consensus on the underlying measures to be explored.

All three studies emphasized the perceived absence of patient education, which contributes to unnecessary ABC. Since patient education is also influenced by interactions with healthcare professionals, this highlights the need to contemplate ways to strengthen the doctor-patient and pharmacist-patient relationships. Previous research in Romania raised concerns that patients may not automatically grant recognition to doctors' legitimacy and instead seek confirmation on their credibility through the success of treatments and feedback from other patients[171]. Patients are increasingly relying on online sources for additional information, explore alternative treatment methods, or sometimes even opting not to follow prescribed treatments, as a means to exert more control over their illness. As suggested by participants in studies I and III, there is a growing distrust in science, which has been further amplified by the pandemic response, challenged by disinformation, and exacerbated by the increased use of social media. These developments and experiences may have reshaped norms characterizing the healthcare professionals- patient relationship, necessitating increased engagement with patients to accommodate their growing agency. With greater amount of information, enabled by technologies, a need may arise for healthcare professionals to 'train' patients on how to evaluate such information. It will be necessary that patients are aware that greater agency may entail greater responsibility and accountability from their part. At a higher level this raises questions regarding strategies to foster trust between patients and healthcare providers. The literature suggests that doctors' attributes of being: compassionate, honest, empathetic, and dependable are what patients value[172]. Furthermore, respect and partnership are critical in forging a trusting physician-patient relationship[173]. However, the advent of AI is likely to fundamentally transform this relationship, in particular patients' expectations from their healthcare providers. For example, a recent cross-sectional study demonstrated that a chatbot

effectively generated high-quality and empathetic responses to patient questions posted in an online forum[174]. As AI will continue to evolve, it will increase on one side the expectations from patients, but it may also alleviate the time demands on doctors and increase precision in medical decision-making.

Nevertheless, all of these factors must be accompanied by endeavors to bridge the 'intention-behavior gap'[175] - recognizing that even with some level of motivation, it may be challenging to adopt a certain behavior when existing barriers are present. Supported by evidence from study II, this indicates the importance of implementing a diverse range of interventions, rather than a limited selection, to comprehensively address factors throughout the behavior change process.

5.1.3   Motivation considerations

Factors influencing reflective and automatic motivation are intertwined with ethical dilemmas surrounding patient welfare. These factors are further compounded by perceptions regarding the ease with which patients can seek treatment elsewhere, their limited awareness of the risks involved, and their tendency to not adhere to prescribed treatments. Additionally, the perceived pressure to switch to another doctor or pharmacy if their demands for antibiotics are not met also plays a role in shaping motivation levels.

Overall studies I and III revealed that healthcare professionals are concerned with patient welfare and perceive that patients from the lower socioeconomic areas are less likely to take antibiotics correctly, engage in preventive measures, and, in certain instances, face limitations in accessing medical care. This may also be grouped or linked to the 'Opportunity' domain where difficulties in access to care were placed. Our findings that socio-economic burden may motivate a certain behavior of healthcare professionals, converge with results from studies which found that antibiotics without medical prescription were dispensed predominantly in lower socioeconomic areas[176], or when there were perceptions that as a result of high associated costs patients were not completing the entire course of antibiotic treatment [177,178]. Hence, it is reinforced that the patient's financial situation plays a significant role concerning unnecessary ABC, as healthcare professionals may view it as an ethical duty to counteract inequities in ensuring access to care and enable positive health outcomes.

A positive aspect observed across all three studies is that respondents acknowledged their crucial role as educators. However, some participants in study III did not perceive family doctors to have a central role in this regard. Instead, they believed that infectious disease specialists or doctors working in hospitals, where AMR is more apparent, held greater responsibility as educators. Due to the qualitative study methodology employed, the complete consensus on this perspective remains unclear and cannot be universally generalized.

In study IV, students expressed a general willingness to engage in various activities on increasing knowledge and optimizing antibiotic use. However, most pointed a lack of interest in conducting research on this subject as part of their dissertation. This may not necessarily signal a lack of interest in the topic. Typically, the dissertation is the primary independent research project while at university for most students in Romania, and it normally focuses on the topic of the future desired specialization, particularly for medical students. Nonetheless, the prevalent response indicating that

the use of antibiotics in Romania will worsen, represents a missed opportunity to motivate students to conduct relevant and impactful research, that would enhance their skills and aid the national approach through cost-effective evidence-generation. Encouragingly, most students expressed interest in participating in national awareness campaigns and offer community interventions such as workshops. This finding holds significant promise for policymakers who could utilize these additional human resources for implementing various campaigns.

On the students' motivations, study IV offers opportunities to reflect on how their professional attitudes and behaviors could be shaped, considering the importance of education and training. Students' recommendations revealed some of their potential values and norms such as responsibility – as students recognized the importance of responsible use of antibiotics, collaboration – although mostly focused within their profession and with patients, critical thinking reliant on evidence-base practice and patient-centered care and continuous learning. These values and norms could determine future healthcare professionals' attitudes and behaviors. Social cognitive theory places emphasis on the learner's active role in constructing their own understanding and knowledge, the concept of self-efficacy, and the significance of observations and modeling in the learning process[179,180]. Research found that medical students who scored higher on measures of empathy and professionalism during their training were more likely to exhibit these qualities as practicing physicians [181]. Therefore, the fact that students showed signs of responsibility, collaboration and critical thinking is encouraging. Within this theoretical framework, there is also an acknowledgment of the influence of social and environmental factors on behavior, with individuals being more inclined to participate in activities that are perceived as socially acceptable or normative. For instance, collaborative practice is recognized as an avenue for enhancing patient care and improving health outcomes[182, 183]. Considering these theoretical foundations and this research findings, several interventions could be implemented with the overarching goal of enhancing preparedness and confidence. These interventions may include: i) evidence-based training focusing on enhancing skills to critically evaluate research studies, ii) interprofessional education facilitated by shared goals and joint training programmes, to foster a deeper understanding on different healthcare workers' roles and responsibilities, and enhance collaboration, teamwork and communication and coordination in patient care; iii) simulations and role-playing exercises to provide practical experience in a controlled environment, iv) mentorship programmes to support modeling of students' behaviors based on professionals who are conscious of their role as mentors.

All these considerations can be also seen through the lens of healthcare professionals' agency and structural factors that can act as barriers and facilitators in their related decision-making process. On the whole, exploration of the findings and their interpretation in relation to recent research in the respective areas highlights important implications. However, current findings cannot support interpretations on the relative importance of these influencing factors, in other words which of these are more important. Investigating relative weights that could be assigned to these factors in influencing behavior on respective target groups (quantify the impact of these variables) should be the subject of future research.

5.2 Community-based behavior change interventions can improve antibiotic use

Findings from study II indicated that multifaceted interventions resulted in more substantial improvements in reported outcomes when compared to interventions with single elements. This converges with previous research that presented emerging evidence on a mix of interventions rather than standalone programmes[45,48,184–186].

While most community-based interventions have an education component, relying exclusively on interventions that focus solely on education is likely to result in improvements of knowledge, attitude and beliefs but have little impact on other outcomes of interest such as antibiotic adherence and use. Most analyzed interventions in this review combined education and persuasion or coercion[187–210]. They had varying degrees of effectiveness raising difficulties in drawing conclusive conclusions. Only few studies reported on costs, providing limited evidence on the cost-effectiveness of such interventions, and indicating a need for further investigation[189,193,207,211].

A smaller number of studies included subsequent follow-up periods. This precludes conclusions regarding the long-term retention of the intervention's impact. Some studies highlighted this limitation and recommended periodic implementation of campaigns whenever feasible. Another potential approach could involve the systematization of specific interventions, such as the incorporation of periodic activities (e.g., courses, school plays on antibiotic-related topics, annual teachers' workshops) into school curricula. These considerations are closely linked to the issue of sustainability, which frequently arises with community-based interventions that might be discontinued after the pilot stage. Achieving sustainability may become even more challenging in the aftermath of the COVID-19 pandemic, which may have diverted public and policy attention.

The systematic review identified opportunities to supplement the traditional healthcare workforce by involving various community-based actors in a manner that promotes ownership and inclusivity. Policymakers could extend their efforts beyond public communication campaigns, which usually aim to enhance awareness and understanding of AMR through effective communication, education, and training. Instead, they can envision the implementation of broader community-based approaches that foster engagement and participation from diverse stakeholders.

5.3 Exploring barriers and enablers through wider lenses

5.3.1 Placing the findings in a socio-cultural perspective

Using a social capital lens can further aid the understanding of this thesis' findings. Research suggests that post-socialist, Eastern Europe states, including Romania, exhibit low levels of bridging and linking social capital[58,212]. The thesis findings support this. Pharmacists' lack of trust in state institutions indicates a low vertical level of trust and weak linking capital, which ultimately contributes to a negative contextual effect on health. The lack of trust exhibited by pharmacists towards state institutions signifies a low level of vertical trust and limited linking capital. As already mentioned low linking capital has a detrimental contextual impact on health. Family doctors similarly alluded to distrust in different structures, albeit for them these were mostly pharmacies or other colleagues. This would point more to a lower level of bonding capital. These findings (the detrimental health outcomes) resonate with those of Collignon et al. [213], who conducted a comparative analysis

of human antibiotic usage, private health care expenditure, tertiary education, economic advancement (per capita GDP), and quality of governance. Their research indicated that corruption is the primary socioeconomic factor contributing to antibiotic resistance. Moreover, the image deficit of pharmacists and the lack of collaboration between professions serve as indicators of low bridging capital, which may hinder the dissemination of information and innovation. Closed networks, such as those formed within siloed work environments, are susceptible to reinforcing negative norms and behaviors within that specific network[55]. Consequently, when there is a higher level of bridging capital, informal social control will be employed to regulate deviant health behaviors, resulting in an amplified feedback learning process that can be advantageous for everyone involved. These findings reinforce the previous findings which highlight the necessity for greater efforts in terms of interdisciplinary collaboration[214] and enhancement of bridging capital[215–217].

Efforts to increase linking capital between healthcare providers and patients/public may benefit from reflections on evolving roles and institutionalized relationships between these groups. This thesis' findings indicate that healthcare professionals perceive patients as lacking education and have concerns about their reliance on medical information obtained from their social network or the internet. As information exchange transforms, there might be a growing need to support greater patient agency through shared decision-making, technology-mediated roles, and collaboration with other healthcare professionals. This may lead to issues of identity foreclosure as doctors and pharmacists' self-social identity may not align with patient expectations. Improving linking capital in this case might be achieved through campaigns that highlight the vital role of healthcare providers while recognizing societal transformations.

Moreover, these challenges pertaining to the doctor-pharmacist and doctor-patient relationship could be explored through cultural lenses. Using Hofstede's model of cultural dimensions, Deschepper et al.[218] uncovered that countries with high Power Distance (high level of hierarchy) – and high Uncertainty Avoidance (low tolerance for uncertainty and ambiguity)- such as Romania, tend to have greater antibiotic use. Within the context of the patient-doctor relationship and interactions between professionals, the high Power-Distance would lead to deference towards the doctor, resulting in less patient involvement in medical decision-making[218]. Nevertheless, this thesis's discoveries imply a multifaceted phenomenon, since although decision-making might appear unidirectional, there are signs of perceived patient influence concerning medical choices. In addition to the growing distrust in science, this trend may indicate a transition in the type of patients from deferent or ignored to critical rather than involved[m]. In relation to the patient-pharmacist relationship, from the pharmacists' perspective there is limited or no deference. However, it cannot be generalized that pharmacists see patients as overall critical. This flags a need to empower healthcare professionals to guide the transition in patient attitudes, by providing them with accurate information and reliable platforms that they can recommend to patients to enhance their health literacy. Healthcare professionals influenced by a high Power-Distance and Uncertainty Avoidance,

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[m] Pechère et al [219] proposed four patients' typologies: i) involved patient - involved in their own medical care, deciding jointly on best approaches; ii) deferent patient - deferent to their doctor and not making joint decisions; iii) ignored patient – reduced interaction with the doctor, feeling ignored but less likely to disagree with the doctor or consider the doctor incompetent; iv) critical patient - doubt the doctor's competence and expertise.

are believed to refrain from acknowledging situations of uncertainty due to the fear that patients might lose confidence in their medical expertise[218]. This aligns with the findings from studies I and III, where pharmacists expressed concerns about patients seeking another pharmacy, and doctors worried about the possibility of losing patients who may find another doctor more willing to prescribe antibiotics. However, in both cases, these concerns may be driven more by economic considerations than the fear of being perceived as less competent. In conclusion, the findings of this thesis indicate that cultural dimensions could indeed play a role in antibiotic use in Romania. Nonetheless, further exploration through studies with larger sample sizes and a more specific focus on these issues would be beneficial to gain a deeper understanding.

5.3.2   Understanding implications through a systems approach

Systems thinking recognizes the complexities of a phenomenon, and the potential interconnectedness and interdependencies of various components of a system, or of systems more broadly. When it comes to ABC and AMR, complexities arise from the relationships and feedback loops between patients, the public, healthcare providers, policymakers, the pharmaceutical industry as well as the agricultural, animal and environment sectors. There is broad consensus that AMR cannot be fully tackled by addressing these components in isolation.

Within this framing, this thesis research contributes to a deeper comprehension of the role of healthcare professionals, particularly in terms of how they perceive their capabilities in relation to patients and broader structural frameworks.

Systems approach also highlights the dynamics that results from healthcare and social systems' structures and functional pathways. This thesis findings highlighted the concerns on how these can negatively affect healthcare professionals' activities. This also included considerations on the policies, regulations, guidelines and surveillance systems. Themes that were less addressed in this thesis research were the availability and accessibility of alternative treatment options. While antibiotics are relatively cheap, the interviews did not explore the accessibility of other-the-counter or other preventive measures that can be accessed at a cost.

While study IV focused on students, which brought light on the educational system implications, a lesser emphasis was facilitated towards the research sector in Romania. While there are several Romanian manufacturers of antibiotics, most of them commercialize generic products. Recent developments signal potential expansion of one of the manufacturers research activities. However, it was evident that from the students' perspective, including pharmacy students, research in this area does not rank high. Therefore, a potential area of research could be to investigate the relationship between a strong research environment and ABC and AMR rates.

An area that was not tackled but was alluded to (in the form of concerns regarding the rural-urban divide) consists of understanding the role of healthcare settings in relation to community environments as well as agriculture and animal health, with a view of optimization the organization of such settings.

Regarding the impact of antibiotic use in livestock and agriculture, there is a paucity of research on these elements in Romania. However, policies and regulations are aligned with EU practices,

oriented towards promoting responsible and judicious antibiotic use. However, this should be further investigated, including research looking at environmental factors – e.g., water contamination especially in rural areas.

Systems thinking also aids the identification of leverage points where targeted activities might have the greatest impact. One starting activity in this respect should be to periodically bring all stakeholders together towards greater interdisciplinary collaboration. Romania has established a national multidisciplinary committee to work on AMR; however, this Committee, meets sporadically, which does not fully support such coordination efforts.

5.4   Methodological considerations

5.4.1   Reflections on difficulties to perform analysis due to data complexities

Study II analysis revealed the difficulties in comparing results across the different studies. Complexities arose from the diversity of settings, target populations, study designs, choice of outcomes, ways of measuring them due to the use of a range of data collection instruments. The later impaired the possibility of a meta-analysis or sub-group analysis. Study IV further delved into the complexities of developing appropriate survey instruments. While building on an existing survey questionnaire, the exploratory and confirmatory factor analysis flagged the need to further improve its structure.

This reveals a cross-cutting need to agree on instruments to capture measures that go beyond laboratory or clinical outcomes (where agreed reported protocols exist).

5.4.2   Limitations of the COM-B model

The BCW which relies on the COM-B model, was extensively used in this PhD and has offered a systematic and comprehensive approach to analyze varying and large (for the systematic review) data. Nevertheless, the extensive application of this approach across various methodologies uncovered a few limitations in addition to the numerous strengths it offered.

COM-B Domains

The framework primarily focuses on individual-level factors, which proved essential for Studies I, III, and IV. While Michie et. al positioned 'Opportunities' as the context related domain, it may be beneficial to incorporate more clearly additional levels of analysis that capture more explicitly interpersonal, organizational, and community-level factors. While norms are captured under 'Social opportunities', it becomes challenging to untangle if these are solely the social or descriptive norms. It also becomes a bit difficult to know how to position these compared to 'Reflexive motivations' domain that captures beliefs about consequences, roles and identity. Furthermore, a clearer differentiation might also aid selection of interventions, that would not only modify behavior but also change the respective norms that condition it. For example, changing a descriptive norm may be

possible by changing empirical[n] expectations, while a social norm might involve both empirical and normative expectations[o] [220,221].

Regarding the 'Motivation' hub, while this domain discussed the beliefs about capabilities and consequences, it is a bit difficult to untangle the risk perception / threat assessment element. For example, are the risk perceptions considering risk probability or risk severity, or both. This would allow a more profound understanding of the consequences, which might not stem only from the individual behavior and may also eventually aid more precise modelling efforts.

Intervention functions

Using all nine domains on the intervention functions proved to be somewhat challenging during the systematic review analysis. This lead, based on previous practices, to merging persuasion and coercion domains. Likewise, distinguishing between education and training posed difficulties since the act of enhancing knowledge or understanding is closely intertwined with impairing skills. A potential addition to these nine functions could be 'Empowerment and ownership' as this would help understand whether an intervention increases the agencies of beneficiaries or persons delivering the intervention as well as the buy-in these have in this endeavor. The studies in this thesis identified these as potential amplifying components.

Policy categories

When considering the integration of community-based interventions within the proposed BCW policy categories, it is probable that they would fall under the categories of 'Service provision' or 'Social planning' domains, however they would be using 'Communication/Marketing' elements as well. The BCW might benefit from a 10th dimension that would integrate multi- or intra- disciplinary engagements, which would bring at the forefront the efforts of both community engagement as well as intra- professional collaboration.

As a general observation, it could be beneficial to supplement the BCW with a 'temporal ring' that specifically focuses on the dynamic aspects of behavior change. This temporal ring could help identify and address stages of change such as adoption, maintenance, and relapse, while also establishing connections to the outcomes that need to be measured.

5.4.3 Methodological considerations related to the qualitative research studies [Studies I and III]

Throughout the qualitative research process, emphasis was placed on ensuring trustworthiness, beginning from the planning stage. The following criteria were carefully considered: credibility, transferability, dependability, and confirmability[86].

Credibility

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[n] Empirical expectations are defined as behaviors individuals adopt because they believe most people conform to that behavior[220]
[o] Normative expectations are defined as behaviors individuals adopt because they believe most people believe they ought to conform to that behvior[220]

Refers to ensuring the study measures what is actually intended[222]. Credibility was sought by attempting to have interviews that allowed deep, appropriate and well-saturated research data[223]. Maximum variation sampling was pursued, deliberately seeking to select a diverse set of respondents, to ensure comprehensive and varied perspectives were captured during the research process.

Study I was able to accommodate longer interviews that facilitate longer and deeper exchanges. In between the data collection timepoints of the two studies, the interviewer was involved in other qualitative research efforts and gained further experience in this respect. Therefore, while Study III interviews were shorter in duration, they were performed by a more skilled and mature researcher.

To limit biased responses or analysis, the interviewer intentionally had no prior acquaintance with any of the participants. To establish rapport and foster open communication, the interviewer shared information about herself and the nature of the research with the participants.

However, there were several limitations, especially concerning the sampling of respondents. In Study I, the number of participants from rural areas and those working in pharmacy chains was relatively small, and no participants were from private universities. In Study III, the research was conducted during the peak of the COVID-19 pandemic, which imposed additional constraints. The geographical reach, work sector, and age representation of participants were limited in Study III. All participants in this study worked in their own practice and not in private clinics. Additionally, only one participant worked in a rural setting, and the overall participants were experienced physicians. Therefore, the voices of young doctors just starting their careers may not have been fully represented in these findings due to the limited age diversity among the participants.

While the interviewer was based in Romania, most of the interviews, for both studies were performed over the phone. This presented challenges in terms of reaching participants and the inability to observe non-verbal cues during the interviews. In Study III, some participants mentioned from the beginning that they could only allocate a limited amount of time for the interview. Each phone interview was recorded, and the investigator made efforts to conduct the interviews in the same manner as face-to-face ones, aiming to ensure consistency and comparability of the data collected. However, it is important to acknowledge that phone interviews might have certain limitations when compared to in-person interviews.

To enhance credibility, the research employed various tactics to ensure the honesty of the informants. Participants were provided with the opportunity to refuse participation in the study if they wished to do so. The researcher aimed to establish rapport with each participant and clarified her independent status during the interviews[222]. While resource limitations, particularly time constraints, allowed for only one member-check of the interpretation of the collected data, peer debriefing also took place to further validate the findings. Additionally, the discussion section of the research explored congruence with previous studies, comparing and contrasting the results to existing literature to strengthen the credibility of the conclusions drawn.

Transferability

Refers to the applicability of the findings to other situations[86]. The PhD author aimed to offer detailed and comprehensive descriptions of the study context, the phenomenon of ABC and AMR, and the collected data – through the inclusion of numerous direct quotations. All these aimed to provide rich and vivid insights so that other researchers and stakeholders can make their own assessments regarding the transferability of the findings to different settings or contexts. The relevance of the findings may be applicable to countries with similar levels of social capital, comparable governance structures, historical and cultural contexts, comparable gross national income per capita, and similar regulatory frameworks concerning antibiotics and the pharmacy and medical professions.

Dependability

Pertains to whether the studies were to be repeated, in the same manner, it would produce similar results[86]. The thesis includes a detailed methodological description, enabling potential replication. Additionally, detailed records of the entire study process were maintained.

Confirmability

Refers to data neutrality [86]. The PhD author, responsible for data collection, took precautions to minimize potential bias arising from her prior knowledge. This was achieved through self-awareness and deliberate naiveté during the research process. To enhance confirmability, a step-by-step account of decisions and procedures was documented in the present thesis and other relevant documents, creating an "audit trail" for the research. The researcher possesses a degree from the Faculty of Pharmacy in Bucharest, Romania. Prior to conducting the research, contemplation on the possibility of encountering the phenomenon of "going native" – compromising her 'outside' perspective, had taken place. Nonetheless, it was deemed unlikely to be a factor due to the absence of the researcher's professional experience in a pharmacy setting or with Romanian governmental authorities.

During the conduct of study III, the PhD author considered potential sources of bias that could arise from the interviewer's prior involvement in study I. To minimize this influence, the interview guide was designed with open-ended questions, which aimed to avoid leading or steering the participants' responses. By using such open-ended questions, the researcher aimed to maintain a neutral stance and obtain unbiased and candid insights from the participants.

Considering the above-mentioned strengths alongside the acknowledged limitations, the researchers involved in these studies believe that these have a good degree of trustworthiness.

5.4.4   Methodological considerations related to the systematic review [Study II]

Reporting bias

Reporting bias may arise from selecting outcomes or studies that reported significant results, after having explored data which would lead to the review including mostly significant results. This can be counteracted by avoiding deviations from an established protocol compiled before any data exploration[224]. For this research, the original protocol was published in PROSPERO database, before

commencing any other research activity. The protocol was respected without making any changes. In reporting the findings PRISMA guidance was followed to ensure comprehensive reporting.

Evidence selection bias

This type of bias may occur when a systematic review does not identify all available related data. This can arise from a limited search strategy (missing identifying published studies due to searching only in a few databases) or from publication bias, where studies that report statistically significant outcomes may be more likely to be published[224]. When it comes to publication bias, due to the nature of interventions, the decision was made not to search clinical trial registries, as they will likely not be an important source of data given their clinical focused research. The team discussed whether Google Scholar should also be added to the list of databases, however due to the wide search terms and exploratory search that yielded many hits, it was not considered necessary, and emphasis was placed on manual search of reference lists from the already identified publications. The systematic review benefited from a comprehensive literature search strategy yielding over 14 000 items. Both quantitative and qualitative studies were included, with the results revealing small availability of the later. In general, this flags a gap, and a need for more qualitative assessments that would offer a greater understanding of the development and implementation of community-based interventions. Publication bias also arises when studies with non-significant, negative results or small sample sizes remain unpublished. However, the impact of this bias may not be significant given the inclusion of studies regardless of sample sizes. Another publication related gap was in finding and including publications from low-income countries. This is a more systematic issue that goes beyond the current research and is likely more symptomatic of limited capacities and capabilities to conduct and publish research in these settings. The search strategy included articles in English, French, Spanish, Italian, Polish and Romanian. Therefore, it is less likely that exclusion of relevant studies may be due to language limitations. Screening was conducted independently by two authors which limited study-selection bias. The results of the final selection were consensus based.

Risk of bias in primary studies

All included studies in the systematic review were critically appraised and results are reported as part of the systematic review. As a meta-analysis was not possible, a sensitivity analyses that might have excluded trials at high risk of bias to understand the effect on the results was not undertaken.

Quality related issues

The wide variability in terms of outcomes and their measurement brought significant challenges to the analysis and precluded any exploratory meta-analysis.

A qualitative synthesis was used instead. However, grouping of the interventions as well as the grouping of outcome measures still faced limitations due to high variability in the way interventions were reported, designed, implemented, the way outcomes were formulated and measured, including the different timelines when they were captured. To minimize these shortcomings the groupings of both interventions and outcomes, were broad. For interventions, the grouping focused on the behavior change components they implied rather than other intervention implementation-related characteristics. Sample size was not an inclusion or exclusion criteria, and to enable an

accurate assessment the harvest plots used to synthesize the various studies reflected this dimension.

Competing interests

No competing interests existed for any of the researchers, however, careful consideration was undertaken to avoid overstating any of the findings that might increase the appeal for acceptance of publication. Full reporting of all methodological steps was sought, reporting of all results including the nonsignificant ones, and there were no attempts to extrapolate findings inappropriately.

Generalizability

The extensive timeframe covered by this review (over 20 years) represents both a strength and a limitation when considering the findings from this systematic review. This does offer a comprehensive body of evidence which allows a more in-depth understanding of the value of community-based interventions. However, at the same time it is a period that has likely seen shifts in the healthcare and social organization in the respective countries.

The search strategy had no geographical or income-level country limitations. However as already discussed most studies were reported from high-income countries. While transferability of findings should be considered with caution, it is not completely limited, studies covering countries from Asia, Northern Africa, North America, Europe, and Australia. The biggest gaps were represented by having no country from South America and Sub-Saharan Africa, and in respect to big geographic countries – the Russian Federation and China.

5.4.5   Methodological considerations related to the quantitative research [Study IV]

Methodological strengths and limitations of this research can be explored by discussing the: i) internal validity of the studies, with attention to: selection bias, confounding and information bias – in particular recall bias (loss to follow-up is not applicable as it was a onetime survey), and ii) external validity or generalizability concerns[225].

Selection bias

This occurs when the population sample included does not represent the overall population[225]. The survey was open to all medical and pharmacy students and efforts of dissemination were done to distribute this through social media channels. It is evident from the response rate that this strategy did not work, likely due to a combination of factors such as lack of incentives, potential fatigue following the online intensive exchanges during the pandemic or lack of interest in the subject. However, these are assumptions, and the reasons for lack of participation through the online survey are not fully known. As only two responses came from online survey, most of the surveys being completed via paper, it is less likely that the survey delivery medium accounts for any potential differences in responses.

In Romania there are 13 relevant universities – of these all have both medical and pharmacy faculties, except one who has only medical faculty. The estimated total of overall medical students is 3898, whereas pharmacy students 705, making this a total of 4603 overall medical and pharmacy

students. There is inconsistent reporting on graduation figures, therefore the admission data was used as a proxy for graduation. Based on 2018 data from University of Medicine and Pharmacy "Carol Davila" Bucharest – a graduation rate is estimated at 92.4 % (calculated by dividing 1223 graduates in 2018 to 1324 initially accepted 6 years earlier). Therefore, an approximate total target population is: 4250. Considering a Confidence Interval of 95%, a margin of error of 5% and a population size of 4250, the ideal sample size would be 353 – meaning that 353 or more measurements/surveys are needed to have a confidence level of 95% that the real value is within ±5% of the measured/surveyed value. A total of 479 answers were received, 233 from medical students (from 7 universities) and 246 from pharmacy students (from 4 universities). Overall, this signifies a representative sample (exceeding the 353 threshold). However, the pharmacy students are better represented compared to the medical ones. If similar ideal samples for each of these are calculated, according to the above-mentioned methodology, this would signify an ideal sample of 348 medical students, and 242 of pharmacy students. The participating universities contain some of the most established and oldest in Romania but also a major private university. This represents a strength of the study. However not all geographical regions in Romania are represented by these universities. Therefore, it is difficult to estimate possible selection bias impact.

Confounding

Participants in this study had mostly the same age (a median age of responders was 24 at medical and 23 at pharmacy faculty). Participants were mostly Romanians, with only 5% having other nationalities, mainly from EU countries. Therefore, the sociodemographic variables such as age, educational level, country of birth were mostly similar. Data on sex or gender were not recorded to avoid any potential issues with anonymity of responses. The questionnaire did not capture background factors such as experiences learning in other universities – whether in Romania or abroad. Past experiences may impact the critical appraisal of teaching standards. Similarly, past internships experiences have not been captured, and these may impact differently the critical appraisal of desired teaching methods. Most participants anticipated they would graduate during the respective year, which does suggest a certain level of confidence in the ability to have undergone the full university education cycle.

Overall, it is deemed that no major confounding factors have intervened.

Information bias

This results from misclassification as part of the method of measurement. The questionnaire was developed based on a previously employed questionnaire for medical students. The study captured self-reported data therefore the measurements were subjective rather than objective. When it comes to the questionnaire design, this was pilot tested to ensure comprehension, therefore it is less likely that the questions were poorly worded or unclear. Still, with more resources, it would have been preferable, for the questionnaire to have been tested on a larger sample, and not only on graduates (even if recently graduated) but on students. The factor analysis results suggest that the questionnaire could be improved overall, which ultimately may reduce the risk of misclassification bias.

The inherently subjective nature of the self-reported data might trigger concerns on response bias such as recall or social desirability bias. Social desirability bias was minimized by requesting anonymous filling in of the surveys.

There were almost no missing responses which represents a strength of this study.

Generalizability

Due to the relative high number of respondents and the relevance of the participating universities, the overall results are generalizable among medical and pharmacy students in Romania. Nevertheless, there are certain geographical areas, where universities exist, and are not covered by the current survey. Therefore, it cannot be considered that the results are fully representative of the entire Romanian medical and pharmacy students' population. As the Romanian curricula is aligned to the European Bologna process and the medical and pharmacy degrees are recognized throughout the EU, some results may be relevant for other EU countries as well. However, Romania has many socio and economic, health and social system particularities that impact the teaching process and students' experiences and expectations, and therefore most findings should be considered as applicable in this context and less generalizable to other countries.

6 Conclusions

The main conclusions across this PhD research are:

- There is promising emerging evidence regarding the benefits of community-based interventions in improving antibiotic use.
- Multifaceted interventions that combine educational aspects with persuasion may be more effective than those solely focused on education.
- There is a need for standardized approaches in study design and outcome measurements related to community-based interventions in improving antibiotic use.
- While there are some indications of the cost-effectiveness of these approaches, the evidence remains extremely limited in this respect.
- In light of the COVID-19 pandemic, policymakers should consider the potential of these interventions, along with clinical-based approaches, as a means of rebuilding trust.
- The inclusive participation community-based behavior change interventions foster can lead to greater public ownership and utilization of community channels.
- Romanian healthcare professionals hold varying perceptions regarding AMR.
- Factors contributing to appropriate antibiotic use and AMR in Romania include the perceived behavior of pharmacists, family doctors, patients, the health system, local contexts, and the impact of the COVID-19 pandemic.
- Various potential interventions to address these determinant factors were suggested, although they primarily focused on patient or public education.
- There are important implications for the education and training of future Romanian healthcare professionals, highlighting the need for further research to establish standardized monitoring and evaluation methods for progress in preparedness, willingness to engage, and teaching preferences regarding antibiotic use.

7 Points of perspective

7.1 Implications

This PhD research has significant and timely implications on a global scale, as well as specific relevance to Romania. To avoid redundancy, as these challenges have been previously discussed in earlier chapters, a concise summary is presented below:

- The research expanded the evidence base for community-based interventions and together with previous efforts helps coagulate better related methodologies. Further endeavors should be undertaken to explore and expand upon these types of initiatives.
- Community-based interventions should be introduced considering the relevant mix of functions, moving beyond mere 'awareness-raising' activities.
- Behavior change interventions will not be successful if contextual factors are not addressed. This research in Romania has identified several such factors that hinder healthcare professionals' ability to fulfill their duties. While this research did not specifically focus on interventions targeting solely healthcare professionals, it is important to explore these interventions separately. Additionally, the additive effect of community interventions to these healthcare professional focused initiatives, should be quantified.
- Significant efforts should be dedicated to fostering greater collaboration between healthcare professionals, including doctors and pharmacists, with a focus on initiating this collaboration during their university training years.
- The relationship between healthcare professionals and the patients / wider public is undergoing significant changes that are expected to occur at a faster pace than previously anticipated. This will mean a transformation of the notion of 'community' and ambulatory care. Interventions should capitalize on the insights gathered from this research regarding the dynamics between doctors, pharmacists, and patients, to inform and shape future interventions effectively.
- A thorough evaluation of the existing curriculum for students should be conducted, with the introduction of optional courses on AMR. Likewise, continuous education courses for professionals should be diversified to encompass the latest developments in this field.
- Universities and students should be more actively involved in the creation and implementation of interventions. This approach could lead to several positive outcomes: i) improving students' subject and profession-related skills (e.g., communication); ii) enhancing research on AMR related issues in Romania; iii) expanding the available human resources capable of delivering such interventions by involving students; iv) positive outcomes on the beneficiaries of such interventions – the wider public.

7.2 Future research

Several future research directions may be considered following our findings. The following research questions could be explored:

Research questions directly linked to this PhD

- What is the optimal measurement of outcomes related to antibiotic use behavior change interventions? A mapping and systematization effort to facilitate evidence assessment.
- What are the potential improvements that can be made to the questionnaire used in study IV ?
- Which community based interventions should be prioritized for implementation in Romania, to optimize antibiotic use and which are the related barriers and enablers of these prioritized interventions? A Delphi study with Romanian policymakers in Romania (the original design of study IV). (and/or run the Delphi exercise with different communities).

Research questions that stem from reflections triggered by this PhD (and the lack of evidence it uncovered in the Romanian setting in certain areas)

- How do social mechanisms influence the diffusion of information within communities, specifically examining the collaborative nature of certain communities and the barriers to knowledge dissemination in others?
- What are the effects of the COVID-19 pandemic on the behavior of healthcare professionals in respect to antibiotic use in Romania?
- How does the implementation and further development of AI impact the relationship between communities and healthcare professionals?
- What are the roles and responsibilities of the veterinarians and students in veterinary universities in Romania in respect to optimizing antibiotic use (similar approach to that of studies I, III and IV)?
- What is the relationship between a research environment (in particular pharmaceutical research, development and manufacturing) and ABC and AMR rates? A multicounty assessment.

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10 Appendices

10.1 Appendix I – Interview Guides – Studies I and III

Interview Guide for study I

Pharmacist's impressions on the patients' knowledge and attitudes

How do the patients act when they ask for antibiotics without having a prescription? How do they act when they are being turned down?
How would you say it is the knowledge of the patients who have a prescription, what is you impression of the medical information they have when they come into the pharmacy and ask for the medicines?
What type of patients ask antibiotics without prescription and is this common?
What type of antibiotics do they usually ask for? (Points to consider: pathologies, dentist, injection formulations, parents asking without prescription?)
How do you think they see the pharmacist when it comes to antibiotics?
How do you feel when patients come with their test results (antibiogram) at the pharmacy and ask for antibiotics? (If yes- What do you think drives them to do this?)

Pharmacist-Doctor Collaboration

How do you see the pharmacist – doctor collaboration in respect to antibiotics?
Could you tell me of an instance when you had a collaboration with a doctor on the subject of antibiotics?
How do you think a doctor would react if you would have to call and ask him/her to change prescriptions if you found it not to be appropriate for the patient in front of you?

Pharmacists responsibilities and potential role in mitigating ABR

What do you think about antibiotic resistance in general? What are you thoughts about the situation in Romania?
How do you see the pharmacist's role in all this?
In respect to antibiotics, what are your thoughts on possible follow-up to ensure compliance to treatment? Who do you think would be best to do this?
What do you think a pharmacist should concentrate on in respect to ABR prevention?
In terms of getting information on antibiotic resistance what is your current practice? (Points to consider: Guidelines? Protocols? How do you find them – up to date? Statistics in Romania)

National stewardship

How do you see the role of the national structures like the Ministry of Health or other institutions and professional associations in respect to antibiotic consumption and antibiotic resistance?
What do you think should be the relationship between these bodies and community pharmacists in relation to antibiotics and antibiotic resistance?

Concluding questions

What should be done to better support the pharmacist's role in respect to proper antibiotics management?
What would you say at the moment are the biggest challenges for a pharmacist to fulfill all its potential in respect to proper antibiotics management?
How do you think this issue should be addressed? What would you like to see improved considering all that we have discussed in respect to antibiotics?

Is there anything else you would like to add about your experience as a pharmacist handling antibiotics or anything else in respect to antibiotic resistance or the role pharmacists play in respect to these issues?

Probing and interpreting questions: to be used to clarify the respondents' replies

Can you help me understand what you mean by that?
Can you provide an example?
Can you elaborate a bit more on that?
Can you tell me more about this?
What do you mean by that?
Could you say something else on this?
Are you telling me that..?

Interview Guide for study III

External context conditions

- What do you think about antibiotic resistance in general? What are your thoughts about the situation in Romania?
- When it comes to key stakeholders in relation to ABR and ABC (AB Consumption), who comes to mind? How do they relate to these issues? What do you see them doing in this respect? How do you think they can be involved/influenced to take positive action?
- What is your role in relation to antibiotics? Have you noticed any changes when it comes to your profession, the way other stakeholders perceive your role in general?
- How do you see the role of the national structures like the Ministry of Health or other institutions/ professional associations/ public/patient associations in respect to antibiotic consumption and antibiotic resistance?
- What do you think should be the relationship between these bodies and family doctors in relation to antibiotics and antibiotic resistance?
- Can you give an example of some pieces of legislation that you know of and are relevant for ABR control?
- What do you think should be done in terms of legislation for better ABR control? [How would this be done? Barriers/Enablers]

Assumptions regarding the ABR problem and implementation of interventions

- In your experience is it common that patients ask to prescribe AB?
- What type of antibiotics do they usually ask for? (Points to consider: pathologies, injection formulations, parents asking without prescription?)
- How would you say it is the knowledge of the patients on AB – do they know what they are for, how to take them and for how long?
- How do you think they see the family doctors when it comes to antibiotics?
- (In your practice) is it common to perform an antibiogram for patients that come to the family doctors?)
- Could you tell me of an instance when you had a collaboration with a colleague (pharmacist or another doctor) on the subject of antibiotics?
- What do you think are some of the social and economic factors that may determine someone to ask for AB without prescription/ determine a healthcare professional to prescribe/dispense AB without prescription in a situation when it is not very clear there is a medical need for it?
- In terms of getting information on antibiotic resistance what is your current practice? (Points to consider: Guidelines? Protocols? How do you find them – up to date? Statistics in Romania)

Impact

- What you think a good intervention address the problem of ABR and ABC should achieve in the long-term?
- How could we measure that?
- How feasible do you think these interventions could be considering the Romanian context?
- What would you say at the moment are the biggest challenges for a family doctors to fulfill all their potential in respect to developing and implementing such interventions?
- How do you think this issue should be addressed? What would you like to see improved considering all that we have discussed in respect to antibiotics?

Resources

- What are some of the resources that may be needed to implement interventions to achieve the changes we just discussed?
- Who would be in a position to supply such resources?
- Who are the stakeholders who should be involved in the development, implementation and evaluation of such interventions? Who do you think should be informed about this? Who do you think may not agree with this intervention and may try to oppose it?

Concluding questions

- What should be done to better support the family doctors' role in respect to proper antibiotics management?
- Is there anything else you would like to add?

10.2 Appendix II –Example of analytic coding process from manifest to latent content level

Meaning unit	Code	Sub-category	Category	Sub-theme	Overarching theme
For the time being I don't see any role [for the Ministry of Health], besides crucifying the pharmacies, because it seems this is what they think is the method of stopping. No! This is not the way, because when you have 4 pharmacies at a crossroad, you won't be the one to start turning down. And they don't aim at educating the target which is the patient and this is what should be done. [P16]	Not satisfied with the Ministry of Health	A strained relationship between the state and the pharmacists	Distrust in state institutions	Antibiotic resistance problem rooted in a low social capital environment	Undervalued medicines' professionals struggling with agency related and structural barriers to meet their deontological duties
	Unfair treatment of pharmacies				
	Unhealthy competition		Facing negative incentives that determine a pharmacist to push the limits of law	Maintaining equilibrium between ethics, law and economy	
	The patient should be educated	Education of the patient – a sustainable solution	Education is needed	Wanting to fulfil their educational role	