Geographical perspective on antibiotic resistance in a metropolitan sewershed

Investigating socio-spatial hotspots of antibiotic use and antibiotic-resistant bacteria in Dortmund, Germany

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Preface

This doctoral thesis is submitted in partial fulfilment of the requirements for obtaining the degree of Doctor of Natural Sciences (*Doctor rerum naturalium*) of the Faculty of Mathematics and Natural Sciences at the University of Bonn. The research project was funded by the Ministry of Culture and Science of the State government of North Rhine-Westphalia (NRW) through the first funding period of the NRW Forschungskolleg "One Health and Urban Transformation – identifying risks and developing sustainable solutions". The work described herein was conducted between November 2017 and September 2021 under the supervision of Prof. Dr. Mariele Evers and Prof. Dr. Thomas Kistemann.

This cumulative doctoral thesis followed a paper-based approach in accordance with the doctorate regulations of the Faculty of Mathematics and Natural Sciences of the University of Bonn. It includes the following three manuscripts (in order of appearance in this thesis):

1. **Schmiege, D.**, Evers, M., Kistemann, T., Falkenberg, T. (2020): What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. International Journal of Hygiene and Environmental Health, 226, 113497, DOI:10.1016/j.ijheh.2020.113497.
2. **Schmiege, D.**, Falkenberg, T., Moebus, S., Kistemann, T., Evers, M. (*under review*): Associations between socio-spatially different urban areas and knowledge, attitudes, practices and antibiotic use: a cross-sectional study in the Ruhr Metropolis, Germany.
3. **Schmiege, D.**, Zacharias, N., Sib, E., Falkenberg, T., Moebus, S., Evers, M., Kistemann, T. (2021): Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing Escherichia coli in urban community wastewater. Science of the Total Environment, 785, 147269, DOI: 10.1016/j.scitotenv.2021.147269.

Additional articles, book chapters and policy briefs written during the doctoral dissertation period are presented in the following (in order of publication):

i. Falkenberg, T., Paris, J.M.G., Patel, K., Arredondo Perez, A.M., **Schmiege, D.**, Yasobant, S. (*forthcoming*). Operationalising the One Health Approach in the Context of Urban Transformation. In: Gatzweiler, F. M. (eds.), Urban Health and Wellbeing Programme, Policy Briefs: Volume 3.

ii. Yasobant, S., Arredondo Perez, A.M., Felappi, J.F., Ntajal, J., Paris, J.M.G., Patel, K., Savi, M.K., **Schmiege, D.**, Falkenberg, T. (2021). Integrating public services under One Health for the mitigation of future epidemics. In: Nima Rezaei, (eds.), Integrated Science of Global epidemics, Springer, UK (In Print)

iii. Brückner, A., Paris, J.M.G., **Schmiege, D.**, Swoboda, P. (2020). Urban transformation and the need for One Health. Recommendations for Ruhr Metropolis. Center for Development Research (ZEF) One Health and Urban Transformation Policy Brief 1/2020. https://www.zef.de/project-homepages/one-health/template-following/policy-briefs.html

iv. **Schmiege, D.**, Perez Arredondo, A. M., Ntajal, J., Minetto Gellert Paris, J., Savi, M. K., Patel, K. Yasobant, S., Falkenberg, T. (2020): One Health in the context of coronavirus outbreaks: A systematic literature review. https://doi.org/10.1016/j.onehlt.2020.100170

v. **Schmiege, D.**, Evers, M., Zügner, V., Rickert, B. (2020): Comparing the German enabling environment for nationwide Water Safety Plan implementation with international experiences: Are we still thinking big or already scaling up? https://doi.org/10.1016/j.ijheh.2020.113553

A complete list of publications and contributions to conferences during the doctoral dissertation period can be accessed at the end of this doctoral thesis.

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3MRGN	Multidrug-resistant Gram-negative bacteria resistant to three of four antibiotic classes (Acylureidopenicillins, 3rd-generation cephalosporins, carbapenems and fluoroquinolones) defined by the KRINKO
4MRGN	Multidrug-resistant Gram-negative bacteria resistant to all four antibiotic classes (Acylureidopenicillins, 3rd-generation cephalosporins, carbapenems and fluoroquinolones) defined by the KRINKO
ABR	Antibiotic resistance
AMR	Antimicrobial resistance
Area A	Area socio-spatially close to the average of Dortmund
Area B	Socio-spatially advantaged area in Dortmund
Area C	Socio-spatially disadvantaged area in Dortmund
ARG	Antibiotic resistance gene
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CFU	Colony-forming unit
COVID-19	Coronavirus disease 2019
ECDC	European Centre for Disease Prevention and Control
E. coli	*Escherichia coli*
EGLV	Emschergenossenschaft and Lippeverband
EID	Emerging infectious disease
EMA	European Medicines Agency
ESBL	Extended-spectrum beta-lactamase
ESBL-Ec	Extended-spectrum beta-lactamase-producing *Escherichia coli*
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
HGT	Horizontal gene transfer
HIC	High-income countries
IACG	Interagency Coordination Group
Inh.	Inhabitants
IPBES	Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services
ISCED	International Standard Classification of Education
ISO	International Organization for Standardization

KAP	Knowledge, attitudes and practices
KRINKO	German Commission for Hospital Hygiene and Infection Prevention (*Kommission für Krankenhaushygiene und Infektionsprävention*)
LMIC	Lower- and middle-income countries
MDRO	Multidrug-resistant organisms
MRGN	Multidrug-resistant Gram-negative bacteria
NRW	North Rhine-Westphalia
OECD	Organisation for Economic Co-operation and Development
OIE	World Organization for Animal Health
OR	Odds ratio
PICOS	Population, intervention, comparator, outcome and study design format
PR	Prevalence ratio
PRISMA	Preferred reporting items for systematic reviews and meta-analyses:
Q1	25^{th} quartile
Q3	75^{th} quartile
Q_{H24}	Average domestic daily discharge
Q_{T24}	Average dry weather daily discharge
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UN GA	United Nations General Assembly
UNEP	United Nations Environment Programme
UNICEF	United Nations Children's Fund
UTI	Urinary tract infection
UV	Ultraviolet
WHO	World Health Organization
WWTP	Wastewater treatment plant

Summary

Antibiotic resistance (ABR) is a serious global health threat. Inadequate and excessive antibiotic use in humans and animals continues to drive the emergence of antibiotic-resistant bacteria. Environmental compartments occupy a pivotal role in the spread of ABR. Wastewater is a central pathway of how antibiotics and their residues, as well as antibiotic-resistant bacteria and associated antibiotic-resistance genes, end up in the environment.

In centralised wastewater systems, wastewater is collected in pipes and discharged to a wastewater treatment plant before being released to surface waters. Current treatment regimens reduce the bacterial load significantly but cannot remove everything. New treatment technologies are expensive and not readily available on a large scale. Therefore, the focus needs to be shifted away from such end-of-pipe interventions towards the catchment area or sewershed of the wastewater treatment plant to reduce the input of antibiotics and antibiotic-resistant bacteria into wastewater at the source. The doctoral thesis followed this approach.

Several point and non-point sources contribute high loads of antibiotics and antibiotic-resistant bacteria into wastewater, but research on the general population is scarce. Most antibiotics used for human medical treatment are administered in the community, i.e. the human outpatient sector. Determinants of antibiotic use are manifold. Moving beyond individual-related factors, the focus of this work was on potential area effects. A lower socio-economic status is often linked to poorer health, and individuals with similar socio-economic backgrounds tend to cluster spatially in urban areas. The doctoral thesis utilised the conceptual interlinkage of spatial segregation and the social determinants of health in the context of antibiotic resistance. The primary goal was to investigate socio-spatial hotspots of antibiotic use in the community and antibiotic-resistant bacteria in untreated municipal wastewater within a metropolitan sewershed.

The doctoral thesis was designed as an empirical study following a quantitative approach with two work strands to investigate antibiotic use and antibiotic-resistant bacteria in untreated municipal wastewater. The first strand consisted of a systematic literature review on antibiotic use in the community, which subsequently informed a cross-sectional household survey in the general population in three socio-spatially different urban areas within a metropolitan sewershed. The second strand dealt with measuring antibiotic-resistant bacteria in untreated municipal wastewater in the three identical areas. This approach enabled an examination of socio-spatial hotspots within a metropolitan sewershed.

The systematic literature review identified various determinants of antibiotic use in the community. Whereas compositional variables, i.e. the characteristics of individuals living in a specific area, predominate, potential area effects of contextual (i.e. opportunity structures in the local environment) and collective (i.e. socio-cultural and historical features) factors on antibiotic use were identified. These findings emphasise the importance of considering both individual- and space-related factors as possible determinants of antibiotic use in the community.

The cross-sectional household survey revealed small-scale area differences between communities within a metropolitan sewershed. Self-reported antibiotic use and related knowledge, attitudes and practices varied between the three socio-spatially different urban areas. Participants living in the socio-spatially disadvantaged area were less knowledgeable, reported more often attitudes contrary to common recommendations, showed lower risk awareness and displayed more often antibiotic use and potential mishandling practices. The situation was often the opposite for participants from the socio-spatially advantaged area. Besides spatial differences, common misconceptions across all areas around antibiotic resistance and the use of antibiotics were also identified. The results underline the necessity to inform the population further on the adequate use and handling of antibiotics. They further highlight the importance of tailoring population-based interventions to the local socio-economic context of different urban areas.

Sampling and analysing wastewater for the occurrence of antibiotic-resistant bacteria complemented those two working packages of the first strand. Over a whole year, untreated municipal wastewater from the three areas was tested once per month for the occurrence of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*). This work demonstrated that the general community is an essential source of phenotypic ESBL-producing *E. coli* in wastewater and revealed seasonal and spatial variations. Counts were higher during the winter months across areas, and in most months, higher in the socio-spatially disadvantaged area compared to the other two areas. Resistance profiles of extracted isolates were also analysed. The proportions of resistant isolates were low, with minimal variation regarding antibiotics mainly used in inpatient health care settings. The proportions did vary for antibiotics, which are administrable in the human outpatient sector. Resistance levels were lowest in the socio-spatially advantaged area. This suggests a higher ABR burden in a socio-spatially disadvantaged area and lower resistance levels in a socio-spatially advantaged area.

Integrating the results, self-reported antibiotic use of all individuals across the three areas covered in the household survey was highest in the winter months. The occurrence of phenotypic ESBL-producing *E. coli* followed this trend. Associations for the other meteorological seasons were less clear. Antibiotic use and the counts of phenotypic ESBL-producing *E. coli* were higher in the socio-spatially disadvantaged area than the other areas pointing towards a possible spatial association.

This doctoral thesis highlights the importance of considering higher spatial resolutions and the local spatial context regarding antibiotic use and related knowledge, attitudes and practices, as well as the occurrence of antibiotic-resistance bacteria in untreated municipal wastewater. Observed spatial variations of those ABR components within a metropolitan sewershed would not have been visible on an aggregated level without such an approach. The doctoral thesis demonstrates the benefit of applying a geographical perspective by explicitly considering the spatial dimension of ABR.

Zusammenfassung

Die Entstehung und Verbreitung von Antibiotikaresistenzen (ABR) sind eine schwerwiegende Bedrohung für die Gesundheit von Menschen und Tieren. Unsachgemäßer und exzessiver Einsatz von Antibiotika sowohl in der Human- und Veterinärmedizin als auch in der Landwirtschaft ist unvermindert einer der treibenden Hauptfaktoren für die Entstehung von antibiotikaresistenten Bakterien. Umweltkompartimente spielen eine wichtige Rolle bei der Verbreitung von ABR, insbesondere Abwasser ist ein zentraler Eintragspfad, über den Antibiotika und entsprechende Rückstände sowie antibiotikaresistente Bakterien und damit verbundene Antibiotikaresistenzgene in die Umwelt gelangen.

In zentralen Abwassersystemen werden Einleitungen in Kanälen gesammelt und anschließend in einer Kläranlage behandelt, bevor diese dem Oberflächengewässer zugeführt werden. Derzeitige Behandlungsmethoden in konventionellen Kläranlagen können die bakterielle Fracht erheblich reduzieren, aber nicht restlos entfernen. Innovative Behandlungstechnologien sind kostenintensiv und nicht ohne Weiteres in großem Maßstab verfügbar. Der Fokus von Interventionen sollte daher in Richtung Verursacher im Einzugsgebiet und mögliche Eintragspfade verlagert werden statt sich weiterhin auf *End-of-pipe*-Lösungsansätze zu konzentrieren. Dadurch kann der Eintrag von Antibiotika und antibiotikaresistenten Bakterien in das Abwasser bereits an der Quelle verringert werden. Diese Dissertation verfolgt einen solchen Ansatz.

Auf der Grundlage verschiedener Studien wurden Punktquellen und diffuse Quellen identifiziert, die große Mengen an Antibiotika und antibiotikaresistenten Bakterien ins Abwasser einleiten. Allerdings gibt es nur wenige Untersuchungen über das potentielle Einleitungsverhalten der allgemeinen Bevölkerung. In der Humanmedizin wird der Großteil der Antibiotika als Medikation im ambulanten Sektor verschrieben. Mögliche Determinanten von Antibiotikanutzung in der allgemeinen Bevölkerung sind vielfältig. Der Schwerpunkt bisheriger Studien lag oft auf individuellen Faktoren. Die Dissertation erweitert diesen Fokus und untersucht neben individuellen Variablen auch raumbezogene Faktoren.

Personen mit einem ähnlichen sozioökonomischen Hintergrund tendieren dazu, sich in städtischen Gebieten räumlich zu konzentrieren. Dazu ist ein geringerer sozioökonomischer Status oft mit einem schlechteren Gesundheitsstatus assoziiert. Räumliche Segregation und die sozialen Determinanten von Gesundheit im Kontext von Antibiotikaresistenz wurden in der Dissertation als konzeptionelle Ausgangspunkte genutzt. Das Hauptziel der Arbeit war die Analyse möglicher sozialräumlicher Hotspots von Antibiotikanutzung in der allgemeinen Bevölkerung und dem Vorkommen von antibiotikaresistenten Bakterien in unbehandeltem kommunalem Abwasser in einem großstädtischen Abwassereinzugsgebiet.

Die Dissertation wurde als empirische Studie mit einem quantitativen Ansatz konzipiert. Zwei Arbeitsstränge wurden entwickelt, um Antibiotikanutzung und das Vorkommen von antibiotikaresistenten Bakterien in unbehandeltem kommunalem Abwasser zu untersuchen. Der erste Arbeitsstrang bestand aus einer systematischen Literaturanalyse zum Thema Determinanten von Antibiotikanutzung in der allgemeinen Bevölkerung. Die Literaturarbeit diente als Grundlage für eine Querschnittserhebung in der allgemeinen Bevölkerung in drei sozialräumlich unterschiedlichen städtischen Gebieten innerhalb eines großstädtischen Abwassereinzugsgebiets. Der zweite Arbeitsstrang beinhaltete die Messung von antibiotikaresistenten Bakterien im unbehandelten kommunalen Abwasser in denselben drei Gebieten. Dieser Ansatz ermöglichte die Untersuchung von sozialräumlichen Hotspots innerhalb eines großstädtischen Abwassereinzugsgebiets.

Im Rahmen der systematischen Literaturanalyse wurde eine Vielzahl von Determinanten der Antibiotikanutzung in der allgemeinen Bevölkerung ermittelt. Während kompositorische Variablen, d. h. die Merkmale der in einem bestimmten Gebiet lebenden Personen, überwogen, wurden potenzielle räumliche Auswirkungen kontextueller (d. h. Gelegenheitsstrukturen im lokalen Umfeld) und kollektiver (d. h. soziokulturelle und historische Merkmale) Faktoren auf Antibiotikanutzung identifiziert. Das unterstreicht, wie wichtig es ist, sowohl individuelle als auch raumbezogene Faktoren als mögliche Determinanten des Antibiotikakonsums in der allgemeinen Bevölkerung zu berücksichtigen.

Der Antibiotikaverbrauch, von dem die Interviewteilnehmenden in der Studie berichteten, und das damit verbundene Wissen sowie die Einstellungen und Praktiken variierten zwischen den drei sozialräumlich unterschiedlichen Stadtgebieten. Studienteilnehmende aus dem sozialräumlich benachteiligten Gebiet waren weniger gut informiert, berichteten häufiger über Einstellungen, die im Widerspruch zu gängigen Empfehlungen stehen und zeigten ein geringeres Risikobewusstsein. Darüber hinaus berichteten sie häufiger von möglichen Fehlhandhabungen im Umgang mit Antibiotika und einem höheren Antibiotikaverbrauch. Bei Studienteilnehmenden aus dem sozialräumlich begünstigten Gebiet war oft die gegenteilige Situation zu beobachten. Neben den kleinräumigen Unterschieden wurden auch über alle Untersuchungsgebiete hinweg geltende Fehlvorstellungen über Antibiotikaresistenzen und den Einsatz von Antibiotika festgestellt. Diese Ergebnisse bestätigen einerseits die Notwendigkeit, die allgemeine Bevölkerung noch besser über den angemessenen Einsatz und Umgang mit Antibiotika aufzuklären, andererseits zeigen sie, wie wichtig es ist, bevölkerungsbezogene Maßnahmen auf den lokalen sozioökonomischen Kontext der verschiedenen städtischen Gebiete abzustimmen.

Die Beprobung und Analyse von Abwasser auf das Vorkommen antibiotikaresistenter Bakterien ergänzte die beiden Arbeitspakete des ersten Arbeitsstrangs. Über ein Jahr lang wurde unbehandeltes kommunales Abwasser aus den drei Gebieten einmal pro Monat auf

Beta-Laktamasen mit erweitertem Spektrum (Englisch: *extended-spectrum beta-lactamase* (ESBL))-produzierende *Escherichia coli* (*E. coli*) untersucht. Diese Arbeit zeigte, dass die allgemeine Bevölkerung eine wichtige Quelle für die Einleitung phänotypischer ESBL-produzierender *E. coli* im unbehandelten Abwasser ist. Saisonale und räumliche Variationen wurden ebenfalls beobachtet. Die Anzahl von ESBL-produzierenden *E. coli* war jeweils in den Wintermonaten und im sozialräumlich benachteiligten Gebiet in den meisten Monaten höher. Darüber hinaus wurden die Resistenzprofile von extrahierten phänotypischen ESBL-produzierenden *E. coli* Isolaten analysiert. Der Anteil von Isolaten mit Resistenz gegenüber Antibiotika, die hauptsächlich im stationären Gesundheitsbereich eingesetzt werden, war gering und variierte kaum. Resistenzen gegenüber Antibiotika, die im ambulanten Bereich verabreicht werden können, zeigten eine höhere Prävalenz und Variabilität. Die Resistenzlevel waren im sozialräumlich begünstigten Gebiet am niedrigsten. Dies deutet auf eine höhere Antibiotikaresistenzbelastung in einem sozialräumlich benachteiligten Gebiet und geringere Resistenzwerte in einem sozialräumlich begünstigten Gebiet hin.

Aus den Ergebnissen geht hervor, dass der selbstberichtete Antibiotikaverbrauch aller Personen in den drei von der Haushaltsbefragung erfassten Gebieten in den Wintermonaten am höchsten war. Das Vorkommen von phänotypischen ESBL-produzierenden *E. coli* folgte diesem Trend. Die Zusammenhänge für die anderen meteorologischen Jahreszeiten waren weniger eindeutig. Sowohl der Antibiotikaverbrauch als auch die Anzahl der phänotypischen ESBL-produzierenden *E. coli* waren in dem sozialräumlich benachteiligten Gebiet höher als in den anderen beiden Gebieten, was auf einen möglichen räumlichen Zusammenhang hindeutet.

Die Dissertation unterstreicht die Bedeutung einer hohen räumlichen Auflösung und des lokalen räumlichen Kontexts für das Verständnis von Antibiotikanutzung und das damit verbundene Wissen, die Einstellungen und Praktiken sowie das Vorkommen von antibiotikaresistenten Bakterien im unbehandelten kommunalen Abwasser. Die beobachteten räumlichen Variationen dieser ABR-Komponenten innerhalb eines großstädtischen Abwassereinzugsgebiets wären ohne einen solchen Ansatz auf aggregierter Ebene nicht sichtbar geworden. Die Arbeit demonstriert somit den Mehrwert einer geographischen Perspektive durch die explizite Berücksichtigung der räumlichen Dimension von ABR.

1. Introduction

1.1. Background

Attaining optimal health for humans, animals and the environment in a globalised and continuously changing world demands a shift towards holistic and systemic approaches. Climate change, environmental degradation, loss of biodiversity and the surge in emerging infectious diseases are among many indications that our current way of living is neither healthy nor sustainable.

The One Health approach offers a way forward for managing health risks at the human-animal-environment interface. It can be defined as "a collaborative, multisectoral, and trans-disciplinary approach - working at local, regional, national, and global levels - to achieve optimal health and well-being outcomes recognizing the interconnections between people, animals, plants and their shared environment." (One Health Commission, 2021) Breaking down current silo thinking to enable integrated and holistic solutions to existing and emerging health issues is at its core (Mackenzie & Jeggo, 2019; Zinsstag et al., 2011). Communication, coordination and collaboration across spatial scales to bridge scientific disciplines and include sectors beyond academia are thereby fundamental (Lebov et al., 2017; Zinsstag et al., 2012).

Historically, human and animal health were not treated separately, and the shared environment played an important role (Bresalier et al., 2020). Still, the perspective shifted from a holistic to a reductionist view on health with an anthropocentric focus during the 20th century (Bresalier et al., 2020). Recent developments such as the rise in emerging infectious diseases (EID), including the Coronavirus disease 2019 (COVID-19) pandemic, or antimicrobial resistance (AMR), have demonstrated that monothematic approaches cannot grasp complex health interactions (see, e.g. Atlas & Maloy, 2014; Osterhaus et al., 2020; WHO, 2021a). Hence, holistic approaches to health that encompass humans, animals and the environment, e.g. EcoHealth, Planetary Health and One Health (Harrison et al., 2019; Lerner & Berg, 2017; Zinsstag, 2012), have (re-)gained (international) attention. Specifically, the One Health approach has been recognised by global political players (e.g. G20, 2021; G7, 2021), leading to institutional collaborations at the international level, e.g. the Tripartite Plus Alliance of the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), the World Organization for Animal Health (OIE) and the United Nations Environment Programme (UNEP) (The Tripartite, 2010, 2017; WHO, FAO & OIE, 2021) or The Lancet One Health Commission (Amuasi et al., 2020).

One Health work streams are divisible into “classical” and “extended” versions of the approach. “Classical” One Health topics have focused primarily on the human-animal interface, e.g. EIDs and zoonotic diseases (Jones et al., 2008; Kelly et al., 2020), food safety and security (Boqvist et al., 2018; Garcia et al., 2020), as well as AMR (Hernando-Amado et al., 2019; McEwen & Collignon, 2018). The environmental domain has been often neglected (Essack, 2018). In recent years, an “extended” understanding of the approach has emerged with a stronger emphasis on the role of the environment to account for the complex interactions at the human-animal-environment interface (Destoumieux-Garzón et al., 2018), also during the COVID-19 pandemic (Schmiege, Perez Arredondo, et al., 2020). The conceptual extension offers new perspectives on “classical” One Health topics (Destoumieux-Garzón et al., 2018) by focusing on social, structural and ecological changes (El Zowalaty & Järhult, 2020; Kock, 2015; Wallace et al., 2015) and including other disciplines and sectors beyond the human and veterinary medical professions (Khan et al., 2018; Mackenzie & Jeggo, 2019). This also expanded the range of topics to include others, such as environmental contamination, chronic diseases and mental health (Amuasi et al., 2020; Lerner & Berg, 2015).

The absence of the environment in earlier One Health studies may be due to conceptual difficulties. These include the conceptual positioning of the environmental component and the lack of a clear definition of “the environment” in the context of One Health, as it can refer to the social environment, built-up or indoor areas, as well as natural surroundings. Particularly the latter aspect has attracted research interest in recent years. Several drivers such as population growth, rapid urbanisation or globalisation increase the human demand for food, housing and trade, resulting in further expansions of the built environment and agricultural areas into hitherto natural habitats (IPBES, 2019; Millennium Ecosystem Assessment, 2005). Resulting anthropogenically induced ecosystem changes, e.g. habitat fragmentation, loss of biodiversity or land degradation, coupled with other significant drivers, e.g. climate change, can subsequently also affect human health (Allen et al., 2017; Jones et al., 2013; Karesh et al., 2012).

The degradation of ecosystems accompanied by a loss of vital ecosystem services caused by human activity is also a severe threat to water compartments. Water is essential for our everyday life. Its importance to humans is underlined by the explicit recognition of access to safe water and sanitation as basic human rights (UN GA, 2010, 2016) and its pivotal role in the 2030 Agenda for Sustainable Development (UN-Water, 2021; UN GA, 2015). Water can both contribute to health and well-being but also harm humans and animals. Blue spaces, for instance, offer many health and well-being benefits (Foley & Kistemann, 2015; Völker & Kistemann, 2011; White et al., 2020). On the other hand, “too much, too little, too polluted” water (see, e.g. Chen, 2018; UNICEF EAPRO, 2013), including (weather-related) hydrological extreme events, lack of access to safe water and sanitation, and the discharge of untreated wastewater into water bodies, can also cause adverse effects on health.

Humans have affected water systems in various ways (Grizzetti et al., 2016; Haddeland et al., 2014), including alterations in water quality. Water pollution is an enormous global challenge with significant implications for health (Schwarzenbach et al., 2010). A wide variety of organic and inorganic contaminants produced by anthropogenic activities is released daily into surface water bodies in massive amounts. Of particular interest are emerging contaminants, which are "[…] found in the environment at trace concentrations with potential, perceived, or real risk to the "One Health" trilogy […]" (Gomes et al., 2020, p. 1). Emerging contaminants include microplastics, pharmaceuticals and personal care products (Wilkinson et al., 2017), as well as antibiotic-resistant organisms and antibiotic resistance genes (ARG) (Pruden et al., 2006; Sanderson et al., 2019).

Antibiotic resistance (ABR), defined as the ability of bacteria to withstand the effects of an antibacterial (see e.g. CDC, 2020; WHO, 2020), is among the most significant global health threats of the 21st century. It is associated with adverse health outcomes in humans (Cassini et al., 2019; CDC, 2019; Founou et al., 2017; Laxminarayan et al., 2013) and animals (Sharma et al., 2018; Woolhouse et al., 2015) and has already significant economic impacts (Dadgostar, 2019; ECDC & OECD, 2019), all of which will likely increase in the future (O'Neill, 2016). Environmental compartments function as recipients, reservoirs, and sources in the development and spread of ABR (Berkner et al., 2014; Pruden et al., 2013).

Wastewater, in particular, occupies a pivotal role. It constitutes a crucial pathway of how antibiotics, their residues and metabolites, antibiotic-resistant bacteria (including multidrug-resistant organisms (MDRO)) and ARGs end up in the environment (Andremont & Walsh, 2015; Caucci & Berendonk, 2014), including water bodies (Baquero et al., 2008; Kümmerer, 2009; Zheng et al., 2021). Wastewater treatment plants (WWTP) are considered as "points of convergence" (Manaia, 2014), providing ideal conditions for the mixture of ABR elements from human, animal and environmental sources (Michael et al., 2013; Rizzo et al., 2013) and horizontal gene transfer (HGT) between bacterial species (Wellington et al., 2013). Albeit conventional WWTPs can reduce bacterial loads significantly (Kistemann et al., 2008), MDRO and ARGs still reach receiving surface waters (Alexander et al., 2020; Huijbers et al., 2015; Müller et al., 2018), causing ecological disturbances (Baquero et al., 2008) and posing health risks to humans (Herrig et al., 2020; Jørgensen et al., 2017; Leonard et al., 2015).

Improving the treatment performance of existing WWTPs regarding MDRO and ARGs by implementing advanced treatment technologies, e.g. ultraviolet (UV) irradiation, ozone treatment or ultrafiltration (Hembach et al., 2019; Jäger et al., 2018), is one way to reduce the ABR burden in the environment. Shifting the focus away from such end-of-pipe approaches towards the catchment area or sewershed to minimise the input of ABR elements into wastewater at the source is a more cost-effective strategy. This strategy requires the identification of relevant dischargers of ABR elements in the sewershed of a wastewater system.

Several studies revealed high loads of antibiotics, their residues, MDROs and ARGs in wastewater from different point and non-point sources, including hospitals (Blaak et al., 2015; Bréchet et al., 2014; Galvin et al., 2010; Harris et al., 2014; Paulshus et al., 2019), drug manufacturers (Larsson et al., 2007; Thai et al., 2018; Topp et al., 2018), slaughterhouses (Alexander et al., 2020; Savin et al., 2020) and livestock farming (He et al., 2020; Manyi-Loh et al., 2018). Albeit being among the bigger dischargers in terms of wastewater volumes produced, research focusing on the potential contributing role of the general population has been scarce.

Each administered antibiotic, regardless of the appropriateness of the therapy, applies selective pressure on the gut bacteria in humans and animals and thereby selects for resistance (Langdon et al., 2016; Pal et al., 2016). Individuals excrete antibiotics, their residues and MDROs with their faeces or urine during and after antibiotic treatment (Kim et al., 2017). MDROs can also colonise the gut of healthy individuals (Karanika et al., 2016), for instance, through travel to high-endemic areas (Woerther et al., 2017), who constitute the second group of excreters in community wastewater.

Globally, dispensing volumes of antibiotics are higher in veterinary medicine than in the human medical sector (Tiseo et al., 2020; Van Boeckel et al., 2019; WHO, 2018). In European countries, dispensing rates have started to converge, mainly driven by a reduction in veterinary medicine (including food-producing animals) (EMA ESVAC, 2020). For human medical treatment, antibiotic consumption increased between 2000 and 2015 globally with high-income countries using the most (Klein et al., 2018).

Geographical differences are observable in paediatric and adult populations between (Blommaert et al., 2014; Gaygısız et al., 2017; Masiero et al., 2010) and within countries (Achermann et al., 2011; Augustin et al., 2015; Sahin et al., 2017), from regional (de Jong et al., 2014; Gahbauer et al., 2014; Kliemann et al., 2016) down to intra-urban variations (Farah et al., 2015; Henricson et al., 1998; Togoobaatar et al., 2010a). Antibiotic use also varies between health care sectors, with up to ten-fold higher consumption rates in the community (i.e. outpatient) compared to the hospital sector (ECDC, 2020a). The distribution of bacterial infectious diseases alone cannot explain exhaustively those variations observed. Thus, additional determinants of antibiotic consumption in the community need to be examined.

Determinants of antibiotic use in the community are manifold. Individual-related variables, such as demographic or socio-economic aspects, dominate the literature (Zanichelli et al., 2019). Several studies investigated the associations between antibiotic use and such factors, often at the national or regional level (see, e.g. Achermann et al., 2011; Blommaert et al., 2014; Kliemann et al., 2016). Evidence for higher spatial resolutions, e.g. intra-urban variations, has been relatively scarce leading to studies calling for small area analyses in Germany (Augustin et al., 2015). Focusing exclusively on individual-related variables disregards the potential influence of area effects on antibiotic use. For instance, depending on the national context and the regulatory system, availability of and access to the health care system, e.g. physicians and pharmacies, may also affect (inappropriate and excessive) antibiotic use (Filippini et al., 2009; García-Rey et al., 2004; Sahin et al., 2017). Therefore, a broader perspective on the determinants of antibiotic use in the community is necessary (Collignon et al., 2018), emphasising both people and places.

Moving beyond biomedical-centred and reductionist approaches to health, a broader focus on social and economic factors (Braveman & Gottlieb, 2014; Hurrelmann & Richter, 2013) and potential area effects is required (Macintyre et al., 2002). The social determinants of health (Dahlgren & Whitehead, 1991, 2007), defined as the “conditions in which people are born, grow, live, work and age” (CSDH, 2008, p. 1), offer such an inclusive approach. They are concerned with health inequalities, i.e. differences in health which can manifest on different levels in society, e.g. across individuals, groups or populations (Jungbauer-Gans & Gross, 2009; Marmot et al., 2008). Inequalities in health tend to follow a social gradient, whereby a lower socio-economic status is often associated with a poorer health status (Braveman et al., 2011; CSDH, 2008). This concept can be applied to both non-communicable and infectious diseases alike (Braveman, 2011; Lampert et al., 2016).

People with similar socio-economic backgrounds tend to cluster spatially in cities translating into an unequal distribution of social groups in urban space, i.e. spatial segregation (Maffini & Maraschin, 2018; Vaughan & Arbaci, 2011). The conceptual link between spatial segregation, the social gradient in health and ABR raises questions about intra-urban differences between socio-spatially diverse urban communities. Identifying such a spatial patterning of antibiotic use and related knowledge, attitudes and practices, as well as the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater in urban areas within a metropolitan sewershed, was the primary goal of this doctoral thesis.

The following sections introduce the motivation (chapter 1.2) and the research questions and objectives (chapter 1.3), position the study within the research framework of the NRW graduate school “One Health and Urban Transformation” (chapter 1.4) and outline the overall structure of the thesis (chapter 1.5).

1.2. Motivation

Under the umbrella of geography with its explicit spatial focus, the doctoral thesis integrated public health and microbiological aspects to assess the local ABR situation in a metropolitan sewershed comprehensively. Situated at the intersection of physical and human geography, it highlighted the relevance of health and medical geography by demonstrating the importance of the spatial dimension, particularly small area variations at the local level (see chapter 2.1), regarding ABR. It offered an interdisciplinary and integrated perspective to a topic of global health concern and contributed to the research gaps highlighted above.

By focusing on wastewater as one of the main pathways of how antibiotics, their residues, MDROs and ARGs end up in the environment, this work is positioned in the rapidly evolving fields of the environmental dimension of ABR in the context of One Health and environmental surveillance of ABR in wastewater. Moving beyond current end-of-pipe approaches centred on WWTPs and already well-established point sources of ABR elements in wastewater, this doctoral thesis shifted the attention towards sub-catchment areas and the general population as an essential contributor and source within an urban sewershed in a metropolitan area. The work is, therefore, situated at the human-environment interface of the One Health trilogy.

As one key driver of ABR, analyses of antibiotic use have been mainly carried out at the national or regional level in previous studies. Higher antibiotic use for human medical treatment in the outpatient sector and variations observable between cities raise questions around small area differences, i.e. within cities, e.g. between neighbourhoods, in the general population. This doctoral thesis intended to close this knowledge gap. Designed as a small area study, i.e. comparing socio-spatially different urban areas within a metropolitan sewershed, it showed the importance to tailor interventions to the local context. Various factors, which are also not distributed equally in space, determine antibiotic use. Utilising the concepts of spatial segregation and the social gradient in health as conceptual starting points, identifying “socio-spatial” hotspots of antibiotic use and the occurrence of antibiotic-resistant bacteria within a metropolitan sewershed was the primary motivation of this doctoral thesis.

1.3. Research questions and objectives

By applying a geographical perspective, the focus of this doctoral thesis was explicitly on spatial and temporal variations of different ABR components. Referring to the term “ABR” complicates the operationalisation because it entails a vast range of substances (e.g. antibiotics and their residues), bacteria (e.g. commensal and pathogenic), resistance genes and resistance profiles (e.g. different clinical relevance). This work focused on two specific aspects of ABR: (i) antibiotic use and related knowledge, attitudes and practices in the community, and (ii) antibiotic-resistant bacteria and their resistance profiles in untreated municipal wastewater.

The fundamental objective underpinning this work was the identification of potential spatial and temporal associations between antibiotic use in the community and the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater at a small scale, i.e. intra-urban, within a metropolitan sewershed. Thus, two overarching research questions (RQ) with their associated research objectives (RO) guided the design of the doctoral thesis:

- RQ 1: What influences antibiotic use in the human outpatient sector, and how do antibiotic use and related knowledge, attitudes and practices in the community vary between socio-spatially different urban areas within a sewershed of a metropolitan area?
    - RO 1.1: Identify determinants of antibiotic use in the community (i.e. human outpatient sector) and categorise their effects into compositional, contextual or collective
    - RO 1.2: Investigate spatial differences regarding antibiotic use and related knowledge, attitudes and practices between socio-spatially diverse urban areas
- RQ 2: How does the occurrence of antibiotic-resistant bacteria and their resistance profiles in untreated municipal wastewater vary between socio-spatially different urban areas and over time within a sewershed of a metropolitan area?
    - RO 2.1: Examine spatial and temporal differences in the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater between socio-spatially diverse urban areas
    - RO 2.2: Investigate spatial and temporal differences in resistance profiles of antibiotic-resistant bacteria isolates in untreated municipal wastewater between socio-spatially diverse urban areas

These questions were divided into three smaller and better manageable working packages, each with specific research questions and objectives (see Table 2 in chapter 2.3.1).

1.4. Research framework: One Health and Urban Transformation

The doctoral thesis was part of the North Rhine-Westphalia (NRW) Forschungskolleg “One Health and Urban Transformation – identifying risks and developing sustainable solutions” funded by the Ministry of Culture and Science of the State government of NRW. This Forschungskolleg is jointly operated by the Center for Development Research (ZEF), the International Centre for Sustainable Development (IZNE) at the Hochschule Bonn-Rhein-Sieg (H-BRS) and the United Nations University – Institute for Environment and Human Security

(UNU-EHS) Bonn, in collaboration with the Department of Geography (Faculty of Mathematics and Natural Sciences, University of Bonn), and the Institute for Hygiene and Public Health (Medical Faculty, University of Bonn).

Investigating various dimensions and transformations of urban systems and their impacts on human, animal and environmental health is at the core of the Forschungskolleg. The One Health approach is utilised to analyse human, animal, and environmental health relationships in urban and peri-urban areas to identify related problems and develop science-based solutions to complex health challenges. Research is carried out in four metropolitan areas in Africa, Asia, Europe and South America: Accra (Ghana), Ahmedabad (India), Ruhr Metropolis (Germany) and São Paulo (Brazil).

This doctoral thesis was part of the first funding period. Applying the One Health approach to cross-cutting topics, four thematic clusters were created: antimicrobial resistance, blue and green infrastructure, food and nutrition, and One Health governance. Besides advancing the own research projects, several joint achievements were made. Through critical reflections and discussions, several frameworks were developed that account for an expanded understanding of the concept and thereby overcome current One Health shortcomings, including the dominance of medical sectors and the pathogenic approach. In addition, during the COVID-19 pandemic, an ad-hoc working group investigated the One Health concept in the context of coronavirus outbreaks contributing to the discussion on the conceptual orientation of the approach (Schmiege, Perez Arredondo, et al., 2020).

Being part of the NRW Forschungskolleg included a continuous learning process through direct exchanges with peers and thereby receiving input from various disciplines for the own work. It further enabled the contextualisation and the (conceptual) transferability of the own findings to the other research areas. Acknowledging that each metropolitan area has its distinct context, their similarities regarding potential health risks and possible solutions enable transfers of knowledge and results (see chapter 7.3).

1.5. Structure of the doctoral thesis

The doctoral thesis is a cumulative dissertation organised into seven chapters. The introduction (chapter 1), the scientific approach (chapter 2) and a description of the study area(s) (chapter 3), as well as the conclusion (chapter 7), frame the three main chapters (chapters 4-6). Each main chapter is a manuscript prepared for publication in an international peer-reviewed scientific journal. Two manuscripts were already published (chapter 4: International Journal of Hygiene and Environmental Health; chapter 6: Science of the Total Environment), whereas the third is under review (chapter 5). Table 1 provides a brief overview of the three manuscripts, including their highlights and main contribution.

Table 1. Overview of the highlights and main contribution of each manuscript

	Publication	Highlights	Main contribution
Chapter 4	Schmiege, D., Evers, M., Kistemann, T., Falkenberg, T. (2020): What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. International Journal of Hygiene and Environmental Health, 226, 113497. DOI: 10.1016/j.ijheh.2020.113497	• In total, 46 determinant groups were identified and categorised as compositional, contextual or collective. • Compositional determinants were researched the most and provided the most substantial evidence. • Potential area effects of contextual and collective factors on antibiotic use in the outpatient sector revealed. • Evidence base biased towards high-income and western countries and often relying on secondary data.	Identification of determinants of antibiotic use in the human outpatient sector and potential area effects
Chapter 5	Schmiege, D., Falkenberg, T., Moebus, S., Kistemann, T., Evers, M. (*under review*) Associations between socio-spatially different urban areas and knowledge, attitudes, practices and antibiotic use: a cross-sectional study in the Ruhr Metropolis, Germany	• Participants in the socio-spatially disadvantaged area showed lower knowledge and risk awareness and reported mishandling practices and antibiotic use more often. Participants in the socio-spatially advantaged area often displayed the opposite. • Around one-third of disease mentions against which an antibiotic was taken are mainly caused by viral pathogens. • The survey revealed the misconception of antibiotic resistance as an individual issue across areas.	Identification of spatial differences regarding antibiotic use and related knowledge, attitudes and practices between socio-spatially diverse urban areas
Chapter 6	Schmiege, D., Zacharias, N., Sib, E., Falkenberg, T., Moebus, S., Evers, M., Kistemann, T. (2021). Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing Escherichia coli in urban community wastewater. Science of the Total Environment, 785, 147269. DOI: 10.1016/j.scitotenv.2021.147269	• The general community is a relevant source of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli)* in wastewater. • Seasonal variation with high numbers of ESBL-producing *E. coli* during winter months • Counts of ESBL-producing *E. coli* vary between socio-spatially different communities. • Variation in resistance only to those antibiotics administrable in outpatient care	Identification of spatial and temporal differences regarding the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater from socio-spatially diverse urban areas

2. Scientific approach

2.1. Theoretical foundation

The doctoral thesis is positioned in and contributes to the holistic and interdisciplinary field of health and medical geography. Combining concepts of geography and health, research in this hybrid field is concerned with the spatial and temporal context of (human) disease, health and well-being, and interactions of space, i.e. a geometric container, or place, i.e. an area loaded with meaning and value, with health outcomes (Kistemann et al., 2019). The explicit consideration of the spatial dimension, e.g. describing and explaining relationships and processes through space or place, is the distinctive feature of health and medical geography (Schweikart & Kistemann, 2017).

Traditionally, medical geography has been concerned with illustrating and analysing spatial patterns and the spread of disease, as well as the planning and provision of health care services (Kistemann et al., 2019). A positivist approach accompanied by quantitative methods and the biomedical model of disease have dominated these research streams. In recent years, there has been a shift towards more inclusive and health-oriented models (e.g. salutogenic approach) through changing philosophical stances with a stronger focus on human agency and the broader social, cultural and political contexts of health (Gatrell & Elliott, 2015; Kistemann et al., 2019). Qualitatively oriented research gained importance and is at the centre of health geography. The spatial turn, a paradigm shift marking the rediscovery of the spatial in many scientific disciplines and thereby expanding the understanding of space, i.e. not just as a passive container but also as a product of social practices and relations, complemented this development (Kistemann & Schweikart, 2017).

Spatial analyses of disease, health and well-being remain a core topic of health and medical geography (Emch et al., 2017). Geographic scales are essential in this context as processes that impact health can operate at different spatial and temporal scales. In addition, interactions of different spatial and temporal levels and the specific spatial context with other contexts also need to be considered (Voigtländer, 2017). Small-scale area studies on a finer geographical scale, e.g. between neighbourhoods, help to reveal spatial patterns and relations, e.g. variations from place to place, that were not visible on an aggregated level (Schweikart & Kistemann, 2017).

Over decades, evidence has accumulated that health outcomes depend on individual-level variables and features of the local environment (Voigtländer, 2017). Recognising the importance of both people and space when considering health outcomes, Macintyre (1997) developed a concept to explain the geographical patterning of health. She conceptualised three types of explanation for geographical variations in health, which were defined as follows:

- Compositional: "[…] the characteristics of individuals concentrated in particular places […]",
- Contextual: "[…] opportunity structures in the local physical and social environment […]",
- Collective: "[…] socio-cultural and historical features of communities." (Macintyre et al., 2002, p. 130)

Recognising that "the distinction between composition and context may not be as conceptually clear or as useful as may appear at first glance", this concept was later revised (Macintyre et al., 2002). The updated approach contained different features of how local areas can promote or damage health, broadly classifiable into material or infrastructural resources and collective social functioning and practices (Macintyre et al., 2002). However, the authors concluded "[…] that it might be helpful, firstly, to distinguish between compositional and contextual explanations for spatial variations in health; secondly, to include collective social functioning and social practices as candidate contextual mechanisms […]" (Macintyre et al., 2002, p. 135). Following this line of argument, the classification into compositional, contextual and collective was applied in this doctoral thesis to structure potential area effects on antibiotic use in the human outpatient sector as the health outcome of interest (see chapter 4).

By investigating spatial patterns of antibiotic use and specific determinants in the human outpatient sector and the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater, this doctoral thesis is situated in the traditional strands of medical geography, epistemologically rooted in a positivist approach. Space is explicitly considered a structuring factor and utilised as a geometric container instead of a meaning- or value-laden place. This work demonstrates the importance of small-scale area variations, i.e. intra-urban, contributing an essential health and medical geography perspective to antibiotic resistance (ABR).

The following sections introduce the conceptual framework (chapter 2.2) of the doctoral dissertation and explain the methodological approach (chapter 2.3), including the working packages and the rationale for selecting the specific bacteria and resistance mechanism.

2.2. Conceptual framework

The conceptual framework unites all relevant aspects and concepts for this doctoral dissertation (see Figure 1). It intends to depict the role of socio-spatial hotspots and the whole range of possible interlinkages along the pathway from antibiotic use over the occurrence of antibiotic-resistant bacteria to the receiving water compartment. The dark grey boxes illustrate the specific conceptual pathway underpinning this work, whereas the light grey boxes represent important aspects, which were not explicitly considered. The coloured boxes and arrows highlight the primary focus of this doctoral thesis.

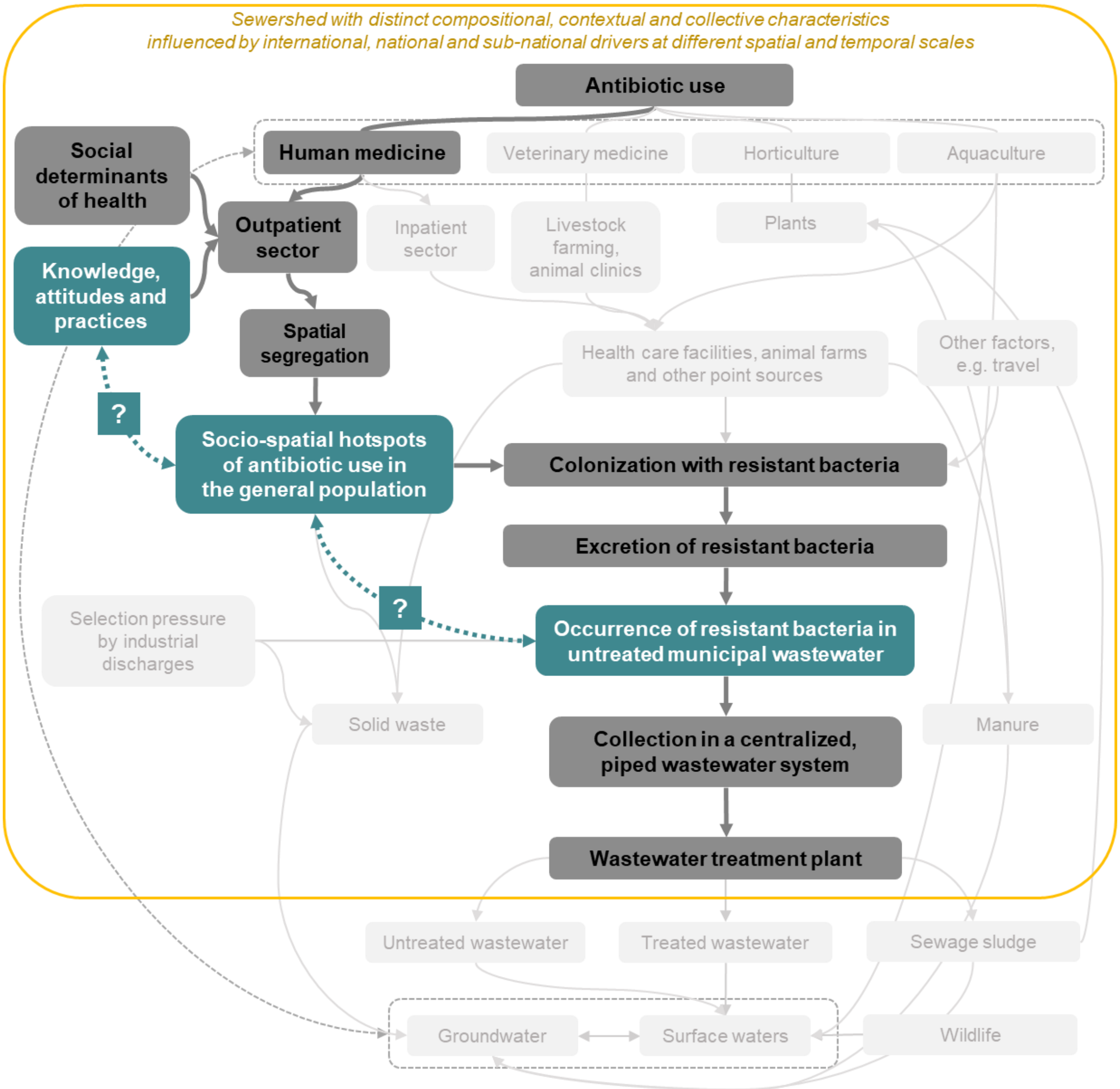


Figure 1. Conceptual framework illustrating possible pathways how antibiotics and antibiotic-resistant bacteria can reach water compartments (dark grey and coloured boxes with bold font highlight the focus of this doctoral thesis)

Bacterial infectious diseases can affect humans, animals and plants alike, which sometimes requires an antibiotic. The administration of antibiotics in human or veterinary medicine and horticulture and aquaculture can be preventive or curative. In human medicine, antibiotics are administered in inpatient, e.g. hospitals or other health care facilities, and outpatient, e.g. medical practices, settings. In many European countries, including Germany, most antibiotics for human medical treatment are used in the outpatient sector (BVL & PEG, 2016; ECDC, 2020a). Various determinants influence antibiotic use in the community, including demographic, non-behavioural and behavioural- and personality-based factors such as knowledge and attitudes (Zanichelli et al., 2019).

Individuals with a similar socio-economic context tend to cluster spatially (Maffini & Maraschin, 2018; Vaughan & Arbaci, 2011). Following the concept of the social gradient in health (Braveman et al., 2011; CSDH, 2008), this could also translate into an unequal distribution of poor health with a higher disease burden in socio-spatially disadvantaged areas. This approach was transferred onto antibiotic use (and not the disease it is supposed to treat) as the health outcome of interest. The clustering of higher antibiotic use among individuals or groups in close spatial proximity, e.g. a neighbourhood, is referred to as a “socio-spatial hotspot”.

Each antibiotic treatment selects for resistant bacteria in the patient’s gut (Langdon et al., 2016; Pal et al., 2016). During and after an antibiotic treatment, patients are colonised by and excrete antibiotic-resistant bacteria and to varying degrees active compounds and metabolites of antibiotics with their faeces (Kim et al., 2017). The higher the antibiotic use in an area, the more people are colonised by antibiotic-resistant bacteria, which are subsequently excreted into wastewater. High antibiotic use could therefore translate into a spatial hotspot of antibiotic-resistant bacteria in untreated community wastewater. The question mark between the coloured boxes flags this potential association, which was the fundamental objective of this doctoral thesis (see Figure 1).

Wastewater receives active compounds and metabolites of antibiotics and antibiotic-resistant bacteria from the general population and other well-established point sources, such as health care facilities (see, e.g. Blaak et al., 2015b; Paulshus et al., 2019), slaughterhouses (see, e.g. Savin et al., 2020) and animal farms (see, e.g. Manyi-Loh et al., 2018). A centralised, piped system collects the wastewater and feeds it to the WWTP. These processes occur within a sewershed with distinct compositional, contextual and collective characteristics influenced by various drivers at different spatial and temporal scales. A sewershed can be defined as an “area of land where all the sewers flow to a single end point [e.g. a WWTP]” (PGH_20, 2021).

Antibiotics, their residues and antibiotic-resistant bacteria reach the receiving surface water directly via untreated wastewater, e.g. through combined sewer overflows due to heavy rainfall (Honda et al., 2020; McLellan et al., 2007), treated wastewater (Cacace et al., 2019), or indirectly via the application of sewage sludge to agricultural fields (Chen et al., 2016; Rahube et al., 2014). Surface waters and groundwater are interconnected in several ways. Different activities in or with water, such as drinking, washing, bathing, leisure activities or irrigation, expose humans and animals alike to antibiotics, their residues and antibiotic-resistant bacteria (see, e.g. Herrig et al., 2020; Leonard et al., 2015) that are now ubiquitous in anthropogenically impacted water compartments (Baquero et al., 2008; Kümmerer, 2009).

The following section (chapter 2.3) describes how the components of interest in the conceptual framework, socio-spatial hotspots of antibiotic use and the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater, were investigated.

2.3. Methodical approach

2.3.1. Introduction of the working packages

The doctoral thesis is an empirical study employing a quantitative approach. Three working packages were formulated at the onset of the dissertation (see Table 2) to assess antibiotic use and its determinants in the community (see chapters 4 and 5), as well as the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater in three socio-spatially different urban areas comprehensively (see chapter 6). Each working package had its study design. Figure 2 displays the main methods (in dark grey) applied in the working package.

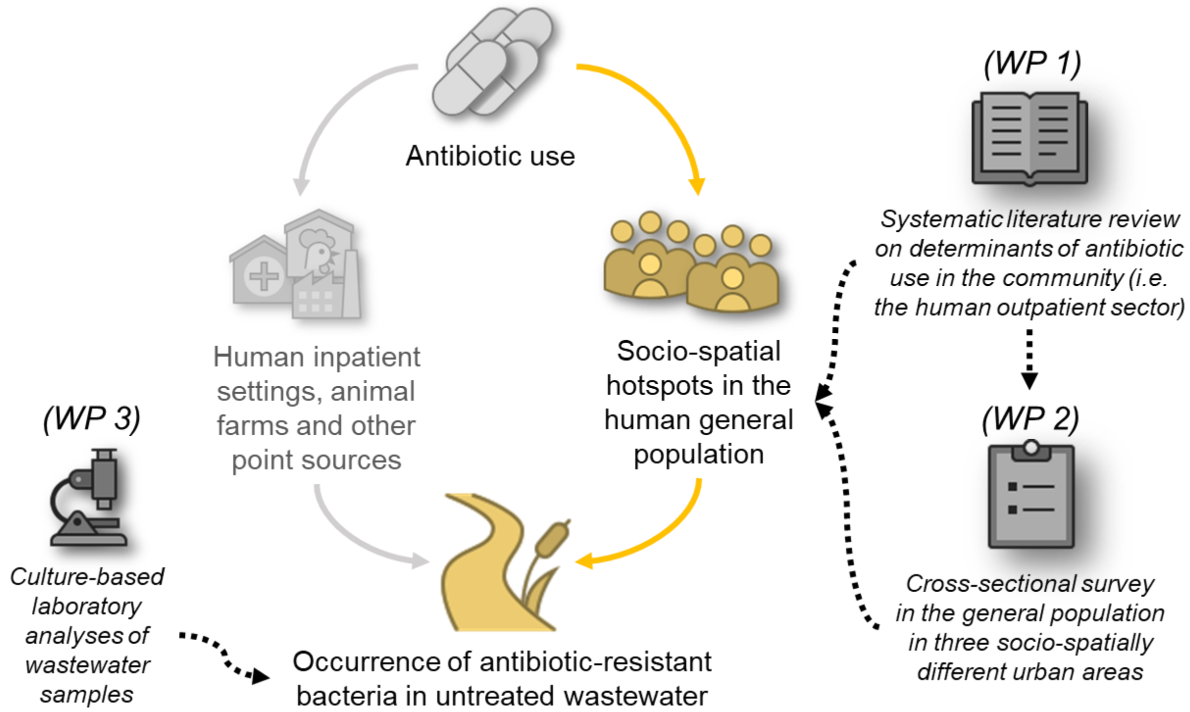


Figure 2. Methodical approach highlighting the main methods used in the working package (Icons: https://icons8.de/)

Table 2. Working packages (WP) of the doctoral thesis linked to the research questions (RQ) and objectives (RO) introduced in chapter 1.3 with their specific research questions and objectives

	WP research questions		WP research objectives	
Working package 1 *(related to RQ 1 and RO 1.1)*	RQ i:	What are compositional, contextual and collective determinants that influence antibiotic use for human medical treatment in the community (i.e. the outpatient sector)?	RO i.i:	To gather available evidence on determinants of antibiotic use in the human outpatient sector.
			RO i.ii:	To categorise the determinants into compositional, contextual and collective groups.
			RO i.iii:	To illustrate the effects of compositional, contextual and collective determinants on antibiotic use in the human outpatient sector.
Working package 2 *(related to RQ 1 and RO 1.2)*	RQ ii:	What are antibiotic use and related knowledge, attitudes and practices in the community in socio-spatially diverse urban areas?	RO ii.i:	To describe self-reported antibiotic use and knowledge, attitudes and practices related to antibiotic use and resistance in the general adult population in three socio-spatially diverse urban areas.
	RQ iii:	What are the relationships between socio-spatially diverse urban areas and knowledge, attitudes, practices and self-reported antibiotic use in the community?	RO iii.i:	To analyse potential area effects on knowledge, attitudes, practices and self-reported antibiotic use.
Working package 3 *(related to RQ 2 and ROs 2.1 and 2.2)*	RQ iv:	What are spatial and temporal differences in the occurrence of antibiotic-resistant bacteria and their resistance profiles in untreated municipal wastewater between socio-spatially diverse areas within a metropolitan sewershed?	RO iv.i:	To test untreated municipal wastewater of three socio-spatially diverse urban areas for the occurrence of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*).
			RO iv.ii:	To identify spatial and temporal differences in the prevalence of multidrug-resistant and ESBL-producing *E. coli* in untreated municipal wastewater.
			RO iv.iii:	To identify spatial and temporal differences in the resistance profiles of ESBL-producing *E. coli* isolates in untreated municipal wastewater.

The first working package (WP 1) was designed as a descriptive study to answer parts of the research question (RQ) 1 through research objective (RO) 1. Gathering available evidence on determinants of antibiotic use in the community (i.e. the human outpatient sector), categorising them into compositional, contextual and collective factors and illustrating their effects were the main goals of this WP (WP ROs i.i-i.iii). This was achieved by employing a systematic literature review with a quantitative summary and qualitative narrative synthesis of the findings. For more details of the approach, please see chapter 4. The results of WP 1 informed the household survey in WP 2.

The results of WP 2 were used to answer the second part of RQ 1 through RO 1.2. The aims of WP 2 were twofold. Firstly, to describe self-reported antibiotic use and knowledge, attitudes and handling practices on antibiotics and antibiotic resistance in the community (RQ ii and RO ii.i). Secondly, to assess spatial differences between socio-spatially different urban areas (RQ iii and RO iii.i). It relied on an observational and retrospective study design using a cross-sectional questionnaire-based household survey in the general adult population in three socio-spatially different urban areas. For more details of the approach, please see chapter 5.

Culture-based laboratory analyses of untreated municipal wastewater samples in the same three socio-spatially different urban areas (WP 3) complemented the other two WPs. It was set up to answer RQ 2 through the ROs 2.1 and 2.2. A descriptive study design was used to explore the prevalence of certain antibiotic-resistant bacteria, extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* (*E. coli*) (RO iv.i and iv.ii), and their resistance profiles (RO iv.iii) in untreated municipal wastewater from three socio-spatially different urban areas over time. For details on the laboratory procedures, please see chapter 6. The following section outlines the rationale for selecting the specific bacteria and resistance mechanism.

2.3.2. The rationale for selecting the bacteria and resistance mechanism

Bacteria are prokaryotic microorganisms (Josenhans & Hahn, 2020; Mims et al., 2006). They can be categorised based on their pathogenic potential into commensal and three different pathogenic groups (i.e. apathogenic or opportunistic, facultative, and obligate) (Exner et al., 2018; Heesemann, 2020). Gram-negative bacteria, so-called due to their stain in the Gram staining method (Kayser, 2005b), are inherently more resistant to antibiotics than gram-positive species due to their double membrane wall and associated additional defence mechanisms (Livermore, 2012). Of particular epidemiological and resistance importance within the gram-negative group are several bacterial species of the *Enterobacteriaceae* family, including *E. coli* (Exner et al., 2017).

E. coli occur naturally in the intestinal tract of humans and animals (Kayser, 2005b) but can also persist in terrestrial and aquatic environments (Van Elsas et al., 2011). It is an indicator organism for faecal contamination of water and foods (Kayser, 2005a; Suerbaum et al., 2020). This species comprises apathogenic, facultative and obligate pathogenic strains, which can cause severe intestinal and extra-intestinal infections, including diarrhoea, urinary tract infections and sepsis, in humans and animals (Suerbaum et al., 2020).

Bacterial infections may require the use of antibacterials. Beta-lactam antibacterials, so-called due to their highly reactive beta-lactam ring (Blair et al., 2015; Pandey & Cascella, 2020), are a commonly used antibacterial group to treat infections caused by gram-negative bacteria. This group includes penicillins, cephalosporins, carbapenems, monobactams and clavams, all of which interfere in the cell wall synthesis in bacteria (Hof, 2019; Kayser, 2005b). Beta-lactam antibacterials comprised more than half of all antibacterials consumed in both the community and the hospital sector in countries in Europe in 2019 (ECDC, 2020a).

Bacteria can defend themselves against beta-lactam antibacterials by producing inactivating enzymes, i.e. beta-lactamases (Witte & Mielke, 2003) rendering the antibacterial ineffective (Babic et al., 2006). Particularly problematic from a health perspective are plasmid-encoded (as opposed to chromosomal localised) extended-spectrum beta-lactamases (ESBL). They can hydrolyse penicillins, first- through third-generation cephalosporins and monobactams (Hof, 2019; Munita & Arias, 2016) and can be transmitted across bacterial species within the *Enterobacteriaceae* family and other Gram-negative pathogens (Suerbaum et al., 2020). ESBL variants can be grouped into nine families (Gniadkowski, 2001; Witte & Mielke, 2003), which are constantly growing in numbers. The CTX-M-group is now the most prevalent after replacing the SHV- and TEM-types (Doi et al., 2017).

ESBL-producing gram-negative bacteria, including *E. coli*, are of particular health concern (WHO, 2017) because they have shifted from an issue initially focused on health care settings to the broader community (Pitout et al., 2005; Woerther et al., 2013). Depending on the species and the antibiotic resistance profile, treatment options for infections caused by ESBL-producing *Enterobacterales* can be severely limited (Pitout & Laupland, 2008), leading to adverse health outcomes and higher costs (Giske et al., 2008).

In many regions globally, the prevalence of ESBL-producing *Enterobacterales* has increased between 1992 and 2016 (Bevan et al., 2017). In European countries, resistance to third-generation cephalosporins among *E. coli* isolates showed an increasing trend since 2015, ranging between 6.2% and 38.6% in 2019 (ECDC, 2020b). In Germany, ESBL-phenotypes of *E. coli* peaked in 2010 at 17.4% and since then showed a downward trend (BVL & PEG, 2016) with resistance to third-generation cephalosporins among *E. coli* isolates at 11.5% in 2019 (ECDC, 2020c).

Their persistence in environmental media and their epidemiological and resistance relevance make ESBL-producing *E. coli* an interesting candidate for monitoring ABR in wastewater, as also outlined elsewhere (WHO, 2021b).

3. Study area

3.1. The geographical setting of the sewershed of the wastewater treatment plant Dortmund-Deusen

Examining potential socio-spatial hotspots of antibiotic use and antibiotic-resistant bacteria in untreated municipal wastewater within a sewershed required a centralised wastewater system and clearly defined catchment areas. In close cooperation with experts from the Emschergenossenschaft, one of the responsible public water boards in the area, the sewershed of the municipal wastewater treatment plant (WWTP) Dortmund-Deusen located in the Ruhr Metropolis, Germany, was selected as a suitable study area.

The WWTP Dortmund-Deusen is located in the north-western part of the city of Dortmund (51° 30’ 58’’ N, 7° 28’ 6’’ E) in the federal state North Rhine-Westphalia, Germany. It is a conventional treatment plant with three treatment steps (i.e. mechanical, biological and chemical) consisting of five process steps before the treated wastewater reaches the receiving surface water: (1) coarse and fine screens, (2) artificially ventilated sand traps, (3) preliminary sedimentation, (4) aeration tanks and (5) secondary sedimentation (EGLV, 2016).

In 2020, the WWTP Dortmund-Deusen treated wastewater of a population equivalent of 584.569 (connected population: 399.425), amounting to an annual wastewater volume of over 47.000.000 m^3 (IT.NRW, 2021). The sewage sludge produced during the wastewater treatment process (2020: 7,574.88 tTS/a; IT.NRW, 2021) was mainly used as a combustible for the production of electricity and heat (EGLV, 2016). The WWTP Dortmund-Deusen receives the vast majority of its wastewater from the city of Dortmund (excluding the districts Mengede, Scharnhorst and Brackel) and small proportions from the neighbouring towns Witten, Holzwickede and Schwerte.

The city of Dortmund is home to over 600,000 people (Stadt Dortmund, 2021) and, as such, the biggest city in the Ruhr Metropolis, an urban agglomeration of over five million inhabitants in the western part of Germany (Keil & Wetterau, 2013). It is among Germany’s largest cities, with over 280 km^2 (Stadt Dortmund, 2021). Moderate temperatures and precipitation year-round describe the temperate climate zone in which it is situated. Between 2000 and 2019, the average annual temperature ranged from 9.4 °C to 12.0 °C, and the total yearly amount of rainfall varied between 529.7 mm and 879.1 mm (Stadt Dortmund, 2021).

Dortmund’s water bodies include the rivers Ruhr and Emscher, the Dortmund-Ems canal, and several smaller lakes due to mining subsidence. However, water bodies accounted for less than 1% of the total area in the city, whereas built-up area (36.4%) and land used for agriculture and horticulture (23.3%) jointly constituted more than half of the total area (Stadt Dortmund, 2021).

3.2. Socio-economic situation and antibiotic use

The population structure in Dortmund in 2020 was as follows (total population of 603.167): around 50.1% were female, and 49.4% male; 16.4% of the inhabitants were below age 18, and 20.3% were older than 65 years; about 19.1% were foreigners, with Turkey, Syria and Poland as the top three countries of origin in terms of the number of people (dortmunderstatistik, 2021b, 2021a; Stadt Dortmund, 2021); in 2018, 35.6% had an immigration background (i.e. foreigners and their children, naturalised persons and their children, (late) emigrants and their children) (Stadt Dortmund, 2019).

Ongoing structural changes from a past centred on the coal and steel industry towards a service-based economy characterise this region (Keil & Wetterau, 2013). In 2019, 40.9% of the population were employed subject to social security contributions (Stadt Dortmund, 2021), of which over 82% work in the tertiary sector (Stadt Dortmund, 2021). The unemployment rate was at 11.6% in July 2021 (Bundesagentur für Arbeit, 2021).

Socio-economic characteristics are not equally distributed over Dortmund but tend to follow a North-South gradient as many other cities in the Ruhr Metropolis (Keil & Wetterau, 2013). Examining different variables at a higher spatial resolution (i.e. the 170 statistical sub-districts) revealed the following picture (Stadt Dortmund, 2019):

- Higher population density, higher proportions of children (below age 18), shorter duration of residence, a much higher ratio of foreigners and people with an immigration background, higher unemployment rates and higher shares of recipients of state transfer payments characterised the Northern inner-city sub-districts.
- On the contrary, the Southern and more outer sub-districts showed higher proportions of people above age 65, higher ratios of pupils with a transition recommendation to high school, much higher proportions of flats in one- or two-family houses, more living space per inhabitant and higher number of private cars per inhabitants.

Two social space analyses, each combining several socio-economic indicators to derive a comprehensive overview, examined the situation in Dortmund. In a social space analysis of the Emscher region, Amonn and colleagues categorised sub-areas based on their socio-structural similarities arriving at six different clusters (Ammon et al., 2011). Following this analysis, the Northern and inner-city sub-areas were considered socially deprived, whereas the Southern and more outer sub-districts appeared relatively privileged. The city of Dortmund also conducted a social space classification through a cluster analysis of 39 sub-city areas (Stadt Dortmund, 2007). They used eight indicators that allowed for a multidimensional approach to social spaces in Dortmund: populations under 18 years, population with an immigration background, recipients of basic benefits, income index, applications to high schools, help in upbringing, overweight children and employed population. Based on those eight indicators, they derived five clusters highlighting the familiar North-South gradient (Stadt Dortmund, 2007). Although this analysis is outdated, the most recent statistics illustrated a comparable situation (Stadt Dortmund, 2018, 2019).

In Germany, approximately 85% of antibiotics for human medical treatment were used in the outpatient sector, with distinct differences between the federal states (BVL & PEG, 2016). Spatial variations were also observable between cities and municipalities: Dortmund ranked second in antibiotic use out of the 26 cities and municipalities in the area of responsibility of the association of statutory health insurance physicians Westphalia-Lippe in 2019 (data from KV Westphalia-Lippe, 2020).

3.3. Selection of the study areas

Examining antibiotic use and the occurrence of resistant bacteria in untreated municipal wastewater, as well as the potential spatial and temporal associations between those at the local level, required clearly defined small-scale areas within the sewershed of the WWTP Dortmund-Deusen. The study area selection was implemented in close consultation with the Emschergenossenschaft. The social space analyses outlined above formed part of the basis for the selection process. Suitable study areas needed to fulfil two criteria: i) representing distinct socio-spatial contexts (i.e. opposing situations) and (ii) the catchment areas should not contain any inpatient health care facility.

Based on those criteria, three study areas were chosen. Figure 3 illustrates the study areas underlaid by a map of the 62 statistical districts colour coded based on a social space cluster analysis (Stadt Dortmund, 2007). The names of the three study areas were derived from the pumping station or storage sewer that drain the respective catchment area: pumping station Dortmund-Erpinghof, storage sewer Dortmund-Am Lohbach and pumping station Dortmund-Osterholz. For easier reference, the study areas are renamed “Area A” (Erpinghof), “Area B” (Lohbach) and “Area C” (Osterholz).

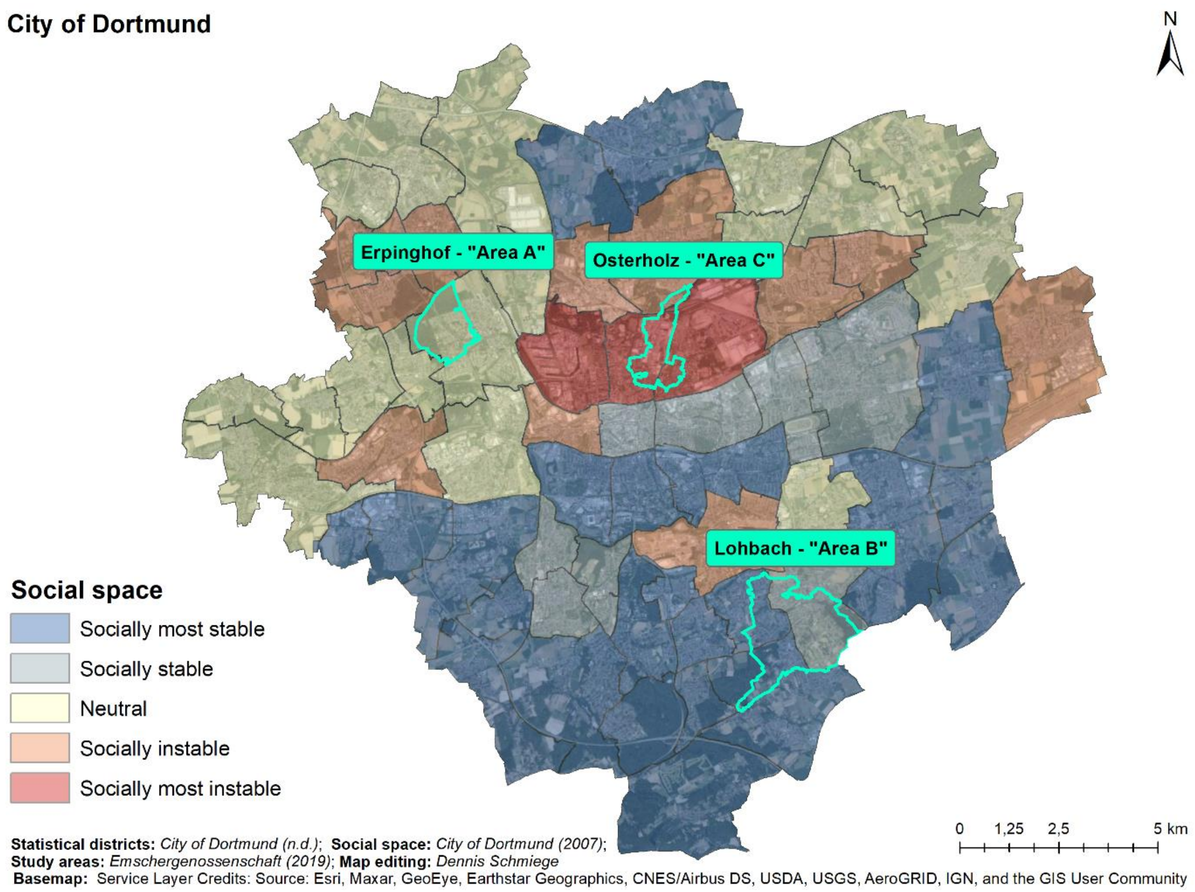


Figure 3. Social space clusters for 62 statistical districts and the selected study areas in Dortmund

The catchment areas do not align with administrative boundaries but cover parts of several statistical sub-districts (i.e. administratively, the highest spatial resolution for which official data exists). Table 3 depicts the area-weighted average of residential, demographic and economic indicators across the statistical sub-districts (partly) included in the respective catchment area.

Assessing those indicators allows for identifying a socio-spatial tendency of the three study areas to the average of Dortmund and each other. Values for Area A were in most cases (8/10) closest to the average of Dortmund, whereas numbers for Areas B and C varied much more. Indicators for Area B revealed a relatively socio-spatially advantaged situation compared to Area C. The latter displayed a disadvantaged situation regarding residential and economic variables. It also had higher shares of young people and foreigners and the lowest percentages of people above age 65.

Table 3. Socio-spatial differences (area-weighted mean values) between the three catchment areas and the average of Dortmund (Stadt Dortmund, 2019)

Indicator / Area *Abbreviation*	**Erpinghof** *Area A*	**Lohbach** *Area B*	**Osterholz** *Area C*	**Dortmund** *NA*
Statistical sub-districts included	Mailoh, Erpinghof-siedlung, Jungferntal	Berghofen Dorf, Berghofer Mark, Benninghofen, Loh, Höchsten, Holzen	Nordmarkt-Süd, Nordmarkt-Südost, Nordmarkt-Ost, Borsigplatz, Westfalenhütte, Obereving	All
Residential				
Settlement and traffic area (%)	42.2	44.9	53.4	40.2
Inhabitants/ha	74.5	46.4	162.4	75.2
Living space/ inhabitant (m^2)	33.4	49.5	27.5	39.4
Flats in one- or two-family houses (%)	19.2	52.0	3.1	23.6
Demographic				
Persons below age 18 (%)	18.1	14.5	23.5	16.2
Persons above age 65 (%)	15.2	26.7	9.8	20.2
Single-parent households (%)	26.8	16.5	26.6	24.6
Foreigners (%)	23.3	5.6	56.9	18.2
Economic				
Employed population (%)	51.7	61.1	42.1	56.3
Unemployed population (%)	12.6	4.1	20.1	9.8
Recipients of state transfer payments (%)	23.3	4.1	40.8	16.6

The three socio-spatial diverse urban areas provided a sound basis for assessing potential differences in antibiotic use and the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater within the metropolitan sewershed. The following chapters 4 to 6 present the three manuscripts in which the antibiotic resistance (ABR) components are analysed.

4. What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector

This chapter was originally published as: Schmiege, D., Evers, M., Kistemann, T., Falkenberg, T. (2020): What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. International Journal of Hygiene and Environmental Health, 226, 113497, DOI:10.1016/j.ijheh.2020.113497.[1][2]

4.1. Abstract

Inadequate and excessive use of antibiotics in humans, animals, and plants has been identified among the key drivers of antibiotic resistance (ABR). In human medicine, the great majority of antibiotics are prescribed in the outpatient sector with profound differences in antibiotic consumption across various geographical scales and between health care sectors; raising questions around the underlying drivers.

Moving beyond individual patient-related determinants, determinants of antibiotic use in the outpatient sector were categorized as compositional, contextual and collective, enabling an analysis of potential area effects on antibiotic use. 592 variables identified in 73 studies were sorted into 46 determinant groups. Compositional determinants provided the strongest evidence with age, education, employment, income, and morbidity exhibiting a clear influence on antibiotic use. Regarding contextual and collective determinants, deprivation, variables around health care services, Hofstede's dimensions of national culture and regulation affect antibiotic use.

The results are biased towards high-income and western countries, often relying on secondary data. However, the findings can be used as signposts for associations of certain variables with antibiotic use, thereby enabling further research and guiding interventions.

4.2. Introduction

In terms of attributable deaths, the currently unfolding global public health crisis of antimicrobial resistance (AMR) bears the risk of potentially surpassing many communicable and non-communicable diseases by 2050 (O'Neill, 2016). AMR is also linked to impediments of medical routine procedures as well as significant additional health care costs (Laxminarayan et al., 2013). Within AMR, particularly antibiotic resistance (ABR) receives a lot of research attention.

[1] Link to the publication: https://doi.org/10.1016/j.ijheh.2020.113497
[2] The numbering of figures and tables was changed to consecutive numbers.

Inadequate and excessive use of antibiotics in humans, animals, and plants has been identified among the key drivers for accelerating this otherwise natural process (Chatterjee et al., 2018; Davies & Davies, 2010). Globally, antibiotic consumption rates increased between 2000 and 2015 with varying magnitudes in higher- (HIC) as well as lower- and middle-income countries (LMIC), and this growth is projected to continue even further (Klein et al., 2018).

Differences in antibiotic consumption are observed not just between country groupings but also between (e.g. Blommaert et al. 2014; Deschepper et al. 2008) and within individual countries (de Jong et al., 2014; Kliemann et al., 2016). Such differences are evident on all spatial scales, from the macro down to the local level (Franchi et al., 2011; Jensen et al., 2016), from cross-country to intra-urban variations (Henricson et zal., 1998b; Togoobaatar et al., 2010b).

Besides geographical differences, there are also variations in antibiotic use in different health care sectors. In Europe, for instance, antibiotic consumption is ten-fold higher in the human outpatient sector as opposed to the hospital sector (ECDC, 2018). In Germany, 85% of all antibiotic prescriptions to humans occur in the ambulatory care sector (BVL & PEG, 2016), underlining the role of the outpatient sector as an important contributor and driver of ABR.

The occurrence and distribution of bacterial infectious diseases alone are not able to explain exhaustively those variations in antibiotic consumption between and within countries and health care sectors. Hence, it is necessary to broaden the focus and examine additional determinants of antibiotic use. In a recent review, Zanichelli et al. (2019) focused on patient-related determinants of responsible antibiotic use, highlighting several crucial factors on the individual level (e.g. demographic and socio-economic characteristics, patient-doctor interactions, and treatment characteristics). However, antibiotic use is not only determined by individual factors, but potential area effects need to be considered, placing the focus on both people and places.

To differentiate the determinants of spatial variation in health and health behaviour, the classification by Macintyre (1997) (compositional, contextual and collective) will be applied. This concept helps to frame and understand the geographical patterning of health and has already been applied to different health outcomes, including mental health and well-being, and neglected tropical diseases (Armah et al., 2015; Collins et al., 2017).

The compositional category entails “the characteristics of individuals concentrated in particular places” (Macintyre et al., 2002, p. 130), such as demographics, while the “opportunity structures in the local physical and social environment” (ibid:130), e.g. housing or access to health services, fall into the contextual category. “Lastly, “socio-cultural and historical features of [the] communities” (ibid:130) like norms and values are captured in the collective category. Revising their classification, Macintyre, Ellaway, and Cummins (2002) argued that collective effects should not be separated from contextual mechanisms anymore, as the distinction between those two appeared to exist rather in theory than in reality. However, for a clearer overview, collective determinants are presented separately in this systematic review. Those categories should, however, not be treated as mutually exclusive but the interactions between conditions of the individual(s) and different features of the neighbourhood should be considered (Macintyre et al., 2002).

The objective of this systematic review is to identify existing evidence on the determinants of antibiotic use in the outpatient sector, across various scales and geographic settings; categorizing their respective effects into compositional, contextual and collective. This overview can guide further research and enables a more layered approach to determinants of antibiotic use in the community, thereby providing a starting point for more targeted interventions (e.g. awareness raising campaigns).

4.3. Materials and methods

4.3.1. Search strategy

A systematic review of peer-reviewed literature was conducted. Three scientific databases, PubMed, ScienceDirect, and Web of Science, were systematically searched during November 2018 using different combinations of indexed and free-text search terms (see supplementary material A[3]). Due to the exploratory and inclusive approach chosen, broad search terms were used, covering three concepts: synonyms for antibiotics, synonyms for antibiotic use, and a broad range of terms for potential determinants. In addition, a search alert was set up in each database in order to receive notifications about the most recent publications. This did not yield any relevant study. Reference lists of studies deemed eligible for the full-text analysis were hand-searched manually. The hand-search also followed a tiered approach. Titles were screened first, followed by abstracts. No date or language restrictions were applied to the literature search. However, in the final data analysis, only publications available in English or German were included.

4.3.2. Selection criteria

Studies were selected based on the criteria illustrated in Table 4, following the population, intervention, comparator, outcome, and study design (PICOS) format (McKenzie et al., 2019). Peer-reviewed studies assessing determinants of human antibiotic use in the outpatient sector or the community were included in this review not limited to a specific geographic setting.

[3] Supplementary material A of this publication can be accessed in chapter i.a in the appendices.

Table 4. Inclusion and exclusion criteria for study selection following the population, intervention, comparator, outcome, and study design (PICOS) format (McKenzie et al., 2019)

Criteria	Inclusion	Exclusion
Population	• Human medicine – outpatient/community • All ages • Both sexes (i.e. male, female) • All geographic settings • All spatial scales	• Human medicine – inpatient sector • Animals • Plants • Agriculture
Intervention	• Variables of any kind that explain variations in antibiotic use	• Studies focusing exclusively on knowledge, attitudes, experiences, perception or awareness around antibiotic use • Compliance with treatment • Any other intervention (e.g. antibiotic stewardship programs)
Comparator	*Not applicable*	
Outcomes	• Antibiotic use in humans (investigated as consumption (including self-medication or misuse), acquisition, prescription or sales) • All antibiotics for systemic use (WHO ATC code J01)	• Antivirals, antimycobacterial, antifungals, or anti-parasitic drugs • Association between antibiotic use and antibiotic resistance • The occurrence of antibiotics in the environment
Study design	• Peer-reviewed studies • Ecological analysis • Cross-sectional, observational, and retrospective studies	• Studies not using data, i.e. editorials, letters, conference abstracts/reports, protocols, and conceptual papers • Systematic reviews • Longitudinal, compositional or descriptive analysis of antibiotic use • Studies with a methodological focus

4.3.3. Data extraction

Essentially, variables influencing antibiotic use in the outpatient sector or the community are of key interest to this systematic review. Information from the included full texts was extracted in a purpose-built standard data extraction form in Microsoft Excel (see research data).

4.3.4. Quality assessment

Only peer-reviewed studies in scientific journals were included. These studies were of observational nature, often using an ecological study design, for which there are no agreed quality assessment tools readily available. In addition, the variety and heterogeneity of the studies made it infeasible to conduct an internally consistent and comparable quality assessment across all included studies. Thus, no structured quality assessment was conducted. However, two key quality criteria for eligible studies were applied: 1) whether they have a reliable measure of antibiotic use, and 2) whether they have a clear reporting of the influence of the variable investigated on antibiotic use. All studies included had to match these two quality criteria.

4.3.5. Data analysis

Due to the heterogeneity of the studies included, a meta-analysis was not feasible; thus, the analysis is based on a quantitative summary and a qualitative narrative synthesis of the findings. The main outcomes of interest are antibiotic use, which here stands as a proxy for acquisition, prescription, sale, reimbursement, and actual consumption data by the respective studies, and its determinants.

After extracting all relevant information into the standard data extraction form, similar variables were grouped into a second purpose-built spreadsheet in Microsoft Excel (see supplementary material B[4]). In order to ensure the transparency and reliability of the grouping, the variables were sorted based on two successive criteria. Fig. 4 illustrates the hierarchy of terminology established as well as an example presented in italics. Variables using the same or similar wording were arranged as one "variable group", e.g. parental employment. If the first criterion did not apply, thematically closely linked variables were also grouped into "variable groups", e.g. fever, cough, earache, and throat soreness, among others, form the variable group "Symptoms". In case multiple variable groups were associated with a certain topic, these were combined into "determinant groups", e.g. employment. Finally, the determinant groups were assigned to one of the determinant categories: collective, compositional, and contextual. All variables and their respective grouping can be accessed in supplementary table C[5].

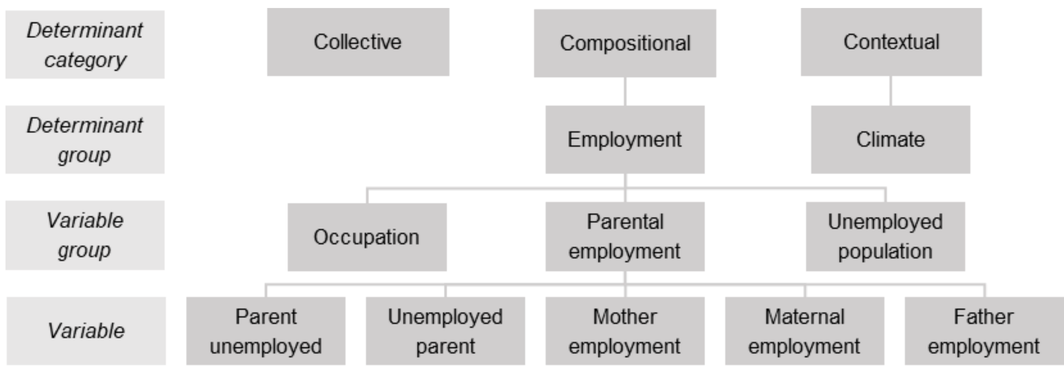


Figure 4. Hierarchy of terminology and grouping of variables shown by means of an example of the determinant group "Employment" starting from the bottom with the variables, which were grouped into the variable group "Parental employment", which was subsequently sorted into the determinant group "Employment" jointly with "Occupation" and "Unemployed population".

The analysis of determinants was implemented at the variable group level whereby the main trend, opposing trends, and non-significant results were examined. The "main trend" of each variable group indicates the direction of influence on antibiotic use exhibited by the majority of

[4] Supplementary material B of this publication can be accessed in chapter i.b in the appendices.
[5] Supplementary material C of this publication can be accessed in chapter i.c in the appendices.

variables within this group, whereas the “opposing trend” shows the inverse direction. “Non-significant” results are also viewed as opposing the main trend but displayed separately from the opposing trend. Generally, the trends are expressed as positive or negative relationships. In only a few cases, it was not possible to distinguish the main trend. Those variable groups are labelled as only “showing differences”, thus not indicating a direction of association.

4.3.6. Risk of bias

Every systematic literature review encounters publication bias. In order to reduce the influence of this bias, both significant and non-significant results were extracted and used in the analysis. However, this does not eliminate the fact that significant results might be published more often. Additional risks of bias are owed to the observational nature and ecological study designs on which the majority of publications rely: confounding bias and ecological fallacy. Many studies used secondary data for analysis with pre-determined sets of variables available, fundamentally an issue of data availability, disabling the opportunity to test for other confounding factors not included in the initial data set. The ecological fallacy is a specific form of confounding whereby an association that exists at the group level is assumed to be also true on the individual level (Levin, 2006). During the interpretation of the results, these potential biases were taken into consideration.

4.4. Results

4.4.1. Study selection

The initial database search yielded 4164 studies that were transferred into the literature management software Mendeley. In order to identify relevant studies for inclusion, the step-wise approach presented in the PRISMA flow chart (Fig. 5) was applied (Moher et al., 2009).

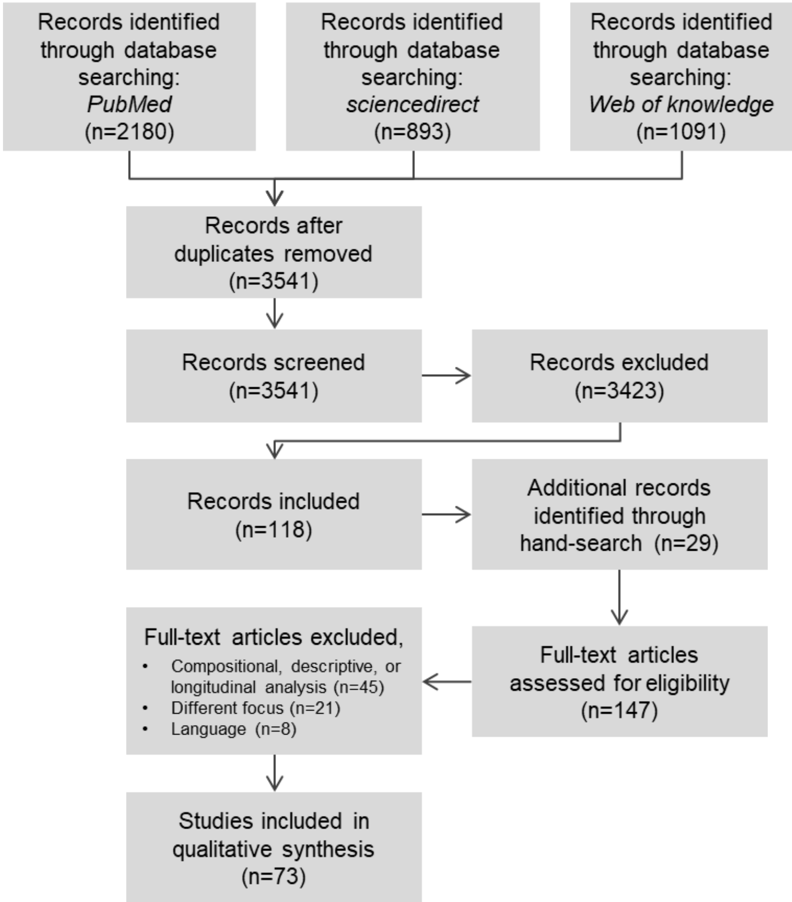


Figure 5. PRISMA flow chart diagram of the systematic review showing the selection process of relevant studies.

After duplicates were removed, 3541 studies remained. Title and abstract screening reduced the number of studies for potential inclusion to 118. The hand-search of the reference lists added 29 studies. 147 full-text articles were obtained and assessed for eligibility. Applying the inclusion and exclusion criteria (see Table 4), 74 full-text articles were excluded. Eventually, 73 studies were included in the qualitative synthesis (references of all 73 studies can be accessed in supplementary material D[6]).

4.4.2. Study characteristics

The 73 studies included cover 30 different countries across the world as well as the European Union (EU) revealing an uneven global distribution of studies on antibiotic use in the community. Grouping the countries into the World Health Organization (WHO) regions (see Tab. 5) underlines this uneven distribution, highlighting the dominance of the WHO European Region.

[6] Supplementary material D of this publication can be accessed in chapter i.d in the appendices.

Table 5. Studies grouped into the WHO regions with the number of countries

WHO region	No. studies		No. countries	Countries included[a]
African Region	1	1%	1	GH
Region of the Americas	9	12%	3	BR, CA, US
Eastern Mediterranean	7	10%	7	AE, IR, JO, LB, SA, SD, SY
European Region	49	67%	17	BE, CH, DE, DK, FR, HR, HU, IL, IT, LT, NL, NO, PL, SE, TR, UK
South-East Asia Region	2	3%	1	IN
Western Pacific Region	5	7%	1	MN, NZ
Total	*73*			

[a] *ISO codes of countries.*

The number of studies per country varies between a single study in the majority of countries and up to seven in Italy and Sweden. Ten studies were conducted on the EU-level. Additional characteristics of the 73 studies included are shown in Table 6.

The majority of studies were implemented at the sub-national level (86%) and in high-income countries (84%). The year of publication ranges between 1998 and 2018 with more than half of the articles published after 2012, clearly showing the increasing research interest. Almost three-quarters of studies were conducted in the general population (73%) relying on secondary data for the analysis (73%). Secondary data, here, refers to data that has not been collected by the authors of the respective paper but by someone else, as opposed to primary data, which is collected directly by the reporting authors, including, for instance, qualitative or quantitative surveys. There is a great variety of analytic methodologies used in the respective studies. Antibiotic use was most often analysed by using prescription data, followed by self-reported use via surveys.

Table 6. Characteristics of all 73 studies included for the final synthesis

Characteristics	**Total (n=73)**
Analytic methodology[a]	
Descriptive statistics	10
Test statistics	12
Correlation	15
Econometrics	4
GEE and MI-GEE	2
Regression[b]	2
Binominal regression	1
Linear regression	12
Logistic regression	23
Ordinary Least Square-regression	2
Poisson-regression	4
Spatial regression	1
Antibiotic use data[c]	
Administered/consumption	4
Claims/reimbursement	6
Dispensing	5
Prescription	34
Sales	9
Self-reported	18
Data type	
Primary data	20
Secondary data	53
Worldbank income group	
High-income countries	61
Lower- and middle-income countries	12
Level of analysis	
Sub-national	63
National	10
Study population	
General population	53
Pediatric population	20
Year range	
1990-1999	2
2000-2009	25
2010-2019	46

[a] The sum of analytic methodologies exceeds the total amount of studies included because some articles used several methods.
[b] In some studies, the method was not further defined than "regression".
[c] The sum of antibiotic use data exceeds the total amount of studies included because two studies used several data types.

4.4.3. Results of the individual studies

Overall, 592 variables were identified in the 73 studies (Tab. 7).

Table 7. Characteristics of studies for each determinant category including their income grouping, study population, and data type

Determinant category	No. studies	No. variables	HIC	LMIC	GP	PP	PD	SD
Compositional	69	325	58	11	50	19	19	50
Contextual	55	223	47	8	44	11	12	43
Collective	14	44	12	2	12	2	4	10
Total	73	592	61	12	53	20	20	53

Note: HIC: High-income countries; LMIC: Lower- and middle-income countries; GP: general population; PP: paediatric population; PD: primary data; SD: secondary data. The values of the determinant groups do not add up to "Total" vertically because one study can investigate factors in different determinant groups.

Compositional variables dominate the determinant categories accounting for more than half of all determinants examined. The majority of studies (57/73) investigated at least one variable of at least two determinant categories. Sixteen studies focused their analysis on only one particular category and in the remaining twelve studies, all three determinant categories were covered.

The 592 variables identified were sorted into 102 variable and 46 determinant groups. Fig. 6 displays the determinant groups with the corresponding number of studies sorted alphabetically, starting on top with the compositional variable: "Age (50)", and then moving around clockwise.

Figure 6. Determinant groups and their respective number of studies in brackets categorized into collective, compositional, and contextual in descending order starting on top with the collective determinant group "Attitude (5)" and then moving clock-wise.

In the following sections, the individual results of each determinant category will be presented. Figures 4-6 illustrate the results for each variable group in alphabetical order. The main trend of each variable group is represented as bars to the right in dark grey, whereas opposing trends and non-significant results are indicated by bars to the left in lighter grey colours. The direction of the main trend, i.e. positive ("+"), negative ("-") or differences ("+/-"), is shown on the right.

This way of presenting the data allows for a visual assessment of the influence the respective variable group has on antibiotic use. It provides an impression of the number of variables investigated per variable group as well as whether there is a main trend, which is potentially counterbalanced by opposing trends or non-significant results. In the determinant group "Sex" (compositional), for instance, 12 variables investigated the influence of sex on antibiotic use in the paediatric population, i.e. variable group “Paediatric: boys”. Five variables linked higher antibiotic use to boys constituting the main trend. Four variables showed lower antibiotic use in boys therefore being an opposing trend and three variables were not significant. Whereas there appears to be evidence for higher antibiotic use in boys (five variables) overall, it is not possible to draw an overarching conclusion for the variable group because main trend and opposing trends as well as non-significant results level each other out. Using another example, the variable group “Disease diagnosis” offers clear evidence. 22 variables showed higher antibiotic use with certain disease diagnoses with only one variable opposing this. An additional ten variables were not significant. As opposed to “Paediatric: boys” here it appears reasonable to conclude that this variable group has a clear one-directional influence on antibiotic use.

4.4.4. Determinant category: compositional

The majority of studies (69/73) investigated compositional determinants, making it the category with the highest number of variables (325/592). Figure 7 presents the results of the variable groups, sorted alphabetically by the corresponding determinant groups. In total, 40 variable groups in 22 determinant groups were examined with seven variable groups being investigated by a single study only.

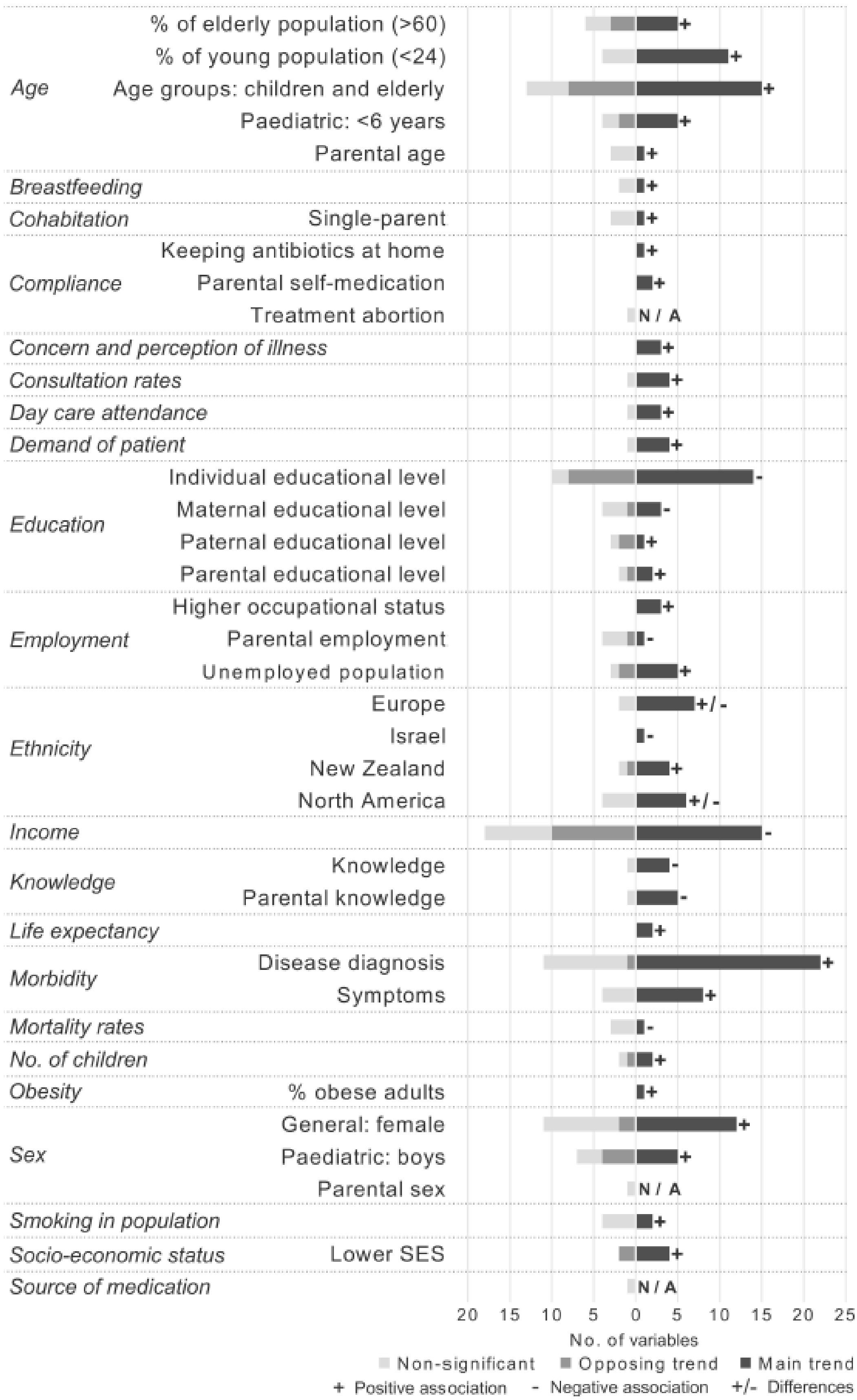


Figure 7. Influence of compositional variable groups on antibiotic use indicated by the main trend to the right and opposed by number of variables in the opposing trend and non-significant results. The direction is displayed as either positive, negative, differences or “not applicable (N/A)”. Determinant groups are displayed in italics.

4.4.5. Determinant category: contextual

Contextual determinants are the group with the second-most factors investigated (232/592) in the second-most studies (57/73). After extracting the data from the literature, contextual determinants could be grouped into 35 variable groups in 14 determinant groups as displayed in Fig. 8.

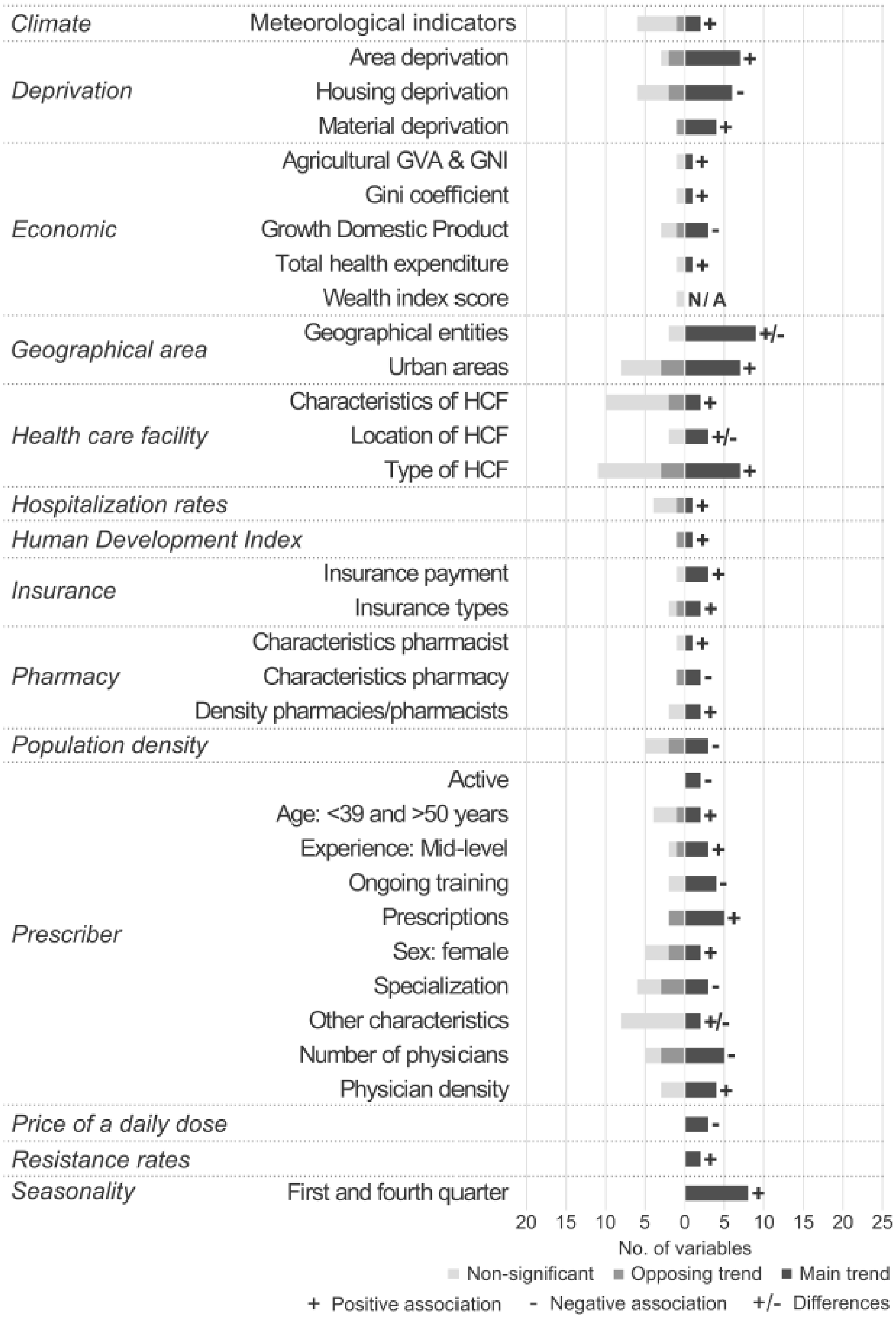


Figure 8. Influence of contextual variable groups on antibiotic use indicated by the main trend to the right and opposed by number of variables in the opposing trend and non-significant results. The direction is displayed as either positive, negative, differences or “not applicable (N/A)”. Determinant groups are displayed in italics.

4.4.6. Determinant category: collective

Figure 9 shows all ten determinant groups with their 27 variable groups categorized as collective determinants. In general, collective determinants were the least researched determinant category with only a few variables (44/292). The majority of variable groups (18/27) were examined by one study only, followed by variable groups with three studies (5/27) and two studies (4/27).

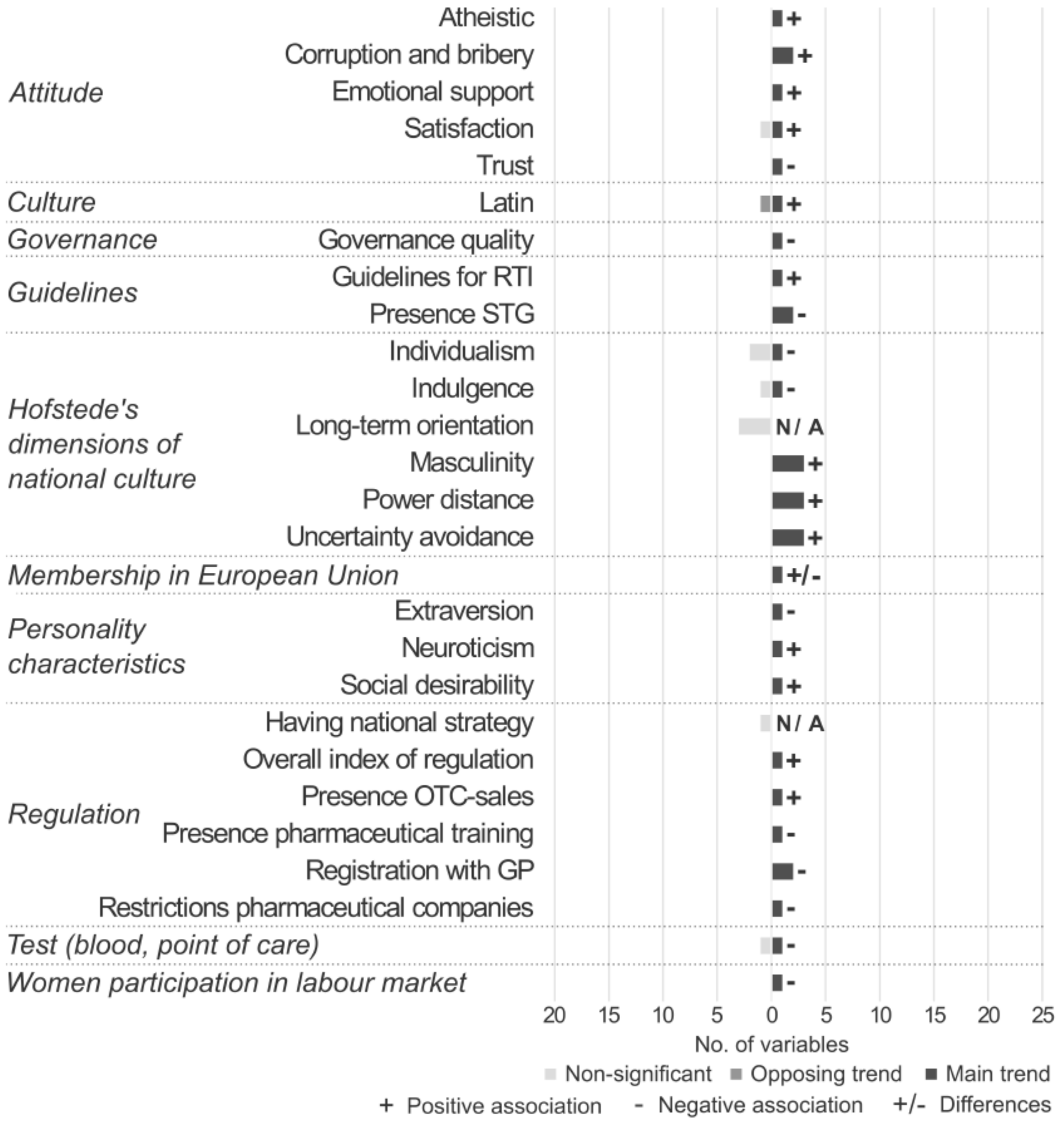


Figure 9. Influence of collective variable groups on antibiotic use indicated by the main trend to the right and opposed by number of variables in the opposing trend and non-significant results. The direction is displayed as either positive, negative, differences or "not applicable (N/A)". Determinant groups are displayed in italics.

4.4.7. Risk of bias across studies

Significant results, which were used to create the main and opposing trends, respectively, should be investigated with caution. They can rely on simple test statistics or be the result of a sophisticated regression model. However, they were grouped together to allow for a clearer results presentation.

4.5. Discussion

4.5.1. Summary of evidence

Categorizing the variables identified into compositional, contextual, and collective determinants revealed large differences in the amount of available evidence for each determinant category, determinant group, and variable group. Globally, there is an uneven distribution of evidence for determinants of antibiotic use in the community. The great majority of studies focused on WHO European Region, followed by the WHO Region of the Americas in which seven out of nine studies were conducted in either the US or Canada. This shows that the findings are biased towards higher-income countries (HIC) and western countries, highlighting that more evidence is needed from lower- and middle-income countries (LMICs) and other regions.

The varying amount of evidence on the determinant category level needs to be considered against the background of the reliance on secondary data in the majority of studies (53/73). Using secondary data often restricted the diversity of variables examined, creating a context in which the choice of variables seemed to be limited and pre-determined. Moreover, in the majority of studies, the choice of variables was rarely explained, justified or discussed but rather taken for granted. This may distort the evidence base towards variables, which are easier to document, more frequently surveyed, and therefore readily available in different databases, such as the demographic standards. This provides a potential explanation for the dominance of compositional determinants. This generates a situation in which the choice of variables appears to be led by a selection "off-the-shelf" approach rather than theory-guided (Mitchell et al., 2000).

4.5.2. Determinant category: compositional

Out of the younger (<24) and elderly (>60) population groups, particularly the age groups <15 and >65 years show positive associations with antibiotic use in the community, supported by studies examining several age groups that show similar trends. Findings in the paediatric population even refine the results for the younger population further by indicating higher antibiotic use in younger children (<6 years). Higher antibiotic use in the elderly population could be linked to increasing (co-)morbidity or higher susceptibility to infectious diseases. Aside from also higher susceptibility, higher antibiotic use in the younger population can possibly be explained through less treatment hesitance in case of uncertainty of a concrete diagnosis or parents' pressure. Concluding, this points to a U-shaped association between age and antibiotic use whereby antibiotic use is higher in the younger and elderly population.

The determinant group "Education" revealed that education influences antibiotic use differently in HICs and LMICs. Whereas there is a negative association with antibiotic use in HICs (12/14 variables), education exhibits a positive relationship with antibiotic use in LMICs (5/6 variables). This association, based on the individual educational level in the general population, also applies to results in the paediatric population, although less pronounced.

Regarding “Employment”, higher occupational status is linked to higher antibiotic use in three studies of which two were conducted in LMICs. The relationship of the unemployed population and antibiotic use was investigated in HICs by studies (6) on the country level indicating a positive association. Findings from the determinant group “Income” point in a similar direction. The main trend (negative association) consists exclusively of variables examined in HICs, whereby half of the variables making up the opposing trend (positive association) are from studies in LMICS.

Integrating the findings reveals further interesting insights. Education, employment, and income all show contrasting trends in the country groupings. Whereas education and income in HICs exhibit a negative association with antibiotic use, the main trend in LMICs is exactly the opposite. Moreover, the unemployed population in HICs indicates a positive relationship, while higher occupation status was linked to higher antibiotic use in LMICs. In addition, “Socio-economic status” (SES), often an aggregate of such indicators, also indicates higher antibiotic use with a lower SES in studies conducted in HICs. These findings highlight potential collinearity among these determinants.

It can only be speculated as to why and how those determinants work differently in those country groupings. In both HICs and LMICs, the disease burden is often higher with lower socio-economic status (due to various reasons). This trend is observable in the data for HICs where lower education, less employment, and lower income leads to higher antibiotic use. However, the opposite is true for data from LMICs. This contrary effect is possibly caused by the effect of access to health care services. In HICs, universal health coverage enables the whole society to seek medical advice and treatment at low to no cost, whereas in LMICs, private payments are often needed to get access to the health care system (Peters et al., 2008). The latter is reflected in the data where higher education, higher occupational status, and higher income are linked to higher antibiotic use in LMICs. Furthermore, poorer population groups in LMICs are often unable to access health services or utilize informal markets to purchase medication (Bloom et al., 2011), which leads to them not appearing in any statistics, highlighting the issue of data availability and data completeness.

Unsurprisingly certain “Symptoms” or “Disease diagnosis” increase antibiotic use as shown in the determinant group “Morbidity”. The evidence base for “Disease diagnosis” is larger than for “Symptoms”, which were investigated by twelve variables in only three studies. Overall, the influence of the determinant group “Morbidity” on antibiotic use was expected as it can be assumed that with certain disease diagnoses or symptoms, antibiotics are prescribed because curing infectious bacterial diseases is the main purpose of their use.

The main trend in the general population regarding “Sex” and antibiotic use points towards higher antibiotic use in females being opposed by mainly non-significant results. Findings in the paediatric population are less conclusive. Main and opposing trends both consist of variables tested in HICs only offsetting each other.

Age, morbidity, and sex are an example for potential confounding among the determinants of antibiotic use. Antibiotic use appears to be higher in females, different disease diagnoses are a strong predictor for antibiotic use, and antibiotic use was found to be higher in the younger and elderly population groups. Bringing those findings together, females around the world tend to live longer than males, and with increasing age, the likelihood for both sexes of acquiring multiple diseases (multi-morbidity) increases as well. Here again, we find an intertwined web of potential pathways of how those determinant groups possibly influence antibiotic use, which requires further investigation.

Lastly, also those variable groups are noteworthy, in which non-significant results prevail. The variable groups “Parental age”, “Breastfeeding”, “Single-parent”, “Parental employment”, “Mortality rates”, and “Smoking in the population” were all tested in at least two different studies. However, the majority of variables tested showed non-significant results implying that those variables may not influence antibiotic use.

4.5.3. Determinant category: contextual

In general, variable groups categorized as contextual show a greater within-group variation of variables than compositional determinants.

Main trends in the determinant group “Deprivation” should be treated with caution because of the diversity of variables included. Trends in “Area deprivation” and “Housing deprivation” are limited to HICs. In “Material deprivation” the main trend indicates a positive association with antibiotic use but encompasses seemingly contrary variables, i.e. “Receiving free access to selected medicine” (HIC) and “Having less access to medical care” (LMIC, antibiotic use without a prescription) are both positively associated with antibiotic use. However, this determinant group is a good example of how compositional (people) and contextual and collective (places) determinants may interact in shaping health outcomes. Concluding, aside from the variables in “Material deprivation”, deprivation in general probably does not affect antibiotic use directly but is rather a proxy for other underlying area factors, e.g. drivers of infectious diseases for which antibiotics are administered.

Owing to the variety of “Geographical entities” examined, ranging from local health units and county of residence over latitude to regions in Europe or US census regions, only differences were detectable. The results, therefore, confirm the basic assumption of this systematic review. In addition, antibiotic use appears to be higher in urban areas. This can be explained through the complex matter of availability and access to health care facilities, services, or medical personnel in urban and rural areas. Here again, we find a potential interlinkage with compositional determinants.

Examining variable groups in the determinant group “Health care facility” (HCF) reveals many non-significant results. The location and characteristics of HCF seem to not play any role, whereas the type of HCF, an indicator for the presence of different institutions, shows a positive association. In addition, no reliable trends can be identified for the determinant group “Pharmacy” due to its diversity of variables. These findings have two implications: 1) they hint at the importance of the existence of health care services and HCFs rather than its characteristics and 2) suggest that there may be additional factors that influence antibiotic use, e.g. the medical personnel working in such facilities.

“Prescriber” is the determinant group encompassing the most variable groups for a single determinant group, indicating high diversity. Owing to this variety, the variable group “Other characteristics” was introduced to cover characteristics that are not included in any of the other groups consisting mainly of non-significant results. Summarizing the results, prescribers, which are active, utilize training opportunities, are mid-age, have lower or higher experience than mid-level, are male, and specialized (vs. general practitioners) tend to prescribe fewer antibiotics. However, those findings need to be treated with great caution as the individual variable groups often consist of a few variables only and are sometimes opposed by an equal number of opposing variables and non-significant results. Moreover, the two variable groups “Age” and “Experience” as well as “No. physicians” and “Physician density” even contrast each other.

Higher antibiotic use in the first and/or fourth quarter of the year is an interesting outcome of the determinant group “Seasonality”. Seasonal variation is sometimes treated as an indicator for potential misuse of antibiotics for viral infections. However, secondary bacterial infections could also play a crucial role in explaining the seasonal variation of antibiotic use. This hypothesis could not be tested here. Linking this finding to meteorological indicators, however, does show that the latter does not have a strong influence on antibiotic use. The majority of indicators, i.e. average temperatures or precipitation, did not show any significant results, with only the “Yearly average dew point”, “The climatological Dantin-Revenga Index”, and “July average temperature” indicating some impact. Integrating those two outcomes hints at other driving factors for seasonality than meteorological variables.

4.5.4. Determinant category: collective

Collective determinants lag far behind in terms of numbers of variables investigated. In addition, the high volume of variable groups (27) with only 44 variables already shows that this determinant category is very heterogeneous. In this context, it is important to note that antibiotic stewardship programs were not explicitly targeted in this systematic review, which would, however, count as collective determinants already showing promising results. Overall, variable groups arranged as collective determinants are characterized by often consisting of a single variable only.

“Hofstede’s dimensions of national culture” were tested in three studies at the EU level in the general population, revealing a positive association between antibiotic use and masculinity, power distance, and uncertainty avoidance as well as a non-significant effect of long-term orientation. Masculinity describes a society that is more competitive thereby preferring work goal items such as earnings, recognition, advancement, and challenge over manager, cooperation, living area, and employment security (Hofstede et al., 2010). Employment and income are determinant groups that could play a role in this context in regard to antibiotic use. Power distance deals with “the way society handles inequality” (Hofstede et al., 2010, p. 54); about a direct connection with antibiotic use can only be speculated but availability and access to health care services could play a role. The association of uncertainty avoidance, i.e. ways to handle uncertainty and ambiguity (Hofstede et al., 2010), and antibiotic use can be established via the doctor-patient relationship. In both cases, patients or doctors, which are more careful and uncomfortable with uncertainty, might use or prescribe more antibiotics, respectively.

The majority of variable groups in the determinant group “Regulation”, i.e. registrations with GPs, restrictions on pharmaceutical companies, and continued pharmaceutical training show negative relationships with antibiotic use (Overall index of regulation: low scores approximated an increase in the level of regulation). Only the presence of over-the-counter (OTC) sales increases antibiotic use. In this line, governance quality and Standard Treatment Guidelines (STG) for hospital care and paediatric conditions are also linked to lower antibiotic use. Contextualizing these findings, this evidence is based on three studies conducted exclusively on the EU-level.

There is an interlinkage between regulatory determinants and contextual determinants. “Price” is also negatively associated in three studies with antibiotic use offering an additional potential intervention point for regulators.

4.5.5. Limitations

Categorizing and grouping the determinants enabled a more detailed analysis providing insightful findings. However, the procedure of creating the categories and groups albeit being based on transparent criteria is ultimately a subjective process. This applies particularly to those variable groups that were formed based on the second criterion, i.e. closely linked variables (that did not use the same wording). In order to minimize introducing potential bias by following this procedure, it was decided to create variable groups on the lowest common denominator before grouping them into determinant groups.

The heterogeneity of studies included in terms of methodologies and settings is simultaneously advantage and limitation of this systematic review. This explorative and inclusive approach allowed for the identification of a variety of variables. However, due to the heterogeneity of methods applied in the included studies, it was not possible to conduct a meta-analysis. The resulting trends of the variables can therefore only be understood as signposts indicating the direction of a potential influence of this variable on antibiotic use. In the same line of argument, the heterogeneity did not allow for a consistent quality assessment of the included studies. However, relying exclusively on peer-reviewed literature may have helped to attenuate the introduction of potential bias.

Lastly, antibiotic use was the outcome measure of interest, which in itself is quite diverse, including administered, claims and reimbursement, dispensing, prescription, sales, and actual self-reported use. Besides the last category, which is also prone to reporting bias, all others are only proxies for a potential consumption of antibiotics. In addition, all of them imply that there is a reporting system in place, in which data can be collected. This might also be the reason, why LMICs are under-represented as they often lack the availability of reliable data.

4.6. Conclusion

Determinants of antibiotic use in the community are manifold. This systematic review identified 592 variables grouped into 46 determinant groups, subsequently categorized as compositional, contextual and collective. Applying this categorization revealed varying evidence bases with compositional determinants being researched the most, followed by contextual and collective. It, therefore, allowed for an analysis of potential area effects on antibiotic use in the outpatient sector highlighting the importance of both people and places.

For compositional determinants, an integrated analysis of education, employment, and income revealed contrary effects of those determinant groups on antibiotic use in HICs and LMICs, potentially through differences in the availability of and access to health care services. In addition, age, morbidity, and sex also exhibit clear trends. Also noteworthy are determinant groups in which non-significant results prevail. In this context, cohabitation, mortality, and smoking appear to not influence antibiotic use significantly. Contextual determinant groups showed a greater within-group variation and less obvious trends. Determinants that present potential area effects, including deprivation, indicate a clear relationship with antibiotic use. Seasonality also seems to be a strong predictor of antibiotic use. Variables around health care services, i.e. health care facility, pharmacy, and prescriber, produced many non-significant results with weak main trends. Regarding collective determinants, only Hofstede's dimensions of national culture and regulation offer some insights.

As argued by Macintyre et al. (2002), compositional, contextual and collective should not be treated as mutually exclusive categories. Findings from this systematic review support this argument as there are several determinant groups, e.g. deprivation and education, income and employment, or regulation and price that indicate interactions between different determinant categories. Therefore, research emphasis should be placed on both people and places when considering health outcomes.

The findings of this systematic review raise several questions around pathways of how certain variables influence antibiotic use calling for disentangling the complex web of determinants. Due to the reliance on secondary data and the associated selection "off-the-shelf" approach, it was often not possible to test for other (confounding) variables other than those readily available from the respective database. This calls for more primary studies with a greater focus on individual determinants. In addition, the evidence is biased towards HICs and western countries, sometimes not allowing for any conclusions drawn for LMICs or other regions, demanding more research in those countries.

Overall, the results function as signposts of potential relationships between variables and antibiotic use in the community and the outpatient sector thereby pinpointing starting points for further research and interventions.

5. Associations between socio-spatially different urban areas and knowledge, attitudes, practices and antibiotic use: a cross-sectional study in the Ruhr Metropolis, Germany

This chapter was submitted as: Schmiege, D., Falkenberg, T., Moebus, S., Kistemann, T., Evers, M. (*under review*): Associations between socio-spatially different urban areas and knowledge, attitudes, practices and antibiotic use: a cross-sectional study in the Ruhr Metropolis, Germany.[7]

5.1. Abstract

Inappropriate and excessive antibiotic use fuels the development of antibiotic resistance. Determinants of antibiotic use, including knowledge and attitudes, are manifold and vary on different spatial scales. The objective of this study was to examine the associations between socio-spatially diverse urban areas and knowledge, attitudes, practices and antibiotic use within a metropolitan city. A cross-sectional survey was conducted in the general population in socio-spatially different areas in Dortmund, Germany, in February and March 2020. Three urban areas were chosen to represent diverse socio-spatial contexts (socio-spatially disadvantaged: A, intermediate: B, socio-spatially disadvantaged: C). Participants were selected via simple random sampling. The questionnaire comprised knowledge and attitude statements and questions around antibiotic use and handling practices. Differences between the areas were examined by estimating odds ratios (OR) and corresponding 95% confidence intervals by multiple logistic regression. Overall, 158 participants were included. Participants of Area C showed the lowest proportions of correct knowledge statements, indicated more often attitudes contrary to common recommendations, lower risk awareness and reported more often antibiotic use (C: 40.8%; A: 32.7%; B: 26.5%) and potential mishandling practices (C: 30.4%; A: 9.6%; B: 17.3%). The multiple logistic regression confirmed these differences. Around 42.3% (C), 33.3% (A) and 20.0% (B) of the diseases mentioned for which an antibiotic was used are mainly caused by viral pathogens. A common misconception across all areas was the perception of antibiotic resistance as an individual rather than a universal issue. This study reveals distinct differences between socio-spatially diverse urban areas within a metropolitan city, regarding knowledge, attitudes and practices around antibiotics and ABR. Our findings confirm that enhanced efforts are required to better inform the population about

[7] The numbering of figures and tables was changed to consecutive numbers.

the adequate use and handling of antibiotics. This study emphasizes the need for future interventions to be tailored to the specific local socio-economic context.

5.2. Introduction

More than 700,000 deaths per year are attributable to drug-resistant infections globally (IACG WHO, 2019), with a projected increase that reaches into the millions in coming decades. Antibiotic resistance (ABR), a natural process whereby bacteria become resistant against antibiotics commonly used to treat infections caused by them (Davies & Davies, 2010), is already a serious global health concern. Antibiotic-resistant infections are not just linked to higher mortality, but also associated with higher morbidity, longer hospital stays and higher medical costs (Laxminarayan et al., 2013; Naylor et al., 2018).

Inadequate and excessive use of antibiotics in humans, animals and plants, have been identified among the key drivers of this “silent pandemic” (Chatterjee et al., 2018; Laxminarayan et al., 2020). Antibiotic consumption in human medicine has increased globally between 2000 and 2015 (Klein et al., 2018) and varies on different spatial scales. For instance, from between countries differences (A. Blommaert et al., 2014) down to intra-urban variations (Henricson et al., 1998; Togoobaatar et al., 2010), and between health care sectors with the great majority of antibiotics used in the community (i.e. outpatient settings) (ECDC, 2020a).

Determinants of antibiotic use in the community are manifold, including individual-related (i.e. compositional) and space-related (i.e. contextual and collective) factors (Schmiege et al., 2020). Identifying modifiable determinants on both the supply (e.g. prescriber) and demand (e.g. patients) sides is crucial to improve the appropriate and further reduce antibiotic use. The general population occupies thereby a pivotal role. Among other determinants of antibiotic use, such as the socio-economic status of patients (Adriaan Blommaert et al., 2013; Hjern et al., 2001; Nitzan et al., 2010; Sahin et al., 2017), knowledge and attitudes towards antibiotic use have also been identified as influencing factors (Zanichelli et al., 2019).

Educational interventions as one component of multifaceted strategies to tackle ABR were anchored in the World Health Organization’s (WHO) Global Action Plan on Antimicrobial Resistance (WHO, 2015b) and subsequently transferred into national action plans, including the German strategy (The Federal Government, 2015). A systematic review on the effectiveness of interventions to improve awareness and behaviour revealed a notable potential in schoolchildren and parents and less clear evidence for the general public (Price et al., 2018). However, identifying and analysing public knowledge and attitudes on antibiotics and ABR, as well as handling practices are important first steps towards assessing patients’ demands and needs. The resulting insights can be used to inform awareness-raising campaigns and to design effective public health policies to tackle ABR.

Previous knowledge, attitude and practice (KAP) studies have focused on various population groups in different countries, e.g. the general population (André et al., 2010; Awad & Aboud, 2015; Effah et al., 2020; El-Hawy et al., 2017; Mouhieddine et al., 2015; Raupach-Rosin et al., 2019; Shebehe et al., 2021; Vallin et al., 2016), (medical) students (Higuita-Gutiérrez et al., 2020; Jairoun et al., 2019; Nogueira-Uzal et al., 2020; Sakr et al., 2020), parents (Napolitano et al., 2013), pilgrims (Yezli et al., 2019) or pharmacists and physicians (Mason et al., 2018; Waseem et al., 2019). As antibiotic consumption and its determinants show spatial variation, patients' demands and needs also vary between and within countries, assumingly also on intra-urban levels, e.g. between different neighbourhoods. However, research, particularly on this geographical aspect and differences between socio-spatially diverse urban areas, is scarce.

In Germany, dispensing volumes of antibiotics were higher in veterinary as compared to human medicine in 2016 (German Environment Agency, 2018) but have significantly decreased since, now being on comparable levels (Wallmann et al., 2020). Regarding human medical treatment, around 85% of antibiotics were used in the outpatient sector (BVL & PEG, 2016) with spatial differences down to the city level (data from (KV Westphalia-Lippe, 2020)). However, there is a paucity of KAP research on antibiotics and ABR in Germany and on intra-urban differences. One study in the federal state Lower Saxony identified good knowledge on antibiotics but limited knowledge on ABR, multi-drug resistant pathogens, and their consequences (Raupach-Rosin et al., 2019). Limited knowledge on the application of antibiotics, inappropriate patient expectations, as well as a discrepancy between knowledge and action, were also highlighted by another survey among 3,100 German-speaking persons (DAK-Gesundheit, 2014).

The rationale of this study was therefore twofold. First, contributing to closing the knowledge gap on KAP regarding antibiotics and ABR in Germany and secondly, examining the associations between KAP, antibiotic use and socio-spatially diverse urban areas. The household survey aimed to assess knowledge and attitudes on antibiotics and ABR, as well as self-reported antibiotic use and handling practices in the general population of three socio-spatially different sub-districts within one city in the Ruhr Metropolis, Germany. This approach allows for the identification of common misconceptions (i.e. across all areas) and potential differences between diverse urban areas and thereby enable more tailored educational or behavioural interventions.

5.3. Material and methods

This study was designed as a cross-sectional, observational study using a structured questionnaire in the adult general population in the city of Dortmund, Germany. The reporting of this study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (von Elm et al., 2008). Tablet-based face-to-face interviews were conducted in the German language in February and March 2020 mainly on weekdays. One weekend day was chosen in addition in each area to reduce sampling bias. Study participants were interviewed in their homes. For this publication, statements were translated into English. All study participants were older than 18 years. Before the interview, they were informed about the nature of the study and provided written informed consent[8]. The Ethics Commission of the medical faculty of the University of Bonn approved this study (registration number: 052/20)[9].

5.3.1. Selection of study areas and sampling procedure

The city of Dortmund is the most populated city in the Ruhr Metropolis with distinct social and ethnic segregation that also translates into health-related environmental inequalities (Flacke et al., 2016). It ranked second in antibiotic use among the 26 cities and municipalities in the region in 2019 (ATC group J01; data from (KV Westphalia-Lippe, 2020)).

In a previous study in the German population, age, immigration status and self-assessed social status were associated with limited health literacy (Schaeffer et al., 2017). Accounting for this and also the socio-economic north-south gradient of the city (Stadt Dortmund, 2019), a multistage sampling approach was used. In the first stage, three urban areas (i.e. Erpinghof, Lohbach and Osterholz) were chosen based on previous studies (Ammon et al., 2011; Stadt Dortmund, 2007, 2018) to represent distinct socio-spatial contexts. Figure 10 displays the differences of socio-spatial indicators between the areas (for detailed information on the indicators see S1 Table[10]). For easier reference, the areas are referred to as Erpinghof – “Area A”, Lohbach – “Area B” and Osterholz – “Area C”.

Differences are particularly observable between Area B and Area C whereas Area A is often located in between those. Area B exhibits a lower share of settlement and traffic area, the lowest population density, the highest living space per inhabitant, and the highest share of flats in one- or two-family houses. It also displays the lowest shares of households with children or foreigners. In terms of socio-economic indicators, the shares of the unemployed population and recipients of state transfer payments are lowest in Area B. Overall, those indicators point towards a comparatively socio-spatially advantaged situation in Area B compared to the other two areas.

[8] The consent form can be accessed in chapter ii.a in the appendices.
[9] The ethical approval can be accessed in chapter ii.b. in the appendices.
[10] Supplementary material S1 of this manuscript can be accessed in chapter ii.c in the appendices.

Figure 10. Socio-spatial structure of the three selected study areas (Data source: Stadt Dortmund, 2019)

In a second step, residential buildings in the three areas were randomly selected. Shapefiles containing all buildings in the respective areas were downloaded (TIM-online, https://www.tim-online.nrw.de/tim-online2/) and prepared for the sampling procedure by selecting only buildings with the official function "residential house". These steps were implemented in QGIS (QGIS Development Team, 2021). Accounting for the different shares of flats in one- and two-family houses between the three areas (see Figure 1), the number of buildings sampled was higher in Area B (300 compared to 200 in Areas A and C). All households in a selected residential building were considered eligible for participation. The study population encompassed all adults (above 18 years) living in one of the three socio-spatially different areas in the city of Dortmund.

Announcement flyers[11] (not revealing the actual topic of the survey to avoid introducing bias) were distributed two weeks before the survey to allow selected households to withdraw before being approached.

5.3.2. Questionnaire

The theoretical framework of this study and the development of the questionnaire were both informed by the KAP model, which postulates that increasing a person's knowledge will prompt a behaviour change (WHO, 2012). The structured questionnaire[12] consisted of four parts: i) knowledge of antibiotics and ABR, ii) attitudes towards antibiotic use and risk awareness of

[11] The announcement flyer can be accessed in chapter ii.d in the appendices.
[12] The full questionnaire of the household survey can be accessed in chapter ii.e in the appendices.

ABR, iii) handling practices and antibiotic use, and iv) demographic standards. Previously tested and used questions were selected from other KAP studies (André et al., 2010; Awad & Aboud, 2015; Jairoun et al., 2019; McNulty et al., 2007; USAID et al., 2008; WHO, 2015a) to ensure comparability. The questionnaire was discussed and refined in different research groups and pre-tested with a few people outside of academia to ensure comprehensibility and determine its duration.

Knowledge on antibiotics and ABR were inquired with nine statements that were read to the participants and to which they were asked to indicate whether they are correct, false or "Don't know". Regarding antibiotics, knowledge was assessed based on five statements covering aspects of efficacy against bacteria and viruses, possible medical indication for the flu and common colds and urinary tract infections (UTI), as well as side effects of antibiotics. For ABR, knowledge statements covered aspects around the consequences of over- and misuse of antibiotics, the interconnectedness of agriculture and human medicine, and the potential consequences of ABR.

Attitudes towards antibiotics and risk awareness of ABR were investigated via five statements each to which participants were asked to respond on a five-point Likert scale from "strongly disagree" to "strongly agree". Attitudes towards antibiotics included the following aspects: behaviour when sick with flu or a common cold and requesting information from the physician when no antibiotic is prescribed, termination of antibiotic treatment when feeling better, keeping antibiotics at home, and passing on antibiotics to relatives or friends. Regarding the risk awareness of ABR, study participants were asked about ABR as an issue on different spatial scales from the global to the family and individual level, ABR as an issue only for those that take antibiotics, and future effectiveness of antibiotics against the same disease.

Inquiring handling practices of antibiotics, study participants were asked whether any household member has ever used an antibiotic to filter out those that never used any. Three questions on their handling practices followed covering the source of antibiotics, general treatment adherence, and disposal of antibiotics. For each question, interviewees could choose multiple times from a pre-determined list of answers. For all statements, questions and corresponding answers in German and English language see S2 File (Part A)[13].

Allowing for socio-economic detailed analyses, the demographic items were assessed, including age, gender, origin, civil status, education, training, employment situation, occupational sector, participant's and household net income, religious beliefs and health insurance. The questions are based on the German Federal Statistical Office (Beckmann et al., 2016).

[13] Supplementary material S2 of this manuscript can be accessed in chapter ii.f in the appendices.

5.3.3. Data analysis

All statistical analyses were implemented using R (version 4.1.0, (R Core Team, 2021)). Multiple logistic regression was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI). Outcomes of interest were low knowledge, attitudes contrary to common recommendations, lower risk awareness, potential mishandling or antibiotic use. The outcome variables and covariates including their respective coding are shown in S2 File (Part B). The minimal sufficient adjustment sets were derived using directed acyclic graphs (Shrier & Platt, 2008; Suttorp et al., 2015). Univariate ORs for the area variable were adjusted for confounding by including the following variables in the multivariate analysis: age, immigration background, family status and household income.

In case of a high prevalence of the outcome in cross-sectional studies, the estimation of prevalence ratios (PR) should be preferred because ORs can have some limitations (e.g. overestimation) (Barros & Hirakata, 2003; Deddens & Petersen, 2008; Tamhane et al., 2016). However, problems of convergence are a known issue of log-binomial models used to estimate PRs (Behrens et al., 2004), which was also encountered in this study when adjusting for confounders. Following Zocchetti et al. (Zocchetti et al., 1997), the prevalence of outcomes and exposures in this study are in the majority of cases within a value range in which the overestimation by OR is tolerable. As the focus of our analyses was more on the direction of the effect estimators, it was deemed justified to use ORs to estimate associations.

5.4. Results

The sampled buildings in the three study areas contained 2,396 possibly accessible household units (i.e. no vacancy, functional doorbells) of which 1,382 could be contacted. In total, 158 interviews were conducted before the household survey had to be cancelled prematurely in mid-March 2020 due to the COVID-19 pandemic. This marks a response rate of 11% (158/1,382; Area A: 12% (52/434); Area B: 16% (50/305); Area C: 9% (56/643)). Study participants were almost equally distributed between the three areas. Table 8 illustrates the demographic and socioeconomic characteristics of the interviewees.

Characteristics of the study participants varied profoundly between the three areas with Area B and Area C often showing opposing situations. Compared to Area B, study participants in Area C were younger, less often in a partnership, more often immigrants or descendants of immigrants, had lower education and reported more often incomes below the national average. Except for the indicator gender, characteristics of study participants in Area A were usually positioned between Areas B and C. The distribution of demographic and socio-economic indicators of the study participants between the three areas mirrors the socio-spatial situation indicated by the official city statistics (see Figure 10).

Table 8. Demographic and socioeconomic indicators of the study participants grouped by area

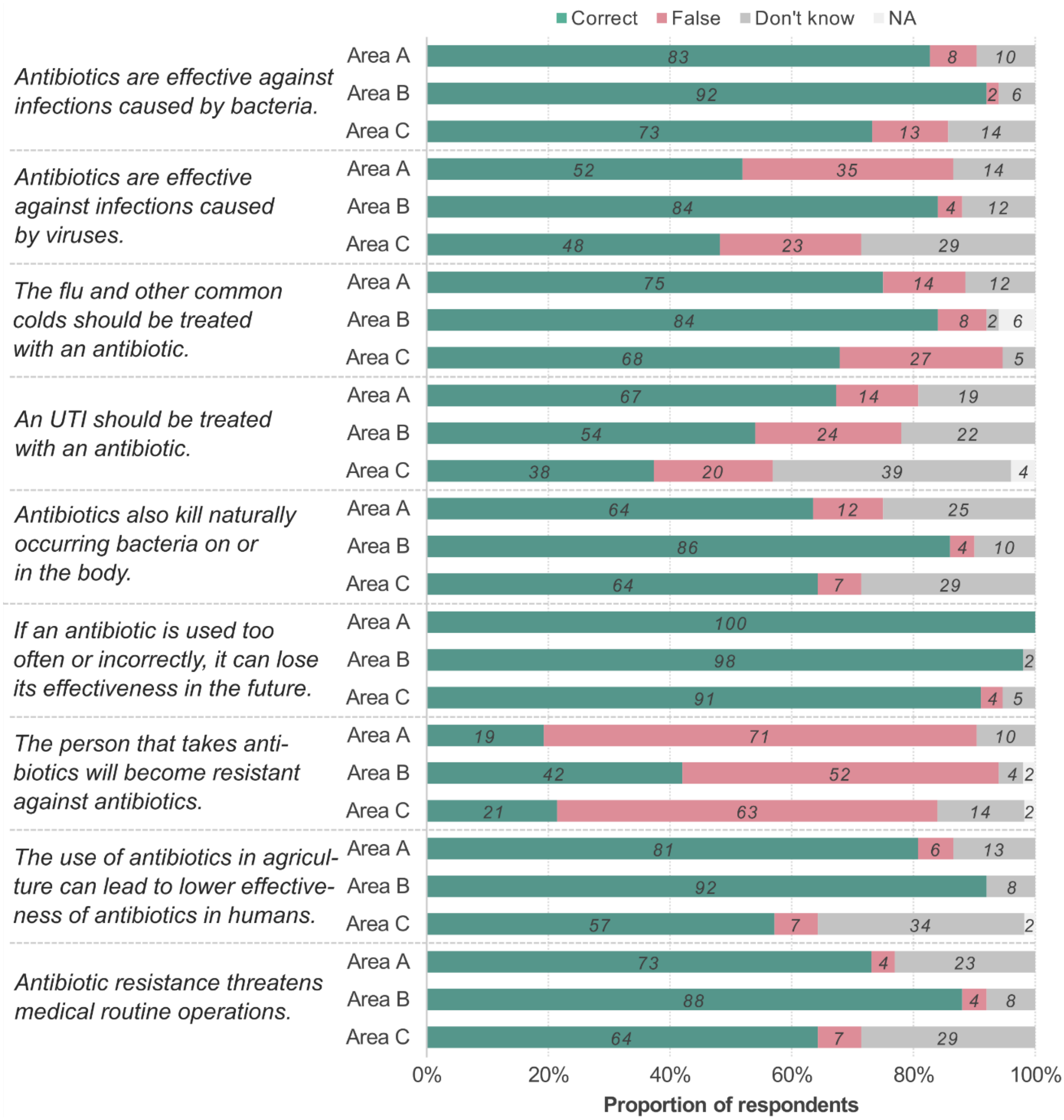
Indicator		**Area A (n=52)** n (%)	**Area B (n=50)** n (%)	**Area C (n=56)** n (%)
Age	Median [Q1-Q3]	48.5 [35.8-63.0]	63 [50.0-70.0]	30 [23.5-41.5]
Gender	Female	29 (55.8)	24 (48.0)	25 (44.6)
	Male	23 (44.2)	26 (52.0)	30 (53.6)
	Diverse	0 (0.0)	0 (0.0)	1 (1.8)
Family status	No partnership	17 (32.7)	18 (36.0)	36 (64.3)
	In a partnership	35 (67.3)	32 (64.0)	20 (35.7)
Origin	German	35 (67.3)	40 (80.0)	19 (33.9)
	Immigrant or descendant of immigrant	17 (32.7)	10 (20.0)	37 (66.1)
Education	Secondary	9 (17.3)	5 (10.2)	20 (37.0)
	Post-secondary non-tertiary	29 (55.8)	19 (38.8)	15 (27.8)
	Tertiary	14 (26.9)	25 (51.0)	19 (35.2)
Income	Median group (€)	1500-1999	2000-2499	1000-1499
	Below the national average	29 (56.9)	17 (36.2)	46 (85.2)
	Equal to or above the national average	22 (43.1)	30 (63.8)	8 (14.8)
Occupational sector	Health and social	9 (17.3)	14 (28.0)	15 (26.8)
	Other	43 (82.7)	36 (72.0)	41 (73.2)

Percentages may not add up to 100% because of rounding. Missing values occurred for age, education and income but were overall very low (max. n=3 for income in Area B).

5.4.1. Spatial variation of knowledge on antibiotics and antibiotic resistance

Participants were asked to indicate for nine knowledge statements whether they are correct or false. Figure 11 illustrates the proportion of interviewees answering the statements correctly segregated by research area. If respondents stated rightly that a statement was false, this was re-coded as answering the statement correctly for this figure.

For the majority of statements, more than half of the respondents answered correctly. Study participants in Area B showed the highest proportions of correct answers to most knowledge statements (except for the UTI and the future effectiveness statements). On the contrary, interviewees in Area C often displayed the lowest proportions. The proportion of respondents answering correctly in Area A was often between the other two areas.



Area A: n=52; Area B: n=50; Area C: n=56. UTI – urinary tract infection. Statements were re-coded that rightly stating a statement was false is shown as "correct".

Figure 11. The proportion of study participants replying to the knowledge statements grouped into the three areas

Knowledge of the majority of study participants on the effectiveness of antibiotics against bacteria was better as compared to viruses. Regarding indications for antibiotic use, most interviewees in all areas knew that antibiotics are not indicated for flu or common colds. However, certainty among respondents was much lower for UTIs indicated by higher proportions of "Don't know". More than two-thirds of study participants were aware of side effects, the connection to the agricultural sector and possible consequences of ABR. The great majority of study participants in all areas answered correctly about the future effectiveness of antibiotics. A common misconception across all areas was that people (and not bacteria) would become resistant to antibiotics. Table 9 presents the association between the area variable and respective eight knowledge statements.

Table 9. Association between false knowledge statements and urban areas (Reference: Area C)

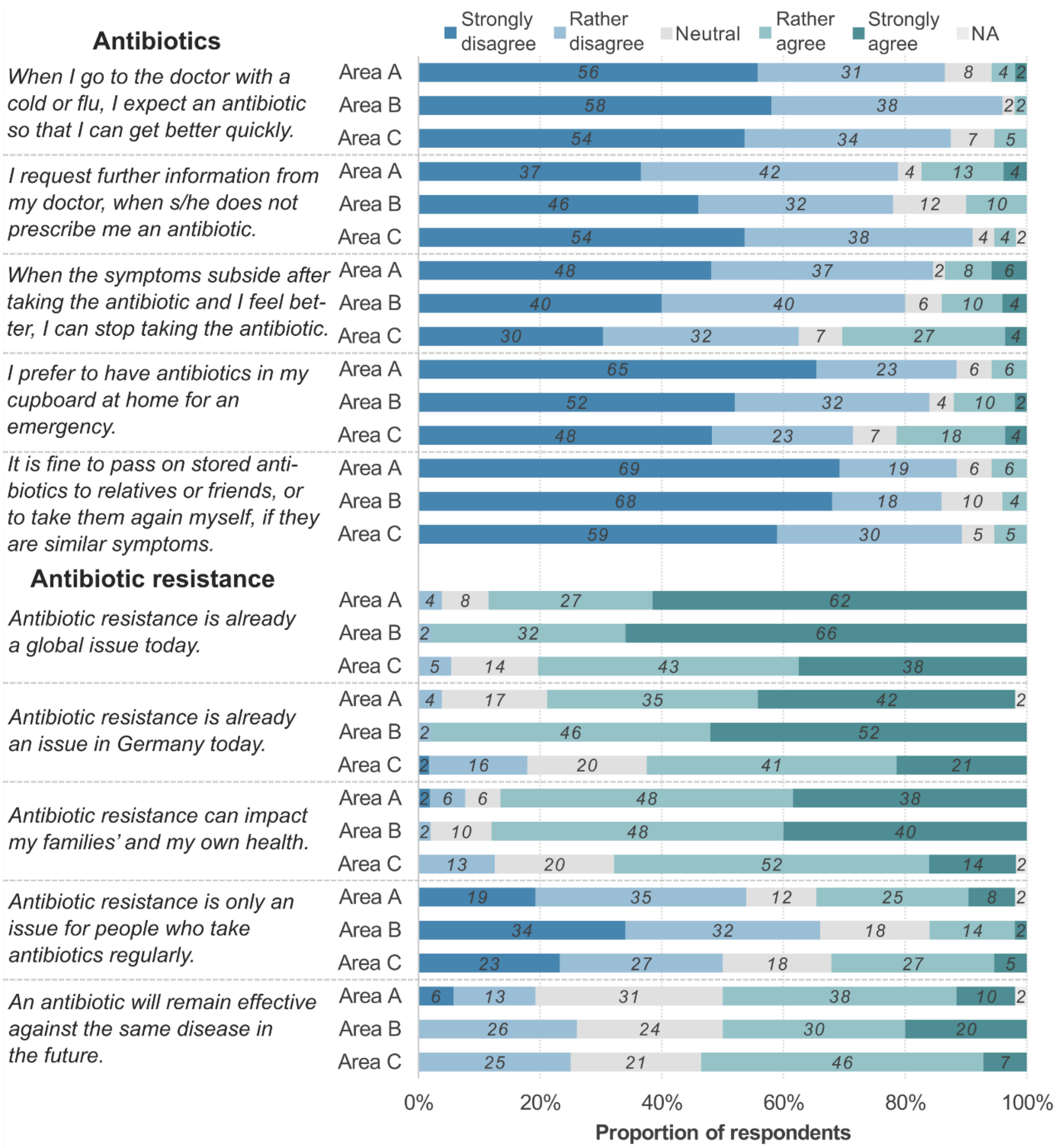
Knowledge statement	Area A Crude OR [95% CI]	Area A Adjusted OR[a] [95% CI]	Area B Crude OR [95% CI]	Area B Adjusted OR[a] [95% CI]
Effective against bacteria	0.57 [0.22-1.43]	0.54 [0.16-1.70]	**0.24** [0.06-0.72]	0.27 [0.05-1.15]
Effective against virus	0.86 [0.40-1.84]	1.03 [0.40-2.64]	**0.18** [0.07-0.43]	**0.24** [0.07-0.74]
Antibiotic use indicated for flu	0.70 [0.30-1.62]	1.09 [0.40-2.96]	**0.25** [0.08-0.70]	0.53 [0.13-2.00]
Antibiotic use indicated for UTI	**0.31** [0.14-0.68]	**0.34** [0.13-0.85]	0.54 [0.25-1.18]	0.64 [0.22-1.83]
Side effects of antibiotic use	1.04 [0.47-2.28]	0.83 [0.31-2.15]	**0.29** [0.10-0.74]	**0.16** [0.04-0.56]
Person becomes resistant	1.17 [0.46-3.06]	1.73 [0.59-5.26]	**0.37** [0.15-0.86]	0.48 [0.15-1.48]
Connection to agricultural sector	**0.33** [0.13-0.78]	0.66 [0.23-1.90]	**0.12** [0.03-0.35]	0.42 [0.09-1.64]
Threat to medical operations	0.66 [0.29-1.50]	1.22 [0.46-3.30]	**0.25** [0.08-0.64]	0.49 [0.13-1.68]

[a] Adjusted for age, immigration background, family status and household income; UTI – urinary tract infection; OR >1 indicates an increased chance of replying incorrectly; the OR for the future effectiveness statement could not be calculated due to very low numbers of false replies.

Adjusted ORs for replying falsely to the knowledge statements were consistently lower in Area B indicating higher knowledge. The differences between Areas C and A were less clear pronounced. Whereas for some knowledge statements adjusted ORs were lower, they were higher for others. Three statements ranged closely around one revealing a rather comparable situation between those two areas.

5.4.2. Spatial variation of attitudes towards antibiotics and antibiotic resistance

Attitudes towards antibiotics and risk awareness of ABR were queried via five statements each. Figure 12 depicts the attitudes of study participants towards antibiotics and ABR in the three areas.



Area A: n=52; Area B: n=50; Area C: n=56

Figure 12. The proportion of study participants replying to the attitude statements grouped into the three areas

The great majority of study participants rather or strongly disagreed with the statements on expectations to receive an antibiotic when visiting the doctor because of flu or a cold, requesting further information from the doctor in the absence of an antibiotic prescription, as well as sharing behaviour or re-use of antibiotics. Only for the statements on treatment adherence and storage willingness, some participants revealed attitudes contrary to common recommendations. About 14% of respondents in Area A and Area B, as well as 27% in Area C rather or strongly agreed that they could stop taking an antibiotic once they feel better. Around 22% of interviewees in Area C rather or strongly agreed that they prefer to store antibiotics at home.

The majority of study participants considered ABR already a global issue today. The numbers slightly declined when moving from the global level to Germany and remained stable when considering ABR as an issue at the family level. About 16% (Germany) and 13% (family) of interviewees in Area C rather or strongly disagreed with these statements. More than half of respondents in all areas rather or strongly agreed that ABR is only an issue for persons who take antibiotics regularly. Comparable to the knowledge statement, this presents an apparent misconception across areas. Half of the study participants in each area rather or strongly agreed that antibiotics will retain their effectiveness in the future. Table 10 illustrates the association of the area variable with the ten attitude statements.

Table 10. Association between attitudes contrary to common recommendations or low risk awareness and urban areas (Reference: Area C)

	Area A		**Area B**	
	Crude OR [95% CI]	Adjusted OR[a] [95% CI]	Crude OR [95% CI	Adjusted OR[a] [95% CI]
Attitudes				
Expect an antibiotic	1.09 [0.35-3.42]	1.99 [0.54-7.69]	0.29 [0.04-1.28]	0.87 [0.10-5.30]
Request further information	**3.42** [1.08-13.07]	1.61 [0.42-6.95]	**3.60** [1.13-13.77]	1.45 [0.32-7.10]
Discontinue when symptoms subside	**0.30** [0.11-0.74]	0.50 [0.17-1.39]	**0.42** [0.17-0.98]	0.79 [0.23-2.66]
Have antibiotics at home	**0.33** [0.11-0.88]	0.65 [0.19-2.12]	0.48 [0.18-1.21]	2.17 [0.53-9.60]
Pass on antibiotics	1.09 [0.32-3.71]	2.51 [0.61-11.50]	1.36 [0.42-4.51]	4.27 [0.88-23.32]
Risk awareness				
ABR as global issue	0.53 [0.17-1.53]	0.83 [0.22-3.04]	**0.08** [0.00-0.45]	0.28 [0.01-2.34]
ABR as issue for Germany	0.46 [0.19-1.07]	1.14 [0.38-3.45]	**0.03** [0.00-0.17]	**0.15** [0.01-0.98]
ABR can impact family and own health	**0.32** [0.11-0.82]	0.43 [0.13-1.29]	**0.28** [0.09-0.74]	0.54 [0.13-1.99]
Only issue for people taking antibiotics	0.82 [0.38-1.76]	1.60 [0.61-4.32]	0.52 [0.23-1.12]	1.06 [0.34-3.35]
Antibiotics will remain effective in future	1.20 [0.56-2.58]	1.68 [0.66-4.39]	1.15 [0.54-2.49]	1.41 [0.49-4.15]

[a] *Adjusted for age, gender, immigration background, family status, household income and occupational sector; ABR: antibiotic resistance; OR >1 indicates increased chance of replying contrary to common recommendations (attitudes) and lower risk awareness (risk awareness).*

Study participants in Area A displayed greater adjusted OR for expecting an antibiotic. Living in Areas A and B was associated with greater adjusted OR for requesting further information and passing on antibiotics to relatives or friends. On the contrary, interviewees in both areas showed lower adjusted OR for discontinuing the antibiotic treatment when the symptoms subside.

Overall, living in Area B was associated with consistently lower adjusted ORs of perceiving ABR as a global issue, for Germany and at the family level. Study participants in Area A, on the other hand, showed similar or greater adjusted ORs (except for ABR impact on families' and own health). ORs were similar or greater in Areas A and B for considering ABR an issue only for those people that take antibiotics and the future effectiveness of antibiotics.

5.4.3. Spatial variation of handling practices of antibiotics and self-reported antibiotic use

Antibiotic handling practices, including the source of antibiotics, general treatment adherence, and disposal, were assessed via three questions (see S3 Figs[14]). Around 87% of participating households have ever used an antibiotic, most of them prescribed from a physician (inpatient and/or outpatient). Only one respondent in Area B and three in Area C indicated that they used an old package. Most of the respondents either followed the doctor's instructions or used the package completely but some reported using an antibiotic until they feel better (Area A: 2.9%, Area B: 3.2%, Area C: 14.8%). Regarding the disposal, participants mentioned most often to consume all antibiotics, return the package to the pharmacy and/or dispose of in the domestic or special waste. Respondents in each area also indicated storing antibiotics at home (Area A: 6.7%, Area B: 11.1%, Area C: 21.4%). None of the interviewees disposed of antibiotics into the toilet, which is much lower as identified in another survey in Germany (15%) (Schreiber, 2011). The statistical analysis of the three reported possible mishandling practices (i.e. using an old package, stop treatment when feeling better and storing antibiotics at home) revealed lower adjusted OR in Area A (0.40, 95% CI: 0.11-1.29) and greater OR in Area B (1.58, 95% CI: 0.44-5.96) compared to Area C.

One-third of the participants (49) reported antibiotic use within the last 12 months (i.e. March 2019-March 2020) amounting to 69 antibiotic treatments (including household members: 95 people and 151 treatments). Self-reported antibiotic use of the interviewees followed a seasonal trend with increasing reported consumption in autumn and the highest values in winter months (47.9% of all mentions). Spatially, most antibiotic use was reported in Area C (40.8%), followed by Area A (32.7%) and Area B (26.5%), translating in adjusted ORs of 0.44 (95% CI: 0.16-1.21) and 0.80 (95% CI: 0.26-2.50) compared to reference Area C. Antibiotics were prescribed in 42.3% (Area C), 33.3% (Area A) and 20.0% (Area B) of the cases for diseases, which are predominantly caused by viral pathogens (i.e. cold, flu and pharyngitis).

5.5. Discussion

This study reveals overall a relatively good knowledge, attitudes that can be evaluated positively, high risk awareness and low mishandling with distinct spatial variation between the three socio-spatially different areas.

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[14] Supplementary material S3 of this manuscript can be accessed in chapter ii.g in the appendices.

The proportions of interviewees answering correctly to the knowledge statements are within similar value ranges compared to other studies in the general population in European countries (André et al., 2010; McNulty et al., 2007; Raupach-Rosin et al., 2019; Vallin et al., 2016; Waaseth et al., 2019) but consistently higher as opposed to studies from non-European middle- and high-income countries (Awad & Aboud, 2015; El-Hawy et al., 2017; Jairoun et al., 2019; Mouhieddine et al., 2015; Yezli et al., 2019; You et al., 2008).

The great majority of study participants replied according to common recommendations for each attitude statement. Attitudes contrary to common recommendations in this study included stopping the antibiotic treatment when the participant felt better and the preference to having antibiotics stored at home, both particularly prevalent in Area C. Proportions were slightly lower as in a study from Sweden (André et al., 2010) but often much higher as found in studies in Kuwait (Awad & Aboud, 2015), Lebanon (Mouhieddine et al., 2015) and Saudi Arabia (Yezli et al., 2019).

This study reveals that there is a need to inform people on the adequate use of antibiotics. Almost 40% of respondents did not reply correctly about the efficacy of antibiotics against viruses, which is slightly higher compared to the other German KAP study (Raupach-Rosin et al., 2019). It is striking that around one-third of the disease mentions against which an antibiotic was reportedly taken are mainly caused by viral pathogens. Acknowledging that there are circumstances in which an antibiotic becomes necessary for one of those diseases (or attendant symptoms), this finding still points towards potentially misused antibiotics in the study population, which was also identified in a previous survey in Germany (DAK-Gesundheit, 2014). It is further necessary to inform people about the correct handling of antibiotics with an emphasis on treatment adherence and disposal (i.e. not storing antibiotics at home), particularly in Area C.

5.5.1. The misconception of antibiotic resistance as an individual issue

The majority of study participants considered ABR as a global issue already today, as well as at the national (Germany) and individual (family and own health) levels. Albeit this tendency, many also indicated that ABR is an individual issue and only for people who take antibiotics regularly. This opinion was prevalent across all three areas revealing a common misconception, which was also identified in other surveys (André et al., 2010; Awad & Aboud, 2015; Wellcome Trust, 2015; WHO, 2015a). It highlights the apparent lack of understanding that ABR is a universal issue that can affect everyone, even if the person did not take an antibiotic. Tackling this, re-framing the messaging (e.g. in information campaigns) by focusing on a sense of personal jeopardy and using human stories and thereby emphasizing the personal relevance was proposed as a way forward (Wellcome Trust, 2019).

5.5.2. Differences between socio-spatially diverse urban areas

Albeit knowledge, attitudes, risk awareness and handling practices were overall fairly well, differences between the three socio-spatially diverse urban areas could be identified pointing towards an unfavourable situation in the socio-spatial disadvantaged area (Area C). Similar differences between affluent and deprived areas were also observed in Greater London (Mason et al., 2018).

The knowledge statements revealed a clear spatial trend with the lowest knowledge in Area C and the highest proportions of participants answering correctly consistently in Area B (one exception: medical indication for UTI). Attitudes and risk awareness between the three areas were more differentiated but still highlighted some spatial tendencies with higher risk awareness in Area B. Potential mishandling practices were most prevalent in Area C but the OR of engaging in such behaviour was higher in Area B. Summarizing, study participants in Area C were less knowledgeable, displayed lower risk awareness and reported more often mishandling practices and antibiotic use whereas participants in Area B usually presented the opposite situation. Interestingly, the occurrence of multidrug-resistant bacteria in urban wastewater sampled from the identical areas revealed the same patterns with higher values in Area C and lower resistance levels in Area B (Dennis Schmiege et al., 2021).

The population structure partly explains the variation of knowledge, attitudes, risk awareness and handling practices between the three urban areas. However, adjusting for those compositional factors, differences in ORs between the three areas remained, highlighting the existence of other unaccounted for determinants, e.g. possible influences of contextual (i.e. opportunity structures in the local physical and social environment) and collective (i.e. socio-cultural features) factors (Macintyre et al., 2002), which require further investigation.

This is the first study to focus explicitly on differences between socio-spatially diverse urban areas relating to KAP on antibiotics and ABR in Germany. Even after controlling for relevant confounders, differences between the areas prevailed underlining the robustness of the results. Albeit the premature cancellation of the survey and the relatively low response rate both resulting in a relatively small sample size, the study population in the three areas still mirrors the situation determined by official statistics. However, the generalisation of findings from this survey to other national and international cities still needs to be validated. Further limitations deserve mentioning. We did not use a validated questionnaire to assess knowledge and attitudes. For instance, it would have been beneficial to ask respondents if they knew what an antibiotic is. Recall bias regarding self-reported antibiotic use may affect the results, which is why we used the meteorological seasons instead of months for reporting. Using OR instead or PR may overestimate the effect when the outcome is highly prevalent. However, only the direction of the adjusted effect estimator was of interest in the statistical analyses.

5.6. Conclusions

This study demonstrates differences between three socio-spatially different areas in a large city in western Germany, regarding knowledge, attitudes, practices and antibiotic use. Knowledge and attitudes on antibiotics and ABR showed distinct spatial differences. Participants of the socio-spatially disadvantaged area (C) were less knowledgeable, had lower risk awareness and reported more often antibiotic use and mishandling practices. The results of this survey, however, need to be validated by quantitative and particularly qualitative research in different population groups and regions. These results can function as a starting point for potential educational interventions. Our results indicate that population-based interventions should be tailored to the specific characteristics (e.g. knowledge, needs, etc.) typical to different socio-economic urban areas to unfold their full potential in informing the public about their individual space for action regarding the global health threat of ABR.

6. Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing *Escherichia coli* in urban community wastewater

This chapter was originally published as: Schmiege, D., Zacharias, N., Sib, E., Falkenberg, T., Moebus, S., Evers, M., Kistemann, T. (2021): Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing Escherichia coli in urban community wastewater. Science of the Total Environment, 785, 147269, DOI: 10.1016/j.scitotenv.2021.147269.[15][16]

6.1. Abstract

Antibiotic resistance (ABR) and the spread of multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* via wastewater to environmental compartments are of rapidly growing global health concern. Health care facilities, industries and slaughterhouses discharge high loads of ABR bacteria with their wastewater. However, the general community is often the biggest indirect discharger. Yet, research focusing explicitly on this important diffuse source is rather scarce raising questions about variations in the occurrence of ESBL-producing *E. coli* in wastewater from different communities and over time.

Between April 2019 and March 2020, wastewater from three socio-spatially different districts in the Ruhr Metropolis, Germany, and the receiving wastewater treatment plant was sampled monthly and analysed for the occurrence of ESBL-producing *E. coli* via culture-based methods. Isolates were validated with matrix assisted laser desorption ionization time of flight mass spectrometry and antibiotic resistance profiles were analysed via microdilution. Results were interpreted using the European Committee on Antimicrobial Susceptibility Testing criteria. The German Commission for Hospital Hygiene and Infection Prevention criteria were used for multidrug-resistance categorization.

Phenotypic ESBL-producing *E. coli* could be isolated from every wastewater sample demonstrating that the general community is an important indirect discharger. The socio-spatially disadvantaged area displayed higher absolute loads of ESBL-producing *E. coli* compared to the other two areas, as well as higher adjusted loads for domestic discharge and inhabitants, particularly during winter, indicating a higher ABR burden. Thirty-two isolates (28.6%) were characterized as multidrug-resistant Gram-negative bacteria (3MRGN). Resistance profiles varied only for those antibiotics, which can be administered in outpatient care. Resistance levels tended to be around 10% lower in the socio-spatially advantaged area.

[15] Link to the publication: https://doi.org/10.1016/j.scitotenv.2021.147269
[16] The numbering of figures and tables was changed to consecutive numbers.

This study shows that spatial and seasonal influences regarding the occurrence of ESBL-producing *E. coli* in wastewater from socio-spatially different communities are identifiable.

6.2. Introduction

Antibiotic resistance (ABR), describing the resistance of bacterial pathogens to antibiotics, is an enormous global public health challenge. In Europe alone, more than 30,000 people presumably died because of an infection with resistant bacteria in 2015 (Cassini et al., 2019). Also, ABR leads to higher morbidity, longer duration of hospital stays and increasing medical costs (Naylor et al., 2018).

Of particular growing health concern are multidrug-resistant Gram-negative bacteria (MRGN) and especially extended-spectrum beta-lactamases (ESBL)-producing *Enterobacterales* (Exner et al., 2017; Giske et al., 2008), including *Escherichia coli*. ESBL-producing *Enterobacterales* carry resistances to beta-lactam antibiotics, i.e. penicillins, cephalosporins and monobactams, a group of antibiotics commonly used for human medical treatment (ECDC, 2020a; Pandey & Cascella, 2020). Pathogens of this type can cause severe diseases in both humans and animals (Davies & Davies, 2010).

ABR in general and ESBL-producing *Enterobacterales* in particular have shifted from an issue originally confined to health-care settings to the broader community (Pitout et al., 2005; Woerther et al., 2013). ABR elements, namely multidrug-resistant organisms (MDRO), antibiotics and their metabolites, as well as antibiotic-resistance genes (ARG), have spread widely through different environmental media (Berendonk et al., 2015; Finley et al., 2013; Wellington et al., 2013). They are now ubiquitous in anthropogenically impacted environmental compartments, e.g. air (Li et al., 2018), soils (Zhu et al., 2019), sediments (Heß et al., 2018) and water (Baquero et al., 2008; Kümmerer, 2009).

Particularly wastewater has been identified as a crucial transport vehicle for ABR (Andremont & Walsh, 2015; Verburg et al., 2019). When wastewater is discharged and collected via centralized systems into wastewater treatment plants (WWTP), these are considered “points of convergence” (Manaia, 2014). They provide ideal conditions for the mixture of ABR elements from various sources (Michael et al., 2013; Rizzo et al., 2013), i.e. humans, animals and the environment. Albeit bacterial removal rates in conventional WWTPs can be several $\log_{10}$-units (Kistemann et al., 2008), ABR elements are still discharged into the receiving surface waters (Müller et al., 2018; Voigt et al., 2020). This can not only cause ecological disturbances in water communities (Baquero et al., 2008) but may also pose a health risk for humans and animals coming into contact with such water (Herrig et al., 2020; Jørgensen et al., 2017; Leonard et al., 2015).

It is well established that certain direct and indirect dischargers contribute high loads of MDRO, ARGs and antibiotic residues to wastewater. Many studies revealed high loads in hospital wastewater (Blaak et al., 2015; Bréchet et al., 2014; Galvin et al., 2010; Harris et al., 2014; Korzeniewska et al., 2013; Müller et al., 2018; Paulshus et al., 2019; Voigt et al., 2020) but also in effluents from drug manufacturers (Larsson et al., 2007), as well as slaughterhouses (Alexander et al., 2020; Savin et al., 2020). In terms of wastewater volumes produced, however, the general community is often the biggest discharger. Yet, research focusing explicitly on this important source is scarce.

Antibiotic use in the community is driven by a variety of factors and varies between and within countries on different geographical scales and between health care sectors (Schmiege et al., 2020). Among other driving factors, several studies revealed differences in antibiotic use and dispensation based on the socio-economic status of patients (Blommaert et al., 2013; Farah et al., 2015; Hjern et al., 2001; Nitzan et al., 2010; Sahin et al., 2017b). In many European countries, the great majority of antibiotics are used in the outpatient sector with beta-lactam antibiotics (WHO ATC groups J01C and J01D) accounting for more than half of all antibiotics used (ECDC, 2020a). In Germany, approximately 85% of antibiotics used for human medical treatment were prescribed in the outpatient sector in 2015 (BVL & PEG, 2016), of which beta-lactam antibiotics constituted around 56% in 2019 (WIdO-AOK Research Institute, 2021).

During and after outpatient antibiotic treatment, individuals excrete MDRO and antibiotic residues (Berkner et al., 2014; Kim et al., 2017), which are discharged with wastewater coming from the general population (as opposed to health care facilities). In addition, healthy individuals can also be colonized with ESBL-producing *Enterobacterales* constituting a second important group excreting such ABR elements in community wastewater (Karanika et al., 2016). Especially international travel to high-endemic areas has been identified as a risk factor for colonization with ESBL-producing *Enterobacterales* (Woerther et al., 2017), also in Germany (Lübbert et al., 2015).

Gaining an overview of the local ABR situation, sampling and analysing wastewater is a promising approach providing complementary health data at lower costs compared to testing an equal amount of individuals living in the same area (Aarestrup & Woolhouse, 2020b; Hendriksen et al., 2019). However, establishing relationships between the occurrence of certain biological biomarkers in wastewater systems and processes in the community, e.g. antibiotic consumption, is among the challenges of this approach (Sims & Kasprzyk-Hordern, 2020). Sewage-based surveillance systems for ABR are already being evaluated (Hutinel et al., 2019; Huijbers et al., 2020). This raises questions about potential variations in the occurrence of MDRO between wastewater from different communities in close spatial proximity, e.g. within a city.

The objective of this study was to explore the prevalence of MRGN and ESBL-producing *E. coli* in community wastewater from socio-spatially different districts within one metropolitan wastewater system over time. A wastewater system in the biggest urban agglomeration with a high population density in Germany, the Ruhr Metropolis, hosting over five million inhabitants (Bonny, 2020), was selected as the study area. Data were analysed with a specific interest in spatial (between the districts) and temporal (between meteorological seasons) trends to gain an indication of the local ABR situation in the general community through the occurrence of ESBL-producing *E. coli* in wastewater.

6.3. Material and methods

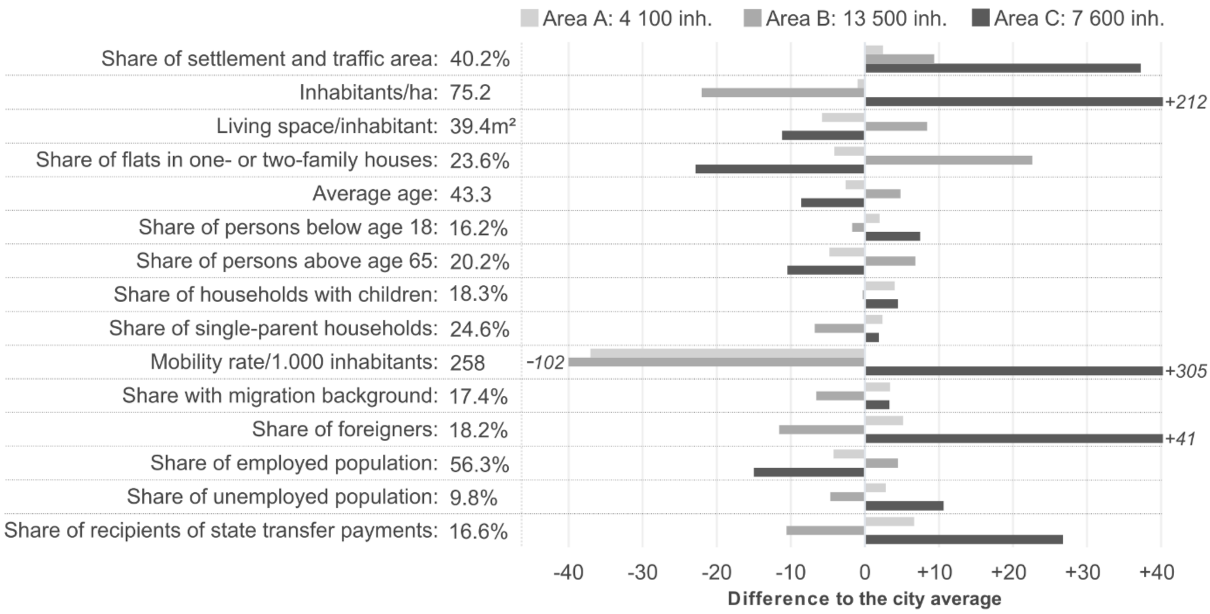
6.3.1. Study area selection

For the analysis of potential differences in community wastewater regarding the prevalence of MRGN and ESBL-producing *E. coli*, the sampling points needed to fulfil two criteria: i) supplying socio-spatially distinguishable population groups and ii) no in-patient health care facility in the catchment area. Ensuring spatial comparability, the sampling points were selected from within a single city located in the Ruhr Metropolis. For anonymization reasons, the name of the study city will not be mentioned.

The study city was chosen due to several factors: i) it is among the most densely populated cities in the Ruhr Metropolis; ii) the city is socio-spatially highly diverse with distinct social and ethnic segregations (Ammon et al., 2011; Stadt Dortmund, 2018) and health-related environmental inequalities (Flacke et al., 2016); iii) it ranked very high (second) among the 26 cities and municipalities in the region in antibiotic use in 2019 (ATC group J01; data from KV Westphalia-Lippe 2020); and iv) the municipal WWTP receives its wastewater almost exclusively from this city. Based on this information, three sampling stations in socio-spatially different districts were selected in close collaboration with the responsible water management association.

Figure 13 illustrates the profound socio-spatial differences of certain indicators between the three catchment areas (more detailed information on the indicators can be accessed in supplementary material A[17]). The Areas A, B and C refer to the catchment areas that are served by the respective sampling point. Each area consists of several statistical sub-districts, the smallest official statistical unit (i.e. highest spatial resolution) in the city. In order to obtain the numbers for the areas, the mean value from the respective statistical sub-districts in each area for each indicator was calculated. These are displayed in Figure 1 as the difference to the city average of the respective indicator.

[17] Supplementary material A of this publication can be accessed in chapter iii.a in the appendices.

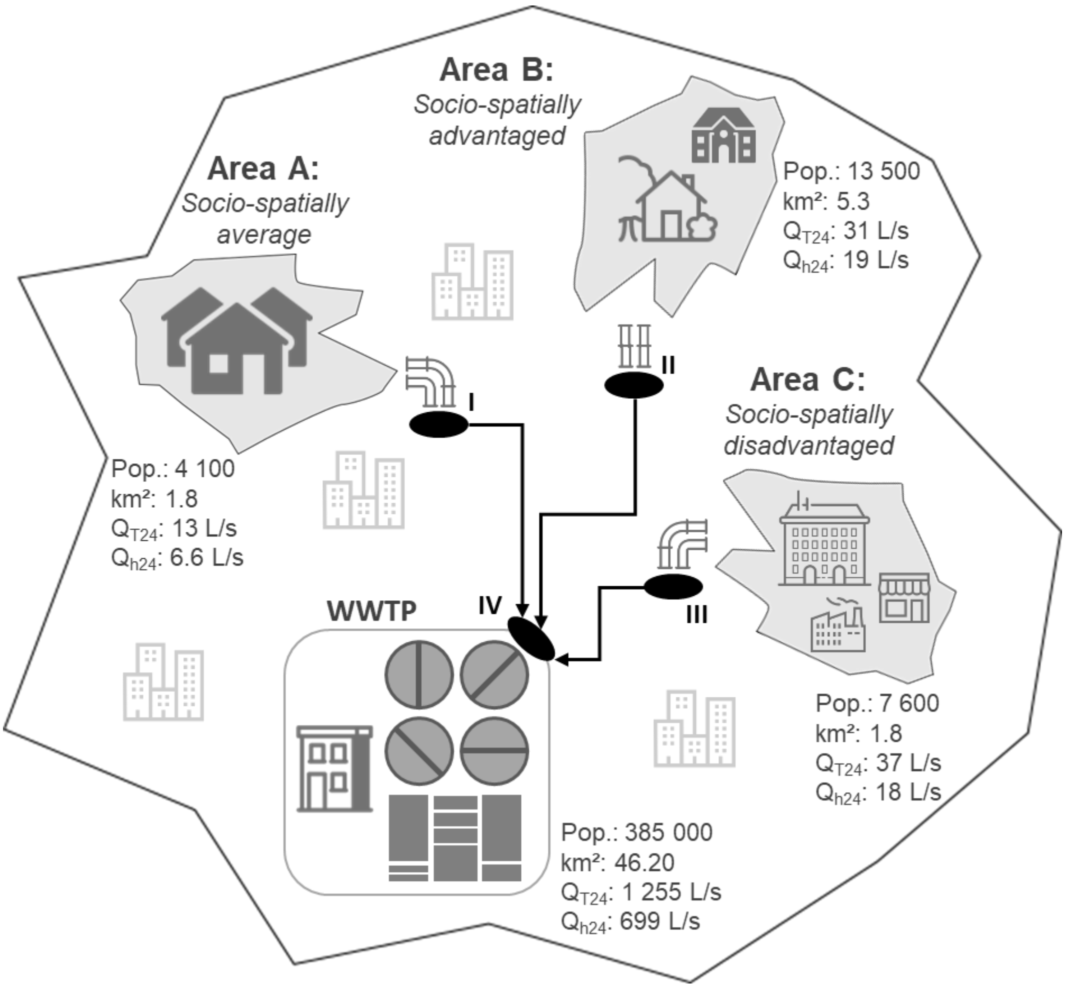


Note: The number provided after each indicator is the average across all districts in the city.

Figure 13. Socio-spatial structure of the study city and the three selected study areas (Data source: City Statistics, 2019)

Whereas the numbers for Area A deviate relatively little from the city average, Area B and Area C present opposing situations regarding the displayed indicators. Area C exhibits extreme values for many settlement structure indicators, i.e. highest share of settlement and traffic area, highest population density, lowest living space per inhabitant, lowest share of flats in one- or two-family hourses. It also differs in terms of population composition, e.g. highest share of persons below age 18 and lowest share of persons above age 65, and social structure indicators, e.g. highest shares of foreigners, of unemployed population and recipients of state transfer payments, pointing towards a disadvantageous situation as opposed to Area B. For easier reference, the areas are hereafter relative to the city average and each other referred to as “Area A”–close to the city average, “Area” B–socio-spatially advantaged, and “Area C”–socio-spatially disadvantaged.

In addition to the three sampling points, the influent of the local municipal WWTP was also tested (see Figure 14). The WWTP treated wastewater of a population equivalent of around 709 000 (connected population: 396 000) in 2019, amounting to an annual wastewater volume of more than 49 000 000 m³ (IT.NRW, 2020). Wastewater passes through three treatment steps before reaching the receiving surface water body. Produced sewage sludge is mainly used as a combustible for the production of electricity and heat.



Note: Q_{T24}: dry weather discharge as daily average; Q_{h24}: domestic discharge as daily average

Figure 14. Schematic sampling design covering three socio-spatially different sub-districts (points I-III) within the study city in the Ruhr Metropolis and the receiving wastewater treatment plant (point IV)

The three community sampling points could only be selected based on socio-spatial indicators and not antibiotic use because of the unavailability of high spatial resolution data of the latter. However, the study city ranked second among its neighbouring cities and municipalities in antibiotic use providing a reasonable starting point for this study. If data are available, antibiotic use as the most prominent direct driver of the occurrence of MDRO and antibiotic residues should be considered for study area selection in future community surveillance studies.

6.3.2. Sampling procedure and laboratory analysis

Between April 2019 and March 2020, wastewater from three peripheral sampling points and one sampling point at the WWTP were sampled once per month, amounting to 48 samples overall. This allowed for a rough overview of the resistance situation but also limits the generalisability of the findings. Ensuring temporal comparability, the sampling was conducted around the same time of the day, on the same day of the week (average starting times for the qualitative random sampling in Area A: 8.00 a.m., Area B: 8.50 a.m. and Area C: 9.30 a.m.) trying to capture the morning toilet routine of the inhabitants. For the three peripheral sampling points, samples were manually collected directly from the pipes of the respective pumping station through qualified random sampling (according to DIN 38402-11:2009-02). For the influent of the WWTP, an automated sampler generated 24h mixed samples at two-hour intervals of which samples were taken from the time window 08.00 a.m.-10.00 a.m. to allow for temporal comparability with the other sampling points. The different sampling types may partially explain the lower variability observed for the WWTP data.

For the investigation of faecal parameters and the impact of antibiotic resistance, the wastewater samples were analysed for the hygienic-microbiological parameter *E. coli* as well as for ESBL-producing *E. coli*. After sampling, the samples were transported under cold conditions (2-8 °C) to the laboratory and analysed within 24 h. For the detection of all cultivable *E. coli,* 1 ml sample and/or dilutions were directly spread on chromocult coliform Agar (CC-Agar, Fa. Merck) and incubated at 36 ± 1 °C for 24 h. The method was adapted from ISO 9308, 2016 (ISO 9308-1:2014/Amd 1:2016), by the addition of antibiotic supplement to the culture medium (2.5 mg vancomycin and 2.5 mg cefsulodine in 500 ml). Following the manufacturer instructions, all lilac colonies were counted as *E. coli*.

The detection of ESBL-producing Gram-negative bacteria of the species *E. coli* was conducted by adapting a method originating from clinical methods (Schreiber et al., 2021). The isolation of the antibiotic resistant target bacteria was executed via direct spreading of different dilutions onto ESBL CHROMagar plates (MAST Diagnostica, Germany). The plates were then incubated for 24 h at 42 °C. Classification and preselection of the grown colonies were implemented following Müller et al., 2018, and Schreiber et al., 2021. The calculation of final bacteria concentrations was done according to ISO 8199, 2018 (ISO 8199:2018-10).

For the resistance characterization, isolates were cultivated on Columbia 5% sheep blood agar (Becton Dickinson GmbH, Germany) at 37 °C for 20-22 h. Fresh cultures were used to validate the species via matrix assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics, Massachusetts, United States). Antibiotic resistance was analysed via microdilution employing the Micronaut-S MDR MRGN-Screening 3 system (MERLIN, Gesellschaft für mikrobiologische Diagnostika GmbH, Bornheim-Hersel, Germany). The generated results were interpreted using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria.

Investigating MRGN, criteria developed by the German Commission for Hospital Hygiene and Infection Prevention (KRINKO) using a definition based on therapeutics, which are primarily used for severe infections (KRINKO, 2012, 2019), were used. KRINKO defined four classes of antibiotics with different lead substances: i) acylureidopenicillins (piperacillin); ii) 3rd generation cephalosporins (cefotaxime and/or ceftazidime); iii) carbapenems (imipenem and/or meropenem); and iv) fluoroquinolones (ciprofloxacin). Based on the number of occurring resistances against these lead substances, the designations 3MRGN and 4MRGN were introduced (KRINKO, 2019).

6.3.3. Data visualization and descriptive statistics

Data visualization and analysis were implemented using R (version 4.0.2, R Core Team 2020). The normality of the data was checked by the Shapiro-Wilk test showing that the distributions of the data of both *E. coli* ($W=0.84$, $p<.001$) and ESBL-producing *E. coli* ($W=0.69$, $p<.001$) differed significantly from normal distributions. Further statistical descriptions therefore relied on non-parametric statistics. Due to the exploratory and descriptive study design, no statistical hypothesis testing was conducted. The small sample size (per area and per meteorological season) and associated low statistical power rendered it unlikely to detect statistically significant differences. Thus, conducting statistical testing was deemed unsuitable.

For the number of *E. coli* and ESBL-producing *E. coli*, the median, and the 25th (Q1) and 75th (Q3) quartiles were computed. If not declared otherwise, data are presented as “(median, Q1–Q3)”. The numbers were presented in colony-forming units (CFU) corrected for the average domestic daily discharge (Q_{H24}) and adjusted for the population living in the respective catchment area. The ESBL-producing *E. coli* load was calculated by multiplying the concentration (CFU/L) with the average dry weather (Q_{T24}) daily discharge.

For the analysis of temporal trends, monthly data of the three sub-districts were aggregated into meteorological seasons to allow for sufficient data points in each category. The months were grouped as follows: March, April and May as spring, June, July and August as summer, September, October and November as autumn, and December, January and February as winter. Isolates were grouped into resistant and non-resistant for further analysis. Proportions, as well as mean and standard deviations, were calculated for each area and season.

6.4. Results

Phenotypic ESBL-producing *E. coli* (ESBL-Ec) were isolated from every sampling point in every month underpinning the important role of the general community as a source of ESBL-Ec in wastewater. In addition, the quantities of *E. coli* and ESBL-Ec varied between sampling points and months.

6.4.1. Variation of the total number of *E. coli*

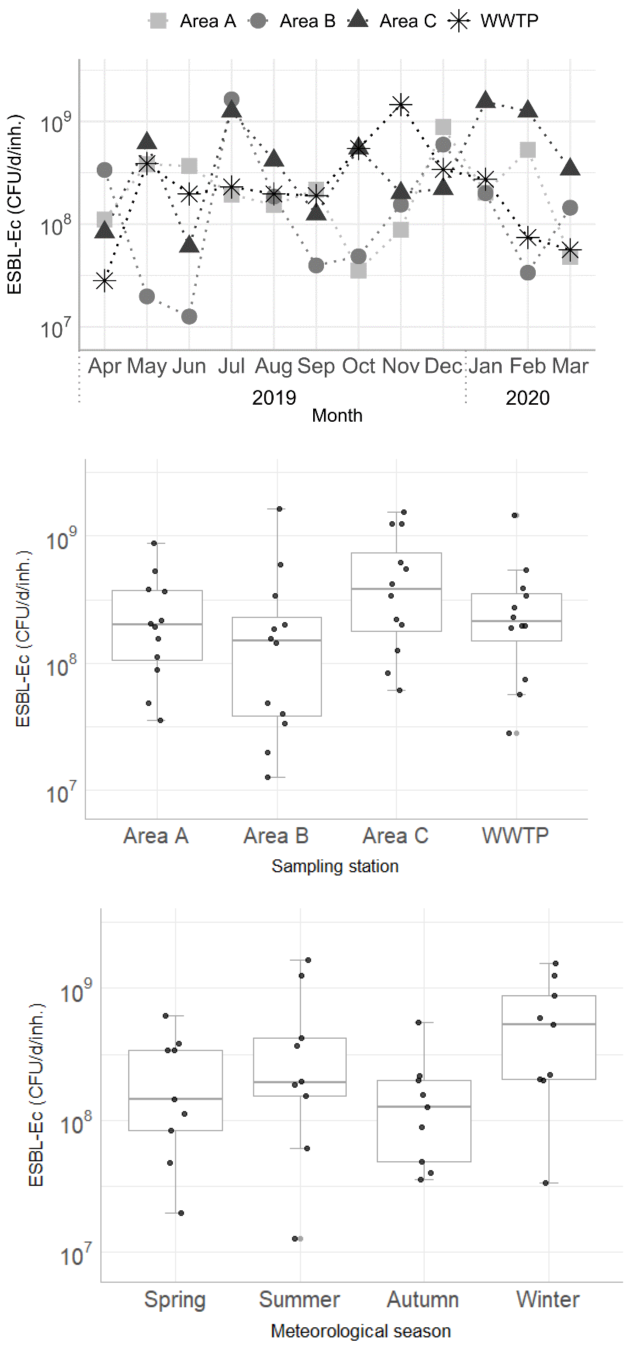
The *E. coli* counts (Figure A in supplementary material B[18]) revealed a uniform spatial pattern with similar medians across all four sampling points (Area A: 1.8×10^{10} CFU/d/inh.; Area B: 2.6×10^{10} CFU/d/inh.; Area C: 2.6×10^{10} CFU/d/inh.; WWTP: 1.4×10^{10} CFU/d/inh.). The summer

[18] Supplementary material B of this publication can be accessed in chapter iii.b in the appendices.

season ($3.8x10^{10}$ CFU/d/inh) showed the highest median followed by autumn ($3.0x10^{10}$ CFU/d/inh), spring ($2.4x10^{10}$ CFU/d/inh.) and the winter season ($1.5x10^{10}$ CFU/d/inh).

6.4.2. Spatio-temporal variation of phenotypic ESBL-Ec

ESBL-Ec concentrations were generally two log_{10}-levels lower compared to the concentration of the total number of *E. coli*. They also displayed greater variations between the sampling points within each month. Figure 15 illustrates the spatio-temporal distribution of ESBL-Ec.



Note: The seasonal figure contains only the data points of the three peripheral sampling points (n=36).

Figure 15. Spatio-temporal (top), spatial (middle) and seasonal (bottom) distribution of ESBL-producing *E. coli* in CFU per day per inhabitant (CFU/d/inh.) for all four sampling points between April 2019 and March 2020

Area B displayed the lowest median ($1.5x10^8$ CFU/d/inh., $3.8x10^7$-$2.3x10^8$ CFU/d/inh.) with outliers (i.e. differences of close to or more than one log_{10}-level to the median of the area) in June, July and August. Area A presented slightly higher values ($2.0x10^8$ CFU/d/inh., $1.1x10^8$-$3.7x10^8$ CFU/d/inh.) and Area C had the highest median ($3.8x10^8$ CFU/d/inh., $1.8x10^8$-$7.8x10^8$ CFU/d/inh). The quantities of ESBL-Ec in the WWTP often resembled the situation across the three sampling points, except for some outlier months (i.e. April and November).

Aggregated into meteorological seasons, values were higher for the winter season ($5.3x10^8$ CFU/d/inh., $2.0x10^8$-$8.8x10^8$ CFU/d/inh.) as compared to the other three seasons (spring: $1.4x10^8$ CFU/d/inh., $8.4x10^7$-$3.4x10^8$ CFU/d/inh.; summer: $1.9x10^8$ CFU/d/inh., $1.5x10^8$-$4.2x10^8$ CFU/d/inh.; autumn: $1.3x10^8$ CFU/d/inh., $4.9x10^7$-$2.0x10^8$ CFU/d/inh.).

Examining relative differences, the ratio of the number of ESBL-Ec to the total number of *E. coli* was calculated (Figure B in supplementary material B). The WWTP had the highest median of the ratios ($1.7x10^{-2}$) followed by Area C ($1.1x10^{-2}$), Area A ($5.5x10^{-3}$) and Area B ($6.4x10^{-3}$). Meteorological seasons displayed stronger pronounced differences. Values for the winter season $4.6x10^{-2}$, $1.1x10^{-2}$-$6.0x10^{-2}$) were much higher compared to all other seasons (spring: $1.1x10^{-2}$, $5.4x10^{-3}$-$1.2x10^{-2}$; summer: $8.5x10^{-3}$, $4.6x10$-^{3}-$2.5x10^{-2}$; autumn: $4.6x10^{-3}$, $1.6x10^{-3}$-$7.4x10^{-3}$).

6.4.3. Spatial variation of the ESBL-Ec load

The absolute load of ESBL-Ec was, on average, one to two log_{10}-levels higher for the WWTP ($8.2x10^{13}$ CFU/d, $6.2x10^{13}$-$1.4x10^{14}$ CFU/d) compared to the three peripheral sampling points. Among those, Area C ($2.9x10^{12}$ CFU/d) displayed higher loads followed by Area B ($2.0x10^{12}$ CFU/d) and Area A ($8.2x10^{11}$ CFU/d). Adjusting the ESBL-Ec load (per 1 000 000 L) revealed a different spatial picture as illustrated in Figure 16.

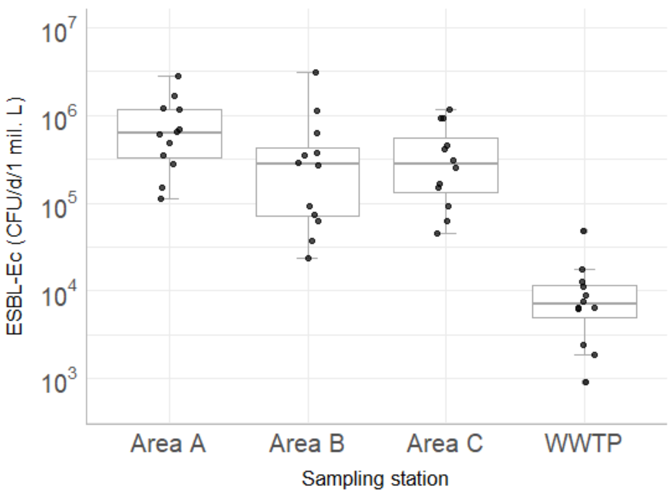


Figure 16. Spatial distribution of the adjusted (per 1 000 000 L) ESBL-producing *E. coli* load in CFU per day (CFU/d) for all four sampling points between April 2019 and March 2020

Here, the load was, on average, one to two log_{10}-levels lower for the WWTP compared to the three sub-districts. Among the three sub-districts, Area A ($6.3x10^5$ CFU/d/1 mil. L, $3.3x10^5$-$1.2x10^6$ CFU/d/1 mil. L) often displayed higher loads followed by Area C ($2.8x10^5$ CFU/d/1 mil. L, $1.4x10^5$-$5.8x10^5$ CFU/d/1 mil. L) and Area B ($2.8x10^5$ CFU/d/1 mil. L, $7.2x10^4$-$4.4x10^5$ CFU/d/1 mil. L). The ESBL-Ec load was higher in winter ($9.4x10^5$ CFU/d) and summer ($4.9x10^5$ CFU/d) and lower in spring ($2.7x10^5$ CFU/d) and autumn ($1.5x10^5$ CFU/d).

6.4.4. Antibiotic resistance profiles of ESBL-Ec isolates

Concerning antibiotic resistance, ESBL-Ec isolates were further analysed for their antibiotic resistance profile. In total, 112 *E. coli* isolates were analysed employing MALDI-TOF MS and microdilution. Table 11 depicts the spatio-temporal distribution of the antibiotic resistance profiles of all ESBL-Ec isolates.

None of the analysed bacteria were tested resistant to amikacin, tigecycline or fosfomycin, neither to imipenem or meropenem, hence not showing any indication for harbouring a carbapenemase gene. Thus, no isolate was characterized as 4MRGN, extensively drug-resistant or pan-resistant. Almost all isolates were tested resistant for piperacillin (112/112) and cefotaxime (111/112). One colistin resistant isolate was identified in the influent of the WWTP in August.

The proportions of isolates resistant to ceftazidime were lower in Area B (34.6%) and similarly high in Area A (56.7%) and Area C (58.6%) with the WWTP (55.6%) closely resembling their situation. Three of four seasons in Area A varied notably around the mean of the three districts for ceftazidime. Whereas Area A and Area B displayed their minimum in autumn, Area C and the WWTP had their maxima. The same spatio-temporal pattern applies to the fluoroquinolone ciprofloxacin whereby Area A and Area B, as well as Area C and the WWTP, showed comparable seasonal trends.

The proportion of isolates showing resistance to chloramphenicol was the lowest among the displayed antibiotics. Resistance rates did not differ much between the areas and the WWTP. However, there is a strong seasonal pattern with much higher values during summer (27.3%) as compared to all other seasons (spring: 11.1%; autumn: 6.7%; winter: 4.5%). Resistance patterns for trimethoprim/sulfamethoxazole also followed a seasonal trend with higher rates in summer (57.6%) and autumn (66.7%) as opposed to spring (40.7%) and winter (22.7%). Spatial differences (Area A: 60.0%; Area B: 50.0%; Area C: 51.7%) were less pronounced but proportions in all areas were higher compared to the WWTP (33.3%).

Table 11. Spatio-temporal variation of antibiotic resistance profiles of ESBL–producing *E. coli* isolates from the wastewater samples by sampling location and meteorological season

Antibiotic			CAZ	CIP	CHL	SXT	3MRGN
Mode of administration			IM/IV	PO/IV/top.	IV/top.	PO/IV	
Location	Season	n	R (%)	R (%)	R (%)	R (%)	Yes (%)
Area A	Spring	9	77.8	44.4	0.0	44.4	44.4
	Summer	7	42.9	14.3	28.6	100.0	14.3
	Autumn	9	22.2	11.1	22.2	77.8	11.1
	Winter	5	100.0	40.0	0.0	0.0	40.0
	All	30	56.7	26.7	13.3	60.0	26.7
Area B	Spring	5	40.0	20.0	0.0	0.0	20.0
	Summer	9	44.4	33.3	44.4	55.6	33.3
	Autumn	7	14.3	0.0	0.0	85.7	0.0
	Winter	5	40.0	20.0	0.0	40.0	20.0
	All	26	34.6	19.2	15.4	50.0	19.2
Area C	Spring	7	57.1	14.3	14.3	71.4	14.3
	Summer	10	40.0	40.0	20.0	50.0	40.0
	Autumn	6	83.3	50.0	0.0	66.7	50.0
	Winter	6	66.7	16.7	16.7	16.7	16.7
	All	29	58.6	31.0	13.8	51.7	31.0
WWTP	Spring	6	50.0	33.3	33.3	33.3	33.3
	Summer	7	42.9	42.9	14.3	28.6	42.9
	Autumn	8	87.5	50.0	0.0	37.5	50.0
	Winter	6	33.3	16.7	0.0	33.3	16.7
	All	27	55.6	35.8	11.8	33.3	37.0

Note: CAZ–ceftazidime; CIP–ciprofloxacin; CHL–chloramphenicol; SXT–trimethoprim-sulfamethoxazole; 3MRGN–Multidrug-resistant Gram-negative bacteria resistant to piperacillin, cefotaxime and ciprofloxacin; IM–intramuscular; IV–intravenous; PO–per os; top.–topical; n–number of isolates; R–resistant.

Of all 112 isolates, 32 (28.6%) were characterized as 3MRGN employing a resistance towards piperacillin, cefotaxime and ciprofloxacin. Twenty-three (71.9%) 3MRGN *E. coli* also showed resistance against ceftazidime. Only one strain showed resistance towards colistin and the combination of piperacillin/tazobactam, respectively. Figure 17 shows the spatial and temporal distribution of 3MRGN *E. coli* isolates.

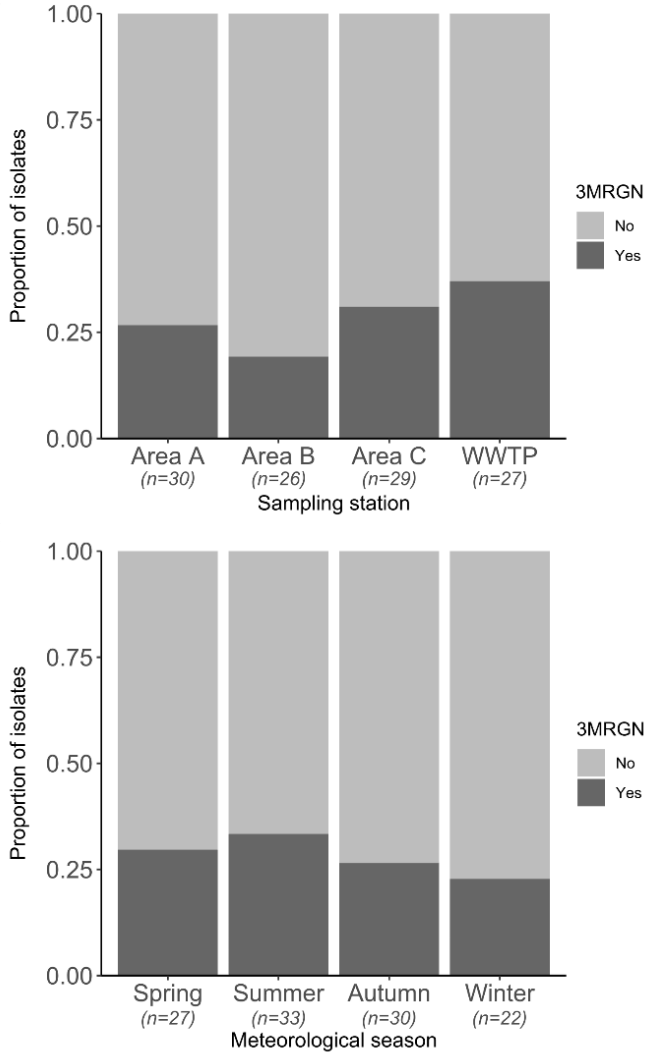


Figure 17. Spatial (top) and temporal (bottom) distribution of the proportion of multidrug-resistant (3MRGN) isolates to all 112 isolates extracted from the wastewater samples

The proportion of 3MRGN *E. coli* isolates is highest for the WWTP (37.0%) and almost twice as high as in Area B (19.2%). The rates increased from spring (29.6%) to summer (33.3%) before declining afterwards again (autumn: 26.7%; winter: 22.7%). Investigating the spatio-temporal variation (see Table 1), the proportions of 3MRGN isolates were highest in Area C (50.0%) and the WWTP (50.0%) in autumn while those numbers were lowest in Area A (11.1%) and Area B (0.0%) in the same season.

6.5. Discussion

Several studies investigated the difference in the prevalence of ESBL-Ec between hospital and community wastewater (Hassoun-Kheir et al., 2020) whereby hospital effluents always contained higher numbers or proportions of ESBL-Ec (Blaak et al., 2015; Galvin et al., 2010; Korzeniewska et al., 2013; Kwak et al., 2015; Lamba et al., 2017). Regarding the concentration of ESBL-Ec in community wastewater, the results of our study (median of all samples: $7.6x10^5$ CFU/L) are in accordance with findings from a study in France ($7.5x10^5$ CFU/L) (Bréchet et al., 2014). However, none of those studies focused explicitly on differences between wastewater from different districts or communities.

6.5.1. Spatial variations of phenotypic ESBL-Ec

Our findings demonstrate small-scale differences between wastewater coming from socio-spatially different communities regarding the occurrence of phenotypic ESBL-Ec. Area C, socio-spatially disadvantaged, displayed the highest number of ESBL-Ec (CFU/d/inh.) in more than half of the months. On the contrary, Area A, the socio-spatial average, and Area B, socio-spatially advantaged, each showed the lowest values in five of 12 months. The absolute ESBL-Ec load (CFU/d) was also highest in seven of 12 months in Area C as opposed to Area A with the lowest load in seven of 12 months. Adjusting the load per 1 000 000 L, Area A, the socio-spatial average, displayed the highest numbers in half of all months whereas Area B and Area C each showed the lowest values in five of 12 months. This indicates that, at least in this study, no socio-spatial gradient regarding the burden of ABR in the community in terms of the occurrence of ESBL-Ec could be determined.

6.5.2. Temporal variations of E. coli and phenotypic ESBL-Ec

The number of *E. coli* followed a seasonal trend. June presented a notable outlier due to a heavy rainfall event before and during the sampling. The seasonality of *E. coli* in (waste)water compartments most likely explained through the influence of different environmental factors (Jang et al., 2017; Petersen & Hubbart, 2020) instead of a systematic variation of people shedding *E. coli* over time. Seasonal differences were also observable for ESBL-Ec (CFU/d/inh.) and the ratio of ESBL-Ec to all *E. coli* displaying higher numbers during the winter season indicating a higher antibiotic resistance burden in cold months possibly through higher infection rates (Martinez et al., 2019) and higher antibiotic use (Achermann et al., 2011; Elseviers et al., 2007). The relatively high ESBL-Ec numbers in summer may be caused by a lower wastewater dilution due to less surface runoff (e.g. rainfall) (Caucci et al., 2016). This hypothesis is supported by a considerable lower concentration of *E. coli* and ESBL-Ec in the month of June because of the heavy rainfall. The ESBL-Ec load (CFU/d) of the three sampling areas followed this temporal trend. Similar seasonal patterns of ESBL-Ec were also observed in other studies (Caucci et al., 2016; Lépesová et al., 2019).

6.5.3. Variations of antibiotic resistance profiles

Isolates showed very low resistance levels (except for cefotaxime and ceftazidime) and no or very little variation regarding resistances to antibiotics that are administered parenterally and therefore mainly used in inpatient health care settings. This was expected because the three sampling points were purposefully chosen to not have an inpatient health care facility in their catchment area. Higher resistance levels for the 3rd-generation cephalosporins cefotaxime and ceftazidime were also identified elsewhere in community wastewater (Bréchet et al., 2014) and at the influent of a WWTP (Korzeniewska et al., 2013; Müller et al., 2018). This may indicate a (fluctuating) exchange of people with inpatient health care facilities, particularly in Area A and Area C.

The antibiotics for which the proportion of resistant isolates varied, i.e. ciprofloxacin, chloramphenicol and trimethoprim/sulfamethoxazole, can all be administered *per os* and/or topically (except for ceftazidime). Resistance levels observed at the influent of the WWTP were much higher for ciprofloxacin (37%) and trimethoprim/sulfamethoxazole (33.3%) as compared to other studies (Blaak et al., 2015; Hutinel et al., 2019; Korzeniewska et al., 2013; Oberlé et al., 2012). Among the three sampling points, Area A, the socio-spatially average, and Area C, socio-spatially disadvantaged, presented similarly high resistance for four of the five antibiotics. On the contrary, Area B, socio-spatially advantaged, always displayed the lowest values among the areas (except for chloramphenicol) hinting at a lower burden of antibiotic resistance.

Notable seasonal resistance patterns were identified for chloramphenicol, which is mainly applied topically as eye or ear drops or an ointment, and trimethoprim/sulfamethoxazole, which is indicated for infections of the upper and lower respiratory tract, infections of the kidneys and the gastrointestinal or urinary tract, as well as male and female genital organs.

6.5.4. MRGN isolates in wastewater

Regarding the occurrence of MRGN in wastewater in Germany, the proportion of 3MRGN bacteria in the wastewater of municipal WWTPs in this study (37% at the WWTP) are higher compared to other studies (15% in Müller et al., 2018 and 22% in Sib et al., 2020). Among the three areas, Area C, socio-spatially disadvantaged, showed the highest percentage of 3MRGN isolates (31%) as opposed to Area B, socio-spatially advantaged, with the lowest (19%). This gap is relatively small but it does align with the other indicators applied here pointing towards a higher ABR burden in Area C and a lower burden in Area B. Differences in the same magnitude are also observable between summer (33%) and winter (22%) seasons.

In this study, no 4MRGN bacteria were identified but the detection of such bacteria was also very low in Müller et al., 2018 (0.7%) and Sib et al., 2020 (1.1%). These low detection rates of highly resistant bacterial isolates are due to the absence of health care facilities in the catchment areas. In hospitals, studies showed a high prevalence of MRGN bacteria in the sanitary facilities of patient rooms (Sib et al., 2019) and the following wastewater pathway (Müller et al., 2018; Sib et al., 2020). In addition, higher percentages of ARB and ARGs were detected if certain (in hospital prescribed) antibiotics are present in wastewater (Voigt et al., 2020), which may support the selection and integration of resistant bacteria in the biofilms of these pipes and hospital wastewater networks (Sib et al., 2019; Voigt et al., 2020).

6.6. Conclusion

Overall, our study shows that the general community is an important contributor of ESBL-producing *E. coli* in wastewater and that differences in the occurrence between wastewater from socio-spatially different communities are observed. Our results further highlight that spatial and seasonal influences of ESBL-producing *E. coli* in wastewater between communities, depicting the human outpatient sector, are indeed identifiable. This result is supported by having found variations of ABR only for those antibiotics, which can be administered in outpatient care. Also, the findings suggest a higher ABR burden in a socio-spatially disadvantaged area and lower resistance levels in a socio-spatially advantaged area.

Further small-scale studies are needed to investigate differences between community wastewater from socio-spatially different areas in more detail with higher sample numbers and by examining other ABR elements, such as ARGs and antibiotic residues, in wastewater samples. Moreover, the spectrum of MDRO should also be extended. In addition, turning the focus “upstream” into the catchment area on the inhabitants and antibiotic use or other possible drivers, such as international travel to high-endemic areas, may provide a clearer picture about potential connections on a small-scale. Establishing a more direct link between antibiotic use and handling practices or other possible (risk) factors for a colonization and the subsequent occurrence of MDRO in stool samples on an individual level provides an interesting starting point and may support the indicative findings of this study.

7. Conclusion

7.1. Main findings

The doctoral thesis demonstrated two crucial aspects by applying a geographical perspective to specific components of antibiotic resistance (ABR). The first working package established the relevance of considering space-related variables as possible determinants of antibiotic use in the community, i.e. the human outpatient sector (see chapter 4). Secondly, findings of the working packages 2 and 3 revealed small-scale area variations, i.e. intra-urban, of (self-reported) antibiotic use and related knowledge, attitudes and practices (see chapter 5), as well as of the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater in three socio-spatially different urban areas (see chapter 6). Combining the results of the last two working packages allowed for an exploration of potential spatial and temporal associations between (self-reported) antibiotic use and the occurrence of antibiotic-resistant bacteria in the same urban areas (at the end of this section).

Various factors influence antibiotic use in the community, i.e. the human outpatient sector. The findings from the systematic literature review (see chapter 4) emphasised the importance of both individual- and space-related determinants (see research question (RQ) 1 and research objective (RO) 1.1). Examining compositional variables, i.e. characteristics of the population living in the area of interest, revealed that demographic factors such as age, sex, education, or income on antibiotic use were well documented but differed between high- compared to low- and middle-income countries. Contextual and collective factors were less researched. Contextual variables affecting antibiotic use in the human outpatient sector included the density of pharmacies or physicians (if a regulated system is in place), different types of deprivation (e.g. area, housing or material) and seasonality. Regulatory factors and Hofstede's dimensions of national culture were in the collective determinants group that showed an association with antibiotic use. These results underline the necessity to consider both people and space as possible determinants of antibiotic use in the community.

Antibiotic use in the community and its determinants vary on different geographical scales. Insufficient knowledge and inappropriate attitudes towards antibiotic use and resistance can also drive antibiotic (mis-)use. The cross-sectional household survey in this doctoral thesis (see chapter 5) identified antibiotic use and related knowledge, attitudes and practices in three socio-spatially different urban areas within a metropolitan sewershed. Participants across all three urban areas revealed the misconception of antibiotic resistance as an individual rather than a universal issue. In addition, around one-third of the diseases mentioned against which an antibiotic was used are mainly caused by viral pathogens. These findings confirmed the need to inform the population further on the adequate use and handling of antibiotics.

Self-reported antibiotic use and related knowledge, attitudes, risk awareness and handling practices differed between the three socio-spatially diverse urban areas (see RQ 1 and RO 1.2). Participants from the socio-spatially disadvantaged area (Area C) had the lowest proportions of correct knowledge statements, indicated more often attitudes contrary to common recommendations, showed lower risk awareness and reported more often antibiotic use and potential mishandling practices. On the contrary, participants in the socio-spatially advantaged area often presented the opposite situation. Such small-scale area differences between communities within a metropolitan sewershed underline the importance of tailoring population-based interventions to the local socio-economic context of different urban areas.

Untreated municipal wastewater from the identical three areas was tested for the occurrence of extended-spectrum beta-lactamases (ESBL)-producing *Escherichia coli* (*E. coli)* via culture-based methods every month over a whole year (see chapter 6). This work established the general community as a relevant source and essential contributor of phenotypic ESBL-producing *E. coli* in wastewater with seasonal and spatial variations (see RQ 2 and RO 2.1). Counts of phenotypic ESBL-producing *E. coli* were higher during winter months. The socio-spatially disadvantaged area (Area C) displayed higher absolute loads of phenotypic ESBL-producing *E. coli* and higher adjusted loads for domestic discharge and inhabitants. This indicated a higher antibiotic resistance burden in the socio-spatially disadvantaged area compared to the other two areas.

Isolates were further analysed for their resistance profiles (see RQ 2 and RO 2.2). Less than one-third of the isolates were characterised as multidrug-resistant Gram-negative bacteria (3MRGN), i.e. resistant to three of the four classes of antibiotics defined by the German Commission for Hospital Hygiene and Infection Prevention (KRINKO) (KRINKO, 2019). Resistance levels were very low with no or minimal variation regarding antibiotics mainly used in inpatient health care settings (i.e. administered parenterally) due to the absence of health care facilities in the three catchment areas. The proportions of resistant isolates varied for antibiotics administered in outpatient care (i.e. per os and/or topically). The socio-spatially advantaged area (Area B) exhibited the lowest resistance levels and around 10% lower levels of 3MRGN isolates than the other two areas, hinting at a lower burden of antibiotic resistance.

Integrating the household survey results and the wastewater samples enabled the comparison of antibiotic use with antibiotic-resistant bacteria in untreated municipal wastewater in the three socio-spatially different urban areas. Self-reported antibiotic use followed the same seasonal trend in all three communities, regardless of considering only the study participants or including their entire households. Starting with lower values in spring and summer, it increased in autumn and peaked during winter. Phenotypic ESBL-producing *E. coli* exhibited a wave-like format over the year with comparably lower counts during spring and autumn, higher values in summer and a peak in winter. Both self-reported antibiotic use and phenotypic ESBL-producing *E. coli* counts were highest in winter indicating a temporal association. Still, there were no clear associations for the other meteorological seasons.

Participants in the socio-spatially disadvantaged area reported higher antibiotic use. This trend was evident for the number of people and the number of treatments regardless of whether investigating the study participants only or including all household members. In the same area, counts of phenotypic ESBL-producing *E. coli* were also highest in most months compared to the other two areas. Acknowledging the gap between antibiotic use in the community and the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater (see chapter 7.2), it still pointed towards a potential spatial association in this area.

The results of this doctoral thesis underline the importance of considering the local spatial context regarding antibiotic use and related knowledge, attitudes and practices, as well as the occurrence of antibiotic-resistance bacteria in untreated municipal wastewater. It further demonstrates the importance of considering finer geographical scales, i.e. higher spatial resolution, when examining antibiotic use and the occurrence of antibiotic-resistant bacteria in community wastewater within a metropolitan sewershed. Without such an approach, certain spatial variations would not have been visible on an aggregated level (e.g. sub-catchment areas vs WWTP, or sub-district vs city level). By explicitly considering the spatial dimension of those ABR components, this doctoral thesis highlights the benefit of applying a geographical perspective at the local level to this health topic of global relevance.

7.2. Research limitations

Every research has its limitations. Each philosophical stance implicitly utilised when designing a study has its implications. As outlined in chapter 2.1, this doctoral thesis is epistemologically rooted in a positivist approach. In distinction to other approaches, space is conceptualised as a geometric container, lesser importance is given to individuals compared to groups, and quantitative methods predominate (Gatrell & Elliott, 2015). Although this approach is well suited for identifying spatial and temporal patterns of antibiotic use and the occurrence of antibiotic-resistance bacteria in untreated municipal wastewater, it does not account for other important aspects. For instance, it was neither investigated how individuals interact with their surrounding neighbourhood (e.g. human agency) nor how the broader social, cultural and political contexts might influence the health outcome.

An overarching limitation of the underpinning research objective was the “black box” in the conceptual framework between antibiotic use in the community and the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater in the same area. Along this conceptual pathway, several uncertainties deserve mentioning but could not be considered in this work. Every antibiotic treatment selects for antibiotic-resistant bacteria in the patient's gut (Ramirez et al., 2020), which are excreted along with unmetabolised antibiotics and their residues in urine and faeces. In addition, antibiotic-resistant bacteria might also colonise the gut of healthy people (Karanika et al., 2016). It is challenging to estimate the number of bacteria and antibiotics in the (human) gut (Sender et al., 2016), let alone human stool, and these numbers most likely vary between individuals. In centralised wastewater systems, sewage containing these ABR elements is collected in pipes. Depending on the system configuration, the sewage mixes with wastewater from other sources, enabling processes such as co- and cross-resistance (Baker-Austin et al., 2006; Berg et al., 2010; Seiler & Berendonk, 2012). These examples highlight the complexity inherent in wastewater as an environmental media and emphasise the difficulties of making assumptions about associations between antibiotic use and downstream occurrence of antibiotic-resistant bacteria in untreated wastewater, even at a small-scale level. Despite such challenges, measuring antibiotic-resistance bacteria, antibiotics or ARGs in wastewater still provides distinct advantages, making it a promising tool to establish environmental surveillance systems of ABR (see chapter 7.3).

Besides this rather general consideration, specific limitations of each working package need to be outlined. Identifying determinants of antibiotic use in the community via a systematic literature review revealed various influencing factors. Available evidence was biased towards high-income and western countries. The heterogeneity of studies regarding methodologies did not allow for a consistent quality assessment of the studies included. The findings, therefore, only served as an indication of a potential influence of the factors on antibiotic use. Nevertheless, they helped to inform the construction of the questionnaire for the household survey.

The main limitation of the household survey in the general population in Dortmund was the low sample size (n=158) due to a meagre response rate and the premature cancellation of the study because of the COVID-19 pandemic. Interested in temporal variations of antibiotic use, recall bias might influence the findings. To reduce the influence of this bias, data were aggregated to meteorological seasons instead of months. Albeit previous KAP studies informed the development of questions and statements, the final structured questionnaire was not validated. Hence, generalisation of the results to other national and international cities requires validation by further research.

Regarding the sampling and analysis of untreated municipal wastewater, certain aspects deserve mention. Socio-spatial indicators guided the selection of the study areas and not actual antibiotic use due to the lack of data availability at such a small scale. This carried the risk of comparing areas that could hypothetically be similar regarding antibiotic use. However, following the social gradient in health and the results of the systematic literature review, this seemed less likely. In addition, the sampling scheme comes with specific implications. Wastewater was sampled during the morning hours once per month via qualitative random sampling (sampling duration: 10 minutes). This allowed only for a snapshot in time, which is why the samples were aggregated into areas and meteorological seasons for analysis. Ideally, an automated sampler collects 24-hour composite samples on several days for each location, increasing representativeness and comparability. However, due to financial reasons, this was not possible for this doctoral thesis. Lastly, it was only possible to detect phenotypic ESBL-producing *E. coli* using culture-based methods; a genotypic confirmation was not implemented.

7.3. Outlook and future research

The geographical approach of the doctoral thesis revealed spatial variations of antibiotic use and related knowledge, attitudes and practices, as well as spatial and temporal patterns in the occurrence of antibiotic-resistant bacteria in untreated municipal wastewater. These findings raise further interesting (research) questions.

This doctoral thesis established that space-related factors are of relevance when considering antibiotic use in the community. Future studies could examine how space (and place) directly or indirectly affect antibiotic use, for instance, through the availability of and access to health care services or environmental conditions that determine the exposure to bacterial pathogens in different contexts (home, work, etc.). Investigating the interactions of different spatial and temporal contexts, possibly at different geographical scales, offers another interesting perspective.

Identifying differences between socio-spatially diverse urban areas with higher antibiotic use in a socio-spatially disadvantaged area raised further questions, primarily on the underlying drivers: Is antibiotic use higher in this area due to a higher (bacterial) infectious disease burden or because of more misuse? The household survey provided a baseline regarding knowledge, attitudes and practices around antibiotic use and resistance. Relevant disease data at such a small spatial scale was not available, and the disease burden was not examined per se in the survey. Participants from the socio-spatially disadvantaged area indeed reported more often potential mishandling practices.

Rooted in a different philosophical stance and employing qualitative methods, further studies could investigate determinants of possible mishandling on the patients' side along the antibiotic use chain (from acquisition over consumption to disposal) in greater depth. Additional studies could also look into the sources of information on antibiotic use and resistance in the general population to identify needs and evaluate the effectiveness of information or awareness campaigns in this context. Further research could focus on the doctor-patient relationship regarding the process of prescribing an antibiotic, revealing concrete drivers on both the supply and demand sides at the local level, which spatial aspects may also influence.

Regular and frequent use of antibiotics has lasting effects on the gut microbiota of humans (Ramirez et al., 2020) and animals (Allen & Stanton, 2014). In the context of humans, such alterations were linked to an increased risk of certain non-communicable diseases such as rheumatoid arthritis, diabetes and obesity (Keeney et al., 2014; Langdon et al., 2016). This has severe long-term health implications. Individuals with higher antibiotic use may find themselves trapped in a perpetual cycle of poor health. This potential public health problem requires further investigation, e.g. via longitudinal studies.

Monitoring ABR at the population level, wastewater-based surveillance systems are a promising approach to complement clinical testing. This concept has been tested for ABR (Aarestrup & Woolhouse, 2020a; Hendriksen et al., 2019), chemical drugs (Daughton, 2018) and different viruses (Heijnen & Medema, 2011; Hellmér et al., 2014), particularly for the poliovirus (Hovi et al., 2012) and SARS-Cov-2 (e.g. Medema et al., 2020; Peccia et al., 2020). So far, it has been mainly applied in public health but is conceptually transferable to the One Health context. Such an integrated approach could provide helpful health information at the local or regional level, especially in the context of ABR, where ARGs can be transferred between bacteria from different sources (Wellington et al., 2013). The main challenge of this approach is establishing relationships between the occurrence of specific biological biomarkers in wastewater systems and processes in the community, e.g. antibiotic consumption (Sims & Kasprzyk-Hordern, 2020).

This challenge presents another opportunity for future research. Further studies could investigate a more direct link between antibiotic consumption and the occurrence of antibiotics and their residues, antibiotic-resistant bacteria, and ARGs in stool samples at the individual level. Testing wastewater for the occurrence of such ABR elements in the neighbourhood where the individuals live, ideally with a high temporal resolution (e.g. weekly sampling), could complement this work. This might help understanding the pathway from the consumption of antibiotics in the community through the (human) gut into wastewater.

The work of this doctoral thesis was conducted in urban areas within a metropolitan sewershed, which is served by a centralised, piped wastewater system with a conventional municipal wastewater treatment plant. Its strength is the small-scale approach. The importance of wastewater-based (public) health surveillance systems (for ABR) has increased over recent years and will likely increase in the future. In large metropolitan sewersheds, it is usually impractical and economically not feasible to test the whole system with a higher spatial resolution than the WWTP level. In this context, the study area selection procedure applied in this doctoral thesis is conceptually transferable to other metropolitan areas with centralised wastewater systems. Depending on the (research) objective, selecting sampling areas within a metropolitan sewershed based on socio-spatial indicators to represent similar or different contexts at a small-scale level could be required. This work presented one application example where such a study area selection was suitable and proved expedient.

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Appendices

Material provided here supports the three main chapters 4 to 6 (i.e. the manuscripts) of the doctoral thesis. Some of the material was already made available online in the process of publishing the manuscripts in peer-reviewed journals. Where applicable, online links are provided for direct access to this material. In addition, further documents were added in the appendices of this doctoral thesis. The appendices are organized along the three chapters.

i. Supplementary material for chapter 4: What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector

a. Search details for each scientific database

The following document was submitted as supplementary material A supporting the publication that constitutes chapter 4 of this doctoral thesis: Schmiege et al. (2020): What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. https://doi.org/10.1016/j.ijheh.2020.113497.

It is available online under the following link: https://ars.els-cdn.com/content/image/1-s2.0-S1438463919309605-mmc1.docx

Search details: PubMed

No search strategies:

1

User query:

(((Antibiotic[Title/Abstract] OR antibacterial[Title/Abstract] OR antimicrobial[Title/Abstract]) AND (use[Title/Abstract] OR consum*[Title/Abstract] OR prescri*[Title/Abstract] OR sale[Title/Abstract])) AND (cultural[Title/Abstract] OR economic*[Title/Abstract] OR social[Title/Abstract] OR socio[Title/Abstract] OR season*[Title/Abstract] OR temporal[Title/Abstract] OR geographic*[Title/Abstract] OR regional*[Title/Abstract] OR spati*[Title/Abstract] OR political[Title/Abstract] OR institutional[Title/Abstract] OR regulatory[Title/Abstract] OR compositional[Title/Abstract] OR contextual[Title/Abstract] OR collective[Title/Abstract]))

Result:

2180

Database:

PubMed

Query translation:

((Antibiotic[Title/Abstract] OR antibacterial[Title/Abstract] OR antimicrobial[Title/Abstract]) AND (use[Title/Abstract] OR (consum[Title/Abstract] OR consumability[Title/Abstract] OR consumable[Title/Abstract] OR consumables[Title/Abstract] OR consumables'[Title/Abstract] OR consumado[Title/Abstract] OR consumate[Title/Abstract] OR consumated[Title/Abstract] OR consumately[Title/Abstract] OR consumating[Title/Abstract] OR consumation[Title/Abstract] OR consumatori[Title/Abstract] OR consumatorio[Title/Abstract] OR consumatory[Title/Abstract] OR consumber[Title/Abstract] OR consumble[Title/Abstract] OR consume[Title/Abstract] OR consume'[Title/Abstract] OR consumea[Title/Abstract] OR consumeables[Title/Abstract] OR consumed[Title/Abstract] OR consumed'[Title/Abstract] OR consumedduring[Title/Abstract] OR consumedfish[Title/Abstract] OR consumedly[Title/Abstract] OR consumen[Title/Abstract] OR consument[Title/Abstract] OR consumentenbond[Title/Abstract] OR consumentism[Title/Abstract] 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Search details: sciencedirect

No search strategies:

17

Total results:

893

Search for

1) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND social)

Results:

89

Search for

2) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND socio)

Results:

27

Search for

3) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND cultural)

Results:

41

Search for

4) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND economic)

Results:

130

Search for

5) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND economical)

Results:

15

Search for

6) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND season)

Results:

37

Search for

7) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND seasonal)

Results:

39

Search for

8) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND temporal)

Results:

38

Search for

9) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND geographic)

Results:

76

Search for

10) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND regional)

Results:

79

Search for

11) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND spatial)

Results:

11

Search for

12) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND compositional)

Results:

81

Search for

13) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND contextual)

Results:

11

Search for

14) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND collective)

Results:

21

Search for

15) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND political)

Results:

13

Search for

16) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND institutional)

Results:

135

Search for

17) (((Antibiotic OR antimicrobial OR antibacterial) AND (use OR consumption OR consum OR prescribing OR prescription)) AND regulatory)

Results:

50

Note: "geographical" and "spatio" did not yield any additional publication and were therefore left out.

Search details: Web of Science

No search strategies:

1

You searched for:

TOPIC: ((antibiotic OR antibacterial OR antimicrobial)) AND TITLE: ((use OR consum* OR sale* OR prescri*)) AND TITLE: ((Soci* OR cultur* OR economic* OR temporal OR spati* OR region* OR season* OR geographic* OR political OR institutional OR regulatory OR compositional OR contextual OR collective))

Results:

1091

b. Data extraction sheet

The Microsoft Excel data extraction sheet is not attached to this doctoral thesis due to its size. However, the file was submitted as supplementary material B supporting the publication that constitutes chapter 4 of this doctoral thesis: Schmiege et al. (2020): What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. https://doi.org/10.1016/j.ijheh.2020.113497.

It is available online under the following link: https://ars.els-cdn.com/content/image/1-s2.0-S1438463919309605-mmc2.xlsx

c. Variable grouping

The following document was submitted as supplementary material C supporting the publication that constitutes chapter 4 of this doctoral thesis: Schmiege et al. (2020): What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. https://doi.org/10.1016/j.ijheh.2020.113497.

It is available online under the following link: https://ars.els-cdn.com/content/image/1-s2.0-S1438463919309605-mmc3.docx

Table C. Variable grouping in descending order: determinant category, determinant group, variable group, and variable with the respective ID of the publication from which the variable was derived

Determinant category	Determinant group	Variable group	Variable	ID
Collective	Attitude	Atheistic	Atheistic vs. Religious	10
		Corruption and bribery	Perception corruption	57
			Experience bribery	57
		Emotional support	Emotional support	44
		Satisfaction	Medical practitioner not acceptable	61
			Satisfaction NHS	56
		Trust	Careful in trusting others	10
	Culture	Latin	Area has Latin or German culture	21
			Latin vs. Non-Latin	22
	Governance	Governance	Governance quality	27
	Guidelines	Guidelines for RTI	Physicians: guidelines for RTIs	10
		Presence STG	Presence STGs hospital care	50
			Presence STGs paediatric	50
	Hofstede's dimensions of national culture	Individualism	Individualism	12
			Individualism	17
			Individualism	27
		Indulgence	Indulgence vs. restraint	12
			Indulgence vs. restraint	27
		Long-term orientation	Long-term orientation	12
			Long-term orientation	17
			Long-term orientation	27
		Masculinity	Masculinity vs. feminity	12
			Masculinity vs. feminity	17
			Masculinity vs. feminity	27
		Power distance	Power distance	12
			Power distance	17
			Power distance	27
		Uncertainty avoidance	Uncertainty avoidance	12
			Uncertainty avoidance	17
			Uncertainty avoidance	27
	Membership in European Union	Membership in European Union	Membership in European Union	50
	Personality characteristics	Extraversion	Extraversion	27
		Neuroticism	Neuroticism	27
		Social desirability	Social desirability	27
	Regulation	Having national strategy	Countries with/without national strategy	50
		Overall index of regulation	Overall index level of regulation	50
		Presence OTC-sales	Presence OTC-sale	50
		Presence pharmaceutical training	Presence continued pharmaceutical training in rational use	50
		Registration with GP	Patients registered with GP	10
			Patients no registration with GP	10

		Restrictions pharmaceutical companies	Restrictions on pharmaceutical companies	10
	Tests (Blood, point of care)	Tests (Blood, point of care)	Point of care test	3
			Patient: Blood test	42
	Women participation in labour market	Women participation in labour market	Women participation	46
Compositional	Age	% of elderly population (>60)	% of population aged >65 years	10
			>65 negatively correlated	22
			% of elderly (>65 years)	26
			% of population >65	39
			% population >60 years old	40
			Population >65 years	45
			% of population 65-79	46
			% of population >80 years	46
			% of population >60 years	47
			% of population aged >64	53
			% of the population >65	67
		% of young population (<24)	Age <20 years	22
			Young population: <14 years old	26
			% aged <2 years	32
			% of population <5	39
			% population 5-15 years old	40
			% population <5 years old	40
			Population <15 years	45
			% of population <14	46
			% of population 15-24	46
			% of population 0–5 years	47
			% of population <14 years	47
			% of the population 0-14 years	50
			% of population aged 0-24	53
			% population <14-year-old	59
			% of the population aged <15 years	67
		Age groups: children and elderly	20-29, 30-39, 40-49, >50	1
			18-64, 65+	3
			Patient age	4
			0-17, 18-39, 40-59, >60	5
			Age	6
			Age	7
			Age	8
			Age	9
			Patient age	11
			Age	14
			10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, >90	15
			0-19, 20-45, 46-70, 71+	16
			Age	19
			Age	21
			Age	23
			Age	24
			0-14, 15-39, 40-59, 60+	25
			Age	29
			Patient mean age	42
			Age	43
			0-4, 5-18, 19-44, 45-64, 65+	52
			0-15, 16-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, 85+	53
			Age	61
			18-39, 40-59, >60	63
			0-5, 6-17, 18-64, 65-74, >75	66
			Age	69
			Age	70

			0-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, >80	72
		Paediatric: <6 years	Age groups: <1, 1-2, 3-6, 7-10, 11-15	13
			Age groups: 0-5, 6-13	18
			Age groups: 0-5, 6-12, 13-17	32
			Age groups: <4, 5-9, 10-14, 14-18, 18+	37
			Age	41
			Mean age of children	65
			Age	65
			Mean age of index child (months)	68
			Child's age: <2, >2 years	73
		Parental age	Parents age	65
			Mean age of mothers (years)	68
			Mother's age: <20, 20-40, >40 years	73
			Father's age	73
	Breastfeeding	Breastfeeding	Breastfed at 6 months of age	47
			Breastfeeding	44
			Still breastfeeding age 8 months	44
	Cohabitation	Single-parent	Single parent	40
			Single parent	34
			Single parent	35
			Cohabitation status	67
	Compliance	Keeping antibiotics at home	Keeping antibiotics home	68
		Parental self-medication	Maternal self-medication	68
			Parental self-prescribing	73
		Treatment abortion	Abandonment of use	73
	Concern and perception of illness	Concern and perception of illness	Perceived severity	61
			Level of concern illness	30
			Perceived infection prone	30
	Consultation rates	Consultation rates	Symptom: previous consultation	42
			Yearly no consultations and home visits per GP	47
			Expensive to consult doctor	61
			Inhabitant's consultation rates	69
			Physician consultation	30
	Day care attendance	Day care attendance	Day care outside home	30
			Out-of-home care	34
			Attending day care	65
			Attending day care centers	65
	Demand of patient	Demand of patient	Asking for antibiotics	20
			Requested medication	42
			Tendency demand antibiotics	68
			Parents pressure	73
			Parents dissatisfaction	73
	Education	Individual educational level	Educational level	1
			Education	5
			Level of education	7
			Education	8
			Education	9
			Education	10
			Education	22
			Educational level	26
			Education	27
			Educational level	28
			Education level	29
			4-year college	33
			BA or greater	39
			Higher education	40
			% illiterate	40
			Patient education	42

			No high school diploma	45
			Education	46
			Education	49
			Children and young people education	49
			Adult skills	49
			Education	61
			Education	66
			No education	70
		Maternal educational level	Maternal education	30
			Mother's highest education	38
			Maternal education	44
			Mother education	65
			Mother education	67
			Mother education	68
			Mother education	73
		Paternal educational level	Paternal education	30
			Father's highest education	38
			Father education	65
			Father education	73
		Parental educational level	Education parents	35
			Adult educational level	48
			Adult educational level	48
			Parents education	65
	Employment	Higher occupational status	Occupation	9
			Patient occupation	42
			Occupation	61
		Parental employment	Parent unemployed	30
			Unemployed parent	34
			Mother employment	38
			Father employment	38
			Maternal employment	44
		Unemployed population	Unemployment rate	10
			Unemployment rate	25
			Unemployment	28
			Unemployed population in labour force	39
			Employment	49
			Population unemployed	70
			Employment rate	31
			Area occupation deprivation	41
	Ethnicity	Europe	Share of foreigners	22
			Country of birth	66
			Patient ethnicity	71
			Parents born outside Nordic	30
			Ethnic status	31
			Parents country of birth	34
			Parents country of birth	35
			Ethnical background	38
			Parents country of birth	44
		Israel	Ethnicity	52
		New Zealand	Ethnicity	53
			Population born overseas	70
			Population identifying as Pacific Island	70
			Population identifying as Maori	70
			Ethnicity	72
			Ethnicity	36
		North America	Race/ethnicity	24
			Black race	33
			Non-white or African-American	39
			African-American alone	39
			Aboriginal population	45
			Visible minority population	45
			Indigenous population	62

			Immigrant population	62
			Race	63
			Race/ethnicity	32
	Income	Income	Monthly income	5
			Monthly income	7
			Income	8
			Patient low income	11
			Income per capita	21
			Income	22
			Household income	28
			Per capita income	33
			Income below poverty	39
			Living in poverty	39
			Mean family income	42
			Low income	45
			Household income	45
			Per capita national income	46
			Monthly net income	47
			Income	49
			Income deprivation	49
			Income deprivation	49
			Income per capita	54
			Annual income inhabitant	55
			Average annual income	58
			Income	61
			Low income	62
			Income	66
			Median personal income	70
			Median family income	70
			Monthly income	2
			Income	31
			Household income	38
			Area income deprivation	41
			Economic stress	44
			Household income	67
			Family income	73
	Knowledge	Knowledge	Do not work on virus	12
			Not effective for colds	12
			Cause side-effects	12
			Unnecessary use ineffective	12
			Questions answered correctly	12
		Parental knowledge	Infection with fever	2
			Used for similiar illness	2
			Treated past year	2
			No health care education	30
			Inadequate knowledge	30
			Knowledge URTIs antibiotics	68
	Life expectancy	Life expectancy	Life expectancy at birth	27
			Life expectancy	40
	Morbidity	Disease diagnosis	Malaria diagnosis	4
			URTI diagnosis	4
			Dermatological disease diagnosis	4
			Musculoskeletal disorder diagnosis	4
			Chronic disease factor	9
			Patient: diabetes	11
			Incidence gastrointestinal infections	21
			Incidence respiratory infections	21
			Incidence of infection	22
			Morbidity indicator	25
			Chronic disease	29
			Symptom: co-morbidity	42
			Campylobacteriosis rate	45

			Prevalence diabetes	47
			Prevalence malignant neoplasms	47
			Prevalence vaccination influenza	47
			Prevalence chronic obsructive pulmonary disease (COPD)	47
			Chronic diseases	52
			Diabetes mellitus	52
			Comorbidity	63
			Disease condition	63
			Co-morbidity: Carlson's index	66
			Limiting long-term illness	71
			Patient: diabetes	11
			Having asthma	30
			Diagnostic conditions	32
			Child: allergies	44
			Child: low birth weight	44
			ICD: Disease of Middle Ear and Mastoid	65
			ICD: Respiratory System Disease	65
			ICD: Genitourinary System Disease	65
			Disease groups	65
			Chronic disease in chid	73
		Symptoms	Symptom: fever	42
			Symptom: cough	42
			Symptom: diarrhoea	42
			Symptom: throat symptom	42
			Symptom: nasal symptoms	42
			Symptom: other symptoms	42
			Symptoms lasting more than 7 days	29
			Symptom: fever	65
			Symptom: throat soreness	65
			Symptom: earache	65
			Symptom: cough	65
			Other symptoms	65
	Mortality	Mortality rates	Mortality rate	45
			Incidence bacterial infections	46
			Mortality rate infectious diseases	54
			Mortality rate	57
	No. of children	No. of children	Number of children	2
			Having siblings	30
			Nr. in the family of brothers and sisters	44
			Number of children	65
	Obesity	% obese adults	Obese adults	32
	Sex	General: female	Gender	1
			Gender	3
			Gender	4
			Gender	5
			Gender	7
			Sex	8
			Gender	9
			Patient gender	11
			Sex	15
			Sex	16
			Gender	23
			Sex	29
			Gender	33
			% female	40
			Patient male gender	42
			Gender	43

			Gender	51
			Sex	53
			Sex	61
			Sex	63
			Sex	66
			Gender	69
			Sex	72
		Paediatric: boys	Patient gender	11
			Gender	13
			Gender	30
			Gender	32
			Sex	35
			Gender	36
			Gender	38
			Sex	41
			Child gender	44
			Gender	65
			Gender	65
			Child gender	73
		Parental sex	Relationship respondent with child	2
	Smoking in population	Smoking in population	Population smoke tobacco	70
			Smoker in the family	30
			Parent smokes daily	34
			Smoking habit parents	35
			Environmental smoking	44
			Maternal smoking	44
	Socio-economic sratus	Lower SES	Patient: social category	11
			Socio-economic level area	20
			Low socioeconomic status	52
			Provincial socio-economic development index	60
			Socio-economic status: Qualified and unqualified workers	31
			Low social status	34
	Source of medication	Source of medication	Source of medication	42
Contextual	Climate	Meteorological indicators	Year average dew point	10
			Climatological Dantin-Revenga Index	26
			Difference mean January and mean July temperature	39
			January average temperature	45
			July average temperature	45
			January total precipitation	45
			July total precipitation	45
			Annual total precipitation	45
	Deprivation	Area deprivation	Deprivation index	15
			Crime deprivation	49
			Health deprivation	49
			Overall index of multiple deprivation	49
			Socio-economic deprivation	49
			New Zealand Deprivation Index	53
			Index of Multiple Deprivation Score	70
			Deprivation index	36
			Area deprivation	41
			Area deprivation: security	41
		Housing deprivation	Average no of people in household	40
			Household size	45
			Homes with premises for bathing and washing	47
			No persons per 100 rooms	47

			Barriers to housing and services	49
			Living environment	49
			Indoor environment	49
			Outdoor environment	49
			Geographic barriers	49
			Wider barriers	49
			Ratio resident household members to no bedrooms in the dwelling	70
			Living in a rental flat	30
		Material deprivation	No persons receiving free access to selected medicines	47
			No persons receiving social assistance	47
			Less access to medical care	61
			Population no access to vehicle or telecommunication	70
			Recipients social benefit	31
	Economic	Agricultural GVA & GNI	Agricultural gross added value	26
			Gross national income	27
		Gini coefficient	Gini coefficient of equivalised disponsible income	28
			Gini coefficient	40
		Growth Domestic Product	Growth domestic product	25
			GDP per capita	26
			GDP per capita	40
			GDP per inhabitant	47
			GDP per capita	50
			GDP in the region	57
		Total health expenditure	Total health expenditure	10
			Total health expenditure	25
		Wealth index score	Wealth index score	68
	Geographical area	Geographical entities	Area borders another country	21
			Local health unit	23
			Region in Europe	29
			Geographical dummy	46
			Latitude	55
			Region	63
			County of residence	66
			Local health district	18
			Location of clinic	30
			US Census region	32
			Mean latitude	56
		Urban areas	Residence area	9
			Residence area	16
			Location	29
			% of urban	40
			Living in Sao Paulo metropolitan area	40
			Rural-urban	42
			Area of residence	51
			Residential location	53
			Municipality type	58
			Practice location	59
			Location	62
			Metropolitan statistical area	63
			Metropolitan statistical area	32
			Domicile	35
			Residence area	36
	Health care facility	Characteristics of HCF	Government facility: Patient volume (OPD)	42
			Government facility: Microscope	42
			Government facility: Bed strength	42
			Government facility: number of doctors	42

			Government facility: get antibiotic amount requested	42
			Government facility: interruptions in antibiotic supply	42
			Government facility: stock antibiotics	42
			Waiting time	61
			Availability index	66
			Practice: longer appointment duration	71
			Practice: practice list size	71
			Practice: list per full-time equivalent GP	71
		Location of HCF	Stratum: urban government, urban private	42
			Government - private	42
			Stratum: rural government, rural private	42
			Practice: location	71
			Distance to medical facility	68
		Type of HCF	Type health facility	4
			Clinics	39
			Kidney dialysis center	39
			General medcial and surgical hospital	39
			Childcare centres	39
			Retail clinics	39
			Clinic present indicator	39
			Private health establishment	40
			SUS health establishment	40
			Government facility: inpatient bed facility	42
			Government facility: biochemistry facility	42
			Government facility: X Ray facility	42
			Government facility: ECG facility	42
			Setting	63
			GP Practice: training, non-training	64
			Practice: Training	71
			Practice: group practice	71
			Ambulatory setting	32
	Hospitalization	Hospitalization rates	Medical discharge	39
			Hospital admittances infectious diseases	40
			Rate of hospitalization	52
			Hospitalization rate all causes	55
			Hospitalization rate	56
	Human Development Index	HDI	Human Development Index	40
			Human Development Index	56
	Insurance	Insurance payment	Patient: reimbursement	11
			No patient copayment	46
			Copayment	54
			Patient: reimbursement	11
		Insurance type	Health insurance status	4
			Medical insurance	61
			Insurance	62
			Insurance type	31
	Pharmacy	Characteristics pharmacist	Pharmacist dispensing policy	20
			Pharmacist belief in generic medicine efficiency	20
		Characteristics pharmacy	No. different products for sale	10
			Share non-prescription antibiotics	20
			Prescription target group	20

		Density pharmacies/pharmacists	Density pharmacies	21
			No. pharmacists	26
			Density pharmacies	47
			No. pharmacists	60
	Population density	Population density	Average population density per km^2	10
			Population density in counties	24
			Population density	25
			Region's population	25
			People per km^2	39
			Population density	40
			Population	40
			Population density	47
	Prescriber	Active	Prescriber: active	11
			Prescriber: active	11
		Age: <39 and >50 years	Prescriber: age	11
			Age physician	28
			Physician: age	42
			Practice: GP age <45 years	71
			Prescriber: age	11
			Prescriber age	18
		Experience: Mid-level	Physician: years since graduation	42
			Time since graduation	59
			Physician career stage	62
			Provider type	63
			Prescriber experience	18
		Ongoing training	Prescriber: qualification	11
			Physician: CME/conferences	42
			Physician: Library books/journals	42
			Physician: Internet surfing	42
			Physician: No of scientific programmes attended in last 2 years	42
			Physician: training courses attended	42
		Prescriptions	No diagnoses by prescriber	4
			No medicines prescribed	4
			Malaria treatment prescription	4
			Multiple prescriptions	20
			Penicillin:cephalosporin rate	26
			Anti-asthmatic prevalence	55
			GP's prescription rate	69
		Sex: female	Prescriber: gender	11
			Physician: gender	42
			Physician's gender	59
			Male physician	62
			Practice: GP female	71
			Prescriber: gender	11
			Prescriber gender	18
		Specialization	Specialization physician	28
			Physician: type of practice	42
			Physician: Highest qualification	42
			% Family physician	62
			Speciality	63
			Practice: GP country of qualification UK	71
			Prescriber: qualification	11
			Specialization practitioner	18
			Practitioner speciality	32
		Other characteristics	No enrolled patients per GP	47
			Inhabitants per medical doctor	57
			Prescriber: region	11
			Physician: Member of professional organization	42

			Physician: medical representativeness	42
			Physician: MIMS/CIMS/IDR	42
			Physician: Facility has antibiotic use guidelines	42
			Schemes remuneration for GP	46
			Prescriber: region	11
			Prescriber organizational arrangement	18
		Number of physicians	No of physicians	22
			No health professionals	26
			No physicians	26
			No odontologists	26
			No veterinarians	26
			No physicians	27
			No prescriber	32
			No paediatricians	55
			No physicians	60
			No paediatricians	56
		Physician density	Density physicians	21
			Physician density	25
			Offices of physicians	39
			Doctor-population ratio	45
			Physician density	46
			Density physicians	54
			Physician density	62
	Price	Price of a daily dose	Price of defined daily dose	21
			Price of a daily dose	22
			Price level of defined daily dose	46
	Resistance	Resistance rates	E. coli percentage intermediate and fully resistant to third-generation cephalosporins	10
			Rate of bacterial resistance	46
	Seasonality	First and fourth quarter	Seasonal variation	3
			Seasonal fluctuation	14
			Seasonal fluctuation	19
			Seasonal variation	21
			Seasonal effects	22
			Season of prescribing	59
			Seasonality	72
			Seasonality	37

d. List of studies included in the systematic literature review

The following document was submitted as supplementary material D supporting the publication that constitutes chapter 4 of this doctoral thesis: Schmiege et al. (2020): What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. https://doi.org/10.1016/j.ijheh.2020.113497.

It is available online under the following link: https://ars.els-cdn.com/content/image/1-s2.0-S1438463919309605-mmc4.docx

Table D. Overview of studies included in the data analysis and their contribution of variables (marked by an "x") to the respective determinant categories compositional (Com), contextual (Con), and collective (Col)

No	Publication	Col	Com	Con
1	Abasaeed et al. (2009)[HS]	-	x	-
2	Abobotain et al. (2013)	x	x	-
3	Achermann et al. (2010)	x	x	x
4	Ahiabu et al. (2016)	-	x	x
5	Al-Azzam et al. (2007)[HS]	-	x	-
6	Augustin et al. (2015)	-	x	-
7	Awad et al. (2005)[HS]	-	x	-
8	Barah & Goncalves (2010)[HS]	-	x	-
9	Berzanskyte et al. (2006) [HS]	-	x	x
10	Blommaert et al. (2014)[HS]	x	x	x
11	Blommaert et al. (2013)	-	x	x
12	Borg (2012)	x	-	-
13	Borgnolo et al. (2001)	-	x	-
14	Ciszewski et al. (2017)	-	x	x
15	Covvey et al. (2014)	-	x	x
16	de Jong et al. (2014)	-	x	x
17	Deschepper et al. (2008)	x	-	-
18	Di Martino et al. (2017)	-	x	x
19	Dziurda et al. (2008)	-	x	x
20	Farah et al. (2015)	-	x	x
21	Filippini et al. (2009)	x	x	x
22	Filippini et al. (2006)	x	x	x
23	Franchi et al. (2011)	-	x	x
24	Gahbauer et al. (2014)	-	x	x
25	Gallini et al. (2012)	-	x	x
26	Garcia-Rey et al. (2004)	-	x	x
27	Gaygisiz et al. (2017)	x	x	x
28	Gianino et al. (2018)	-	x	x
29	Grigoryan et al. (2006)[HS]	-	x	x
30	Hedin et al. (2006)	x	x	x
31	Henricson et al. (1998)	-	x	x
32	Hersh et al. (2011)	-	x	x
33	Hicks et al. (2015)[HS]	-	x	x
34	Hjern et al. (2001)	-	x	x
35	Hjern et al. (2000)	-	x	x
36	Hobbs et al. (2017)	-	x	x
37	Holstiege et al. (2014)	-	x	x
38	Jensen et al. (2016)	-	x	-
39	Klein et al (2015)	-	x	x
40	Kliemann et al. (2016)	-	x	x
41	Koller et al. (2013)	-	x	x
42	Kumar et al. (2008)	x	x	x
43	Majeed & Moser (1999)[HS]	-	x	-

44	Mangrio et al. (2009)	x	x	-
45	Marra et al. (2010)	-	x	x
46	Masiero et al. (2010)	x	x	x
47	Matuz et al. (2005)	-	x	x
48	Melander et al. (2003)	-	x	-
49	Mölter et al. (2018)	-	x	x
50	Mueller & Östergren (2016)	x	x	x
51	Muscat et al. (2006)[HS]	-	x	x
52	Nitzan et al. (2010)	-	x	x
53	Norris et al. (2011)[HS]	-	x	x
54	Ortiz & Masiero (2013)	-	x	x
55	Piovani et al. (2014)	-	x	x
56	Piovani et al. (2012)	x	-	x
57	Rönnerstrand & Lapuente (2017)	x	x	x
58	Russo et al. (2018)	-	x	x
59	Safaeian et al. (2015)	-	-	x
60	Sahin et al. (2017)	-	x	x
61	Saradamma et al. (2000)	x	x	x
62	Schwartz et al. (2018)	-	x	x
63	Shapiro et al. (2014)[HS]	-	x	x
64	Steinke et al. (2000)[HS]	-	-	x
65	Stojanovic-Spehar et al. (2008)	-	x	-
66	Ternhag et al. (2014)	-	x	x
67	Thrane et al. (2003)	-	x	-
68	Togoobaatar et al. (2010)[HS]	x	x	x
69	Walle-Hansen et al. (2018)	-	x	x
70	Walls et al. (2015)	-	x	x
71	Wang et al. (2009)[HS]	-	x	x
72	Williamson et al. (2016)	-	x	x
73	Zhang et al. (2005)	-	x	-

Please note: [HS] marks studies identified via the manual hand-search of reference lists.

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ii. Supplementary material for chapter 5: Associations between socio-spatially different urban areas and knowledge, attitudes, practices and antibiotic use: a cross-sectional study in the Ruhr Metropolis, Germany

a. Consent form

Fragebogen-ID:

Informationsschrift und Einwilligungserklärung zur Erhebung und Verarbeitung anonymisierter Interviewdaten

In der vorliegenden Umfrage geht es um die Benutzung, das Wissen und die Einstellung von und über Antibiotika in der Bevölkerung in Dortmund. Diese Umfrage wird durchgeführt im Rahmen eines Promotionsprojekts an der Universität Bonn in dem Forschungskolleg „One Health und urbane Transformation" gefördert durch das Land Nordrhein-Westfalen. Ziel dieser Umfrage ist ein besseres Verständnis über den Umgang mit Antibiotika im ambulanten Sektor.

Die Teilnahme an dem Interview erfolgt freiwillig und ist unentgeltlich. Es besteht zu jeder Zeit die Möglichkeit, das Interview abzubrechen oder die Einwilligungserklärung zu widerrufen, ohne dass Ihnen dadurch irgendwelche Nachteile entstehen. Die Kontaktdaten dazu finden Sie entsprechend unten.

Die Umfrage dauert 20 Minuten und beinhaltet Fragen über die Handhabung von Antibiotika im Alltag sowie Fragen rund um das Wissen und die Einstellung von Antibiotikabenutzung. Weiterhin gibt es Fragen zu so genannten Risikofaktoren, d.h. speziellen Merkmalen oder Gegebenheiten, für die Kolonisierung, d.h. die Besiedelung oder das Vorkommen, des menschlichen Darms mit einer bestimmten Bakteriengruppe.

Ihre Antworten werden mit einem Tablet erfasst und in Zahlen umgewandelt. Der Computer erstellt aus den Angaben aller Befragten z.B. Tabellen mit Häufigkeiten und Mittelwerten. Die Ergebnisse der Befragung werden ausschließlich in anonymisierter Form ausgewertet. Alle Angaben zur Identifizierung von Personen in jeglicher Schriftform werden entfernt, um Rückschlüsse auf Einzelpersonen zu verhindern. Die Antworten werden vertraulich behandelt. Da die Daten ohne Personenbezug verarbeitet werden, sind ein späterer Widerruf und eine Löschoption nicht mehr möglich.

Die Ergebnisse dieser Umfrage werden ausschließlich zu wissenschaftlichen Zwecken innerhalb des NRW Forschungskollegs „One Health und urbane Transformation" benutzt und nicht mit Dritten geteilt. Eine Veröffentlichung der Ergebnisse in einem wissenschaftlichen Journal ist geplant.

Ich bin damit einverstanden, im Rahmen des genannten Promotionsprojekts freiwillig an einem Interview teilzunehmen und bestätige hiermit, dass ich die aufgeführten Punkte gelesen und verstanden habe.

☐ ja
☐ nein

Dortmund, den

Ort, Datum / Unterschrift

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Anhang

Erklärung zum Datenschutz und zur absoluten Vertraulichkeit Ihrer Angaben

Diese Studie wird im Rahmen des NRW Forschungskollegs „One Health und urbane Transformation" von der Universität Bonn durchgeführt. Die Arbeit der Universität Bonn folgt streng den Vorschriften des Bundesdatenschutzgesetzes und der Datenschutz-Grundverordnung. Ihre Antworten werden unter Wahrung der datenschutzrechtlichen Bestimmungen ausschließlich für dieses Forschungsprojekt wissenschaftlich ausgewertet. Hierzu werden Ihre Antworten im Fragebogen in Zahlen umgewandelt und ohne Ihren Namen oder Ihre Adresse in einen Computer eingegeben. Dieser Computer erstellt aus den Angaben aller Befragten z. B. Tabellen mit Häufigkeiten und Mittelwerten. Die Ergebnisse der Befragung werden also ausschließlich in anonymisierter Form ausgewertet. Das bedeutet, niemand kann später aus den Ergebnissen erkennen, von welcher Person die Angaben gemacht worden sind.

Die Angaben aus dem Fragebogen werden nur durch eine Codenummer Ihrer Einverständniserklärung verknüpft. Spätestens am Ende des Forschungsprojekts in 12 Monaten werden die Codenummern vernichtet. Eine Zuordnung der Antworten zu einer Person ist dann unmöglich.

Ihre Teilnahme an dieser Befragung ist freiwillig. Durch die Nicht-Teilnahme entstehen Ihnen keine Nachteile. Ich möchte Sie aber um Ihre Unterstützung bitten, da wir die Angaben wirklich aller ausgewählten Personen benötigen. Sie können absolut sicher sein, dass niemand erfährt, welche Antworten Sie gegeben haben und keine Daten an Dritte weitergegeben werden, die eine Identifizierung Ihrer Person erlauben.

Ich danke Ihnen für Ihre Unterstützung und Ihr Vertrauen!

Dennis Schmiege

b. Ethical approval of the University of Bonn

Rheinische Friedrich-Wilhelms-Universität
Medizinische Fakultät
Ethik-Kommission

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KRa/Ro

Ethik-Kommission - Medizinische Fakultät Bonn
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Herr
Prof. Dr. Kistemann
IHPH – Institut für Hygiene und Öffentliche
Gesundheit/Public Health
Universitätsklinikum Bonn
Venusberg-Campus 1
53127 Bonn – durch Boten

Lfd. Nr. 052/20
Bitte stets angeben!

Betr.: **Ihr Antrag an die Ethik-Kommission**
Promotionsarbeit D. Schmiege
Antragsteller: **Prof. Dr. Kistemann**
Studientitel: **Wissen, Einstellung und Handhabung von Antibiotika und deren Determinanten in der allgemeinen Bevölkerung in Dortmund, Ruhr Metropole**

Auflistung der eingereichten Unterlagen siehe Anlage

Sehr geehrter Herr Professor Kistemann,

die Ethik-Kommission für klinische Versuche am Menschen und epidemiologische Forschung mit personenbezogenen Daten der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn hat die o. g. Unterlagen geprüft und sieht die Punkte unseres Schreibens vom 13.02.2020 ausreichend beantwortet.

Die Ethik-Kommission hat nun, aufgrund der vorgelegten Unterlagen, gegen die geplante Studie keine berufsethischen oder berufsrechtlichen Bedenken zu erheben.

Änderungen im Prüfplan müssen der Ethik-Kommission mitgeteilt werden und bedürfen der erneuten Beratung.
Des Weiteren müssen Änderungen bei den beteiligten Prüfärzten der Ethik-Kommission unverzüglich mitgeteilt werden.

Die ärztliche und juristische Verantwortung des Leiters der klinischen Prüfung und der an der Prüfung teilnehmenden Ärzte bleibt entsprechend der Beratungsfunktion der Ethik-Kommission durch unsere Stellungnahme unberührt.

Bankverbindung: Deutsche Bank Bonn SEPA: IBAN: DE91380700590031379100; BIC: DEUTDEDK380
BLZ: 380 700 59; Konto-Nr. 313 791, Unterkonto "Ethik-Kommission V-099.0068"
Bei Auslandsüberweisungen: Deutsche Bundesbank, Filiale Köln, BLZ 370 000 00, Konto-Nr. 38 0015 22).
SEPA : IBAN: DE58370000000038001522, BIC MARKDEF1370

Ethik-Kommission Bonn Lfd. Nr. 052/20 09.04.20

2

Die Ethik-Kommission der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn arbeitet gemäß den nationalen gesetzlichen Bestimmungen und den ICH-GCP Richtlinien. Den Beratungen der Ethik-Kommission der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn liegt gemäß der gültigen Berufsordnung die maßgebende Deklaration des Weltärztebundes von Helsinki in der letzten revidierten Fassung zugrunde.

Mit freundlichen Grüßen

Prof. Dr. K. Racké
Vorsitzender der Ethik-Kommission

c. Detailed information on the indicators used for study area selection

The following document was submitted as supporting information 1 supporting the publication that constitutes chapter 5 of this doctoral thesis: Schmiege et al. (*under review*): Associations between socio-spatially different urban areas and knowledge, attitudes, practices and antibiotic use: a cross-sectional study in the Ruhr Metropolis, Germany.

Supporting information 1

Table. Definitions of indicators used for study area selection

Indicator	Full name in reference	Pages	Additional information
Settlement and traffic area	Share of settlement and traffic area of the total area 2018 (%)	10-11	--
Inhabitants/ha	Inhabitants (main residential population) as of 31.12.2018 per hectare of settlement area	16-17	--
Living space/inhabitant	Living space per inhabitant (population entitled to reside) in buildings with residential space on 31.12.2016 (sqm)	94-95	--
Share of flats in one- or two-family houses	Share of apartments in one- and two-family houses in all apartments in residential buildings as of Dec. 31, 2016 (%)	90-91	--
Share of persons below age 18	Percentage of 0- to under-6-year-olds in the main resident population as of Dec. 31, 2018 (%) + Percentage of 6- to under-18-year-olds in the main resident population as of Dec. 31, 2018 (%)	20-21 + 22-23	--
Share of persons above age 65	Percentage of 65- to under-80-year-olds in the main resident population as of Dec. 31, 2018 (%) + Percentage of 80-year-olds and older in the main resident population as of Dec. 31, 2018 (%)	30-31 + 32-33	--
Share of households with children	Share of households with children under 18 in all households as of 12/31/2018 (%)	84-85	--
Share of single-parent households	Percentage of single-parent households among all households with children under 18 on Dec. 31, 2018	86-87	--
Share with migration background	Persons with German citizenship and migration background as a percentage of the main resident population in 2018 (%)	64-65	Persons with a migration background include*: • Foreigners and their children • Naturalized persons and their children • (Late) emigrants and their children **Basis for the assignment is the MigraPro method in which migration background is approximately derived from the population register.*
Share of foreigners	Persons with exclusively non-German citizenship as a percentage of the main resident population in 2018 (%)	66-67	--
Share of employed population	Proportion of employees subject to social security contributions (at place of residence) in the population aged 18 to under 65 in December 2018 (%)	100-101	--

Indicator	Full name in reference	Pages	Additional information
Share of unemployed population	Unemployed registered with the Federal Employment Agency as a percentage of the labor force (employed + unemployed) in December 2018 (%)	108-109	--
Share of recipients of state transfer payments	Recipients of state transfer benefits (social minimum income benefits) as a percentage of the main resident population in December 2018	118-119	Includes basic cover for jobseekers (code of social law (SGB II)), basic cover in old age or in the event of reduced earning capacity (code of social law (SGB XII)), assistance for living expenses, and standard benefits under the Asylum Seekers Benefits Act.

Reference

City Statistics. (2019). *Statistikatlas. Dortmunder Stadtteile* (Issue 215). https://www.dortmund.de/media/p/statistik/pdf_statistik/veroeffentlichungen/statistikatlas/215_-_Statistikatlas_-_2019.pdf, last accessed 09.08.2021

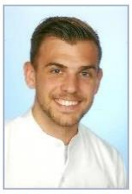
d. Announcement flyer

UNIVERSITÄT BONN | GEOGRAPHIE | Zentrum für Entwicklungsforschung Center for Development Research University of Bonn | ihph

Seien Sie dabei!

Hiermit möchten wir Sie herzlich zu einer Haushaltsbefragung der Universität Bonn einladen.

Worum geht's? Medikamentennutzung
Wann? Februar und März 2020
Wer führt die Befragung durch?



Dennis Schmiege

Malena Joost

Leonard Aurisch

Sehr geehrte Damen und Herren,

im Februar und März 2020 werden unsere Interviewer in Ihrem Stadtbezirk unterwegs sein und Sie zum Thema Medikamentennutzung befragen. Diese Befragung dauert etwa 20 Minuten. Ihre Teilnahme ist dabei von entscheidender Bedeutung und leistet einen wertvollen Beitrag!

Das Land Nordrhein-Westfalen fördert dieses internationale Forschungsprojekt im Rahmen des Forschungskollegs „One Health und urbane Transformation". Ihre Teilnahme ist anonym und selbstverständlich freiwillig. Ihre Daten werden strikt vertraulich behandelt, nicht an Dritte weitergegeben und ausschließlich zu wissenschaftlichen Zwecken benutzt.

Für Ihre Teilnahme möchten wir uns vorab ganz herzlich bei Ihnen bedanken!

Wir verbleiben mit freundlichen Grüßen

Prof. Dr. Mariele Evers | Prof. Dr. Thomas Kistemann | Dennis Schmiege

Sollten Sie Fragen haben oder nicht teilnehmen wollen, können Sie uns wie folgt erreichen:

Dennis Schmiege
Geographisches Institut der Universität Bonn,
Meckenheimer Allee 166, 53115 Bonn
E-Mail: d.schmiege@uni-bonn.de

Finanziert durch
Ministerium für Kultur und Wissenschaft des Landes Nordrhein-Westfalen

e. Full questionnaire of the household survey

The survey questionnaire was coded in the free and open source software KoBoToolbox (https://www.kobotoolbox.org/). The interviews in the general population were carried out tablet-based and face-to-face. Attached in the following is the PDF version of the tablet-based questionnaire, which means that skip logics cannot be displayed but are indicated by the light grey text.

Haushaltsbefragung_Fragebogen_FINAL

Allgemeine Angaben

Datum

yyyy-mm-dd

Untersuchungsgebiet

- ◯ Erpinghof
- ◯ Am Lohbach
- ◯ Osterholz

Interviewer

- ◯ Leonard Aurisch
- ◯ Malena Joost
- ◯ Dennis Schmiege
- ◯ Andere/r und zwar...

Name

Einverständniserklärung der/des Teilnehmenden

Bevor wir mit dem Interview beginnen können, müssten Sie mir noch Ihr Einverständnis geben. Dazu möchte ich Sie noch auf ein paar Punkte hinweisen.

Die Umfrage wird in etwa 20 Minuten dauern und beinhaltet Fragen über die Handhabung von Antibiotika im Alltag, Risikofaktoren für die Kolonisierung mit einer bestimmten Bakteriengruppe, sowie Fragen rund um das Wissen und die Einstellung von Antibiotikabenutzung. Hinzu kommen einige Angaben zu Ihrer Person, um eine detaillierte Analyse der Daten zu ermöglichen.

Ihre Teilnahme erfolgt freiwillig und ist unentgeltlich. Sie können das Interview zu jeder Zeit abbrechen, ohne dass Ihnen dadurch irgendwelche Nachteile entstehen. Ihre Antworten werden strikt vertraulich behandelt. Alle Angaben zur Identifizierung der Person werden entfernt, dadurch sind keine Rückschlüsse auf Einzelpersonen möglich. Die Ergebnisse werden ausschließlich zu wissenschaftlichen Zwecken benutzt und nicht mit Dritten geteilt.

All diese Information und die Kontaktdaten finden Sie zusätzlich auf der Einwilligungserklärung, die wir Ihnen aushändigen.

Haben Sie soweit alles verstanden oder war etwas unklar? Haben Sie ansonsten Fragen an mich, bevor wir mit dem Fragebogen beginnen?

Ist der/die Teilnehmende einverstanden?

- ◯ Ja
- ◯ Nein

Welches Geschlecht hat die teilnehmende Person?

- ◯ männlich
- ◯ weiblich
- ◯ divers
- ◯ Keine Angabe

Risikofaktoren für Kolonisierung

Ich möchte gerne mit Fragen zu so genannten Risikofaktoren beginnen, welche ein Anhaltspunkt für Antibiotikanutzung sein können.

Sind Sie in den vergangenen 12 Monaten außerhalb Deutschlands gereist?

SOWOHL URLAUBS- ALS AUCH DIENSTREISEN ZÄHLEN HIER.

- ◯ Ja
- ◯ Nein

Wie oft waren Sie im Ausland?

EIN EVENT ZÄHLT ALS 1.

____

In welchem Land/in welchen Ländern waren Sie im Ausland?

MEHRFACHNENNUNGEN BITTE DURCH EIN KOMMA TRENNEN.

____

Hatten Sie während einer dieser Aufenthalte gesundheitliche Probleme?

- ◯ Ja
- ◯ Nein

In welchem Land/in welchen Ländern traten Gesundheitsprobleme auf?

____

Hatten Sie während einer dieser Aufenthalte Kontakt mit dem Gesundheitssystem vor Ort?

- ◯ Ja
- ◯ Nein

In welchem Land/inwelchen Ländern hatten Sie Kontakt mit dem Gesundheitssystem?

MEHRFACHNENNUNGEN BITTE DURCH EIN KOMMA TRENNEN.

____

Wie oft nehmen Sie Fleisch zu sich?

- ◯ täglich oder mehrmals täglich
- ◯ 4-6 Mal pro Woche
- ◯ 1-3 Mal pro Woche
- ◯ weniger als einmal pro Woche
- ◯ nie
- ◯ Keine Angabe

Welche Tierarten verzehren Sie am meisten im Alltag?
MEHRFACHNENNUNG MÖGLICH.

- ☐ Geflügel
- ☐ Rind
- ☐ Schaf
- ☐ Schwein
- ☐ Weiß nicht
- ☐ Keine Angabe

Haben Sie Haustiere?

- ◯ Ja und zwar...
- ◯ Nein
- ◯ Keine Angabe

Bitte nennen Sie uns jeweils die Anzahl und die Haustierart für alle Tiere in Ihrem Besitz.
FALLS MEHRERE HAUSTIERARTEN GENANNT WERDEN, BITTE DURCH EIN KOMMA TRENNEN

____

Wie ist Ihr Gesundheitszustand im Allgemeinen?

- ◯ Sehr gut
- ◯ Gut
- ◯ Mittelmäßig
- ◯ Schlecht
- ◯ Sehr schlecht
- ◯ Keine Angabe

Haben Sie in den vergangenen 12 Monaten einen Hausarzt (Allgemeinmediziner) oder Facharzt in einer Praxis konsultiert, um sich selbst beraten, untersuchen oder behandeln zu lassen?

- Ja, einen Hausarzt
- Ja, einen Facharzt
- Ja, einen Hausarzt und einen Facharzt
- Nein
- Keine Angabe

Wie oft haben Sie einen Hausarzt konsultiert?

______

Wie oft haben Sie einen Facharzt konsultiert?

______

Was für einen Facharzt haben Sie konsultiert?

______

Hat sich bei Ihnen in den vergangenen 12 Monaten eine Untersuchung oder Behandlung verzögert, weil die Entfernung zu weit war, es Probleme gab, dorthin zu kommen oder wegen zeitlicher Probleme (Terminvergabe)?

MEHRFACHNENNUNG MÖGLICH.

- Ja, weil die Entfernung zu weit war
- Ja, weil es Probleme gab, dorthin zu kommen
- Ja, aufgrund zeitlicher Probleme
- Nein
- Keine Angabe

Hat sich bei Ihnen in den vergangenen 12 Monaten eine Untersuchung oder Behandlung aus anderen Gründen verzögert?

- Ja
- Nein
- Weiß nicht
- Keine Angabe

Bitte benennen Sie die anderen Gründe.

______

Haben Sie in den vergangenen 12 Monaten als stationärer Patient, das heißt über Nacht oder länger, im Krankenhaus gelegen?

- Ja
- Nein

Wie viele Nächte haben Sie insgesamt in den letzten 12 Monaten als stationärer Patient im Krankenhaus gelegen?

____

Wurden Sie in den vergangenen 12 Monaten als Tagespatient in ein Krankenhaus aufgenommen?

- ◯ Ja
- ◯ Nein

Wie oft wurden Sie in den vergangenen 12 Monaten als Tagespatient in ein Krankenhaus aufgenommen?

____

Haben Sie eine chronische Krankheit oder ein lang andauerndes gesundheitliches Problem?

- ◯ Ja und zwar...
- ◯ Nein
- ◯ Keine Angabe

Bitte nennen Sie uns Ihre chronische Krankheit/en.

MEHRFACHNENNUNGEN BITTE DURCH EIN KOMMA TRENNEN.

____

Haushaltzusammensetzung

Um die nachfolgenden Fragen zur Antibiotikanutzung einfacher zu gestalten und besser einsortieren zu können, werde ich Sie kurz zu Ihrer Haushaltszusammensetzung und Wohnsituation befragen.

____

Haben Sie in den vergangenen 12 Monaten ununterbrochen in dieser Wohnung/diesem Haus gewohnt?

- ◯ Ja
- ◯ Nein

Seit wann wohnen Sie in dieser Wohnung/diesem Haus?

ANGABE VON MONAT. JANUAR, FEBRUAR UND MÄRZ EXISTIEREN FÜR 2019 UND 2020.

- ○ Januar 2019
- ○ Januar 2020
- ○ Februar 2019
- ○ Februar 2020
- ○ März 2019
- ○ März 2020
- ○ April 2019
- ○ Mai 2019
- ○ Juni 2019
- ○ Juli 2019
- ○ August 2019
- ○ September 2019
- ○ Oktober 2019
- ○ November 2019
- ○ Dezember 2019
- ○ Weiß nicht
- ○ Keine Angabe

Waren Sie in den vergangenen 12 Monaten länger als ein Monat am Stück nicht zuhause?

- ○ Ja
- ○ Nein

In welchen Monaten waren Sie nicht zuhause?

ANGABE VON MONATEN. JANUAR, FEBRUAR UND MÄRZ EXISTIEREN FÜR 2019 UND 2020.

- ☐ Januar 2019
- ☐ Januar 2020
- ☐ Februar 2019
- ☐ Februar 2020
- ☐ März 2019
- ☐ März 2020
- ☐ April 2019
- ☐ Mai 2019
- ☐ Juni 2019
- ☐ Juli 2019
- ☐ August 2019
- ☐ September 2019
- ☐ Oktober 2019
- ☐ November 2019
- ☐ Dezember 2019
- ☐ Weiß nicht
- ☐ Keine Angabe

Welchen Familienstand haben Sie?

- ◯ Verheiratet oder eingetragene Lebenspartnerschaft und lebe mit meinem/meiner (Ehe)Partner/in zusammen
- ◯ Verheiratet oder eingetragene Lebenspartnerschaft und lebe von meinem/meiner (Ehe)Partner/in getrennt
- ◯ Ledig
- ◯ Geschieden oder eingetragene Lebenspartnerschaft aufgehoben
- ◯ Verwitwet oder eingetragene Lebenspartner/in verstorben
- ◯ Keine Angabe

Leben Sie zurzeit mit einer Person aus Ihrem Haushalt in einer Partnschaft?

- ◯ Ja
- ◯ Nein
- ◯ Weiß nicht
- ◯ Keine Angabe

Wie viele Personen leben ständig in Ihrem Haushalt, Sie selbst eingeschlossen?

____

Wie viele Personen davon sind unter 5 Jahre alt?

____

Wie viele Personen davon sind zwischen 5 und 18 Jahre alt?

____

Wie viele Personen davon sind zwischen 65 und 79 Jahre alt?

____

Wie viele Personen davon sind über 80 Jahre alt?

____

Antibiotikanutzung

Antibiotika sind Medikamente, die bei bestimmten Erkrankungen und gegen bestimmte Erreger verschrieben werden. Bekanntere Klassen sind etwa Penicilline (z.B. Amoxicillin, Cefuroxim) und Cephalosporine, aber auch Tetracycline (z.B. Doxycyclin) und Chinolone (z.B. Ciprofloxacin) werden verschrieben. Antibiotikaresistenz hingegen beschreibt einen Prozess, bei dem ein Antibiotikum seine Wirksamkeit gegenüber bestimmten Erregern verliert.

Die folgenden Fragen drehen sich um die Einnahme und Handhabung solcher Medikamente von Ihnen oder von einem anderen Haushaltsmitglied.

Wurde in Ihrem Haushalt jemals ein Antibiotikum genutzt?

- ○ Ja
- ○ Nein
- ○ Weiß nicht
- ○ Keine Angabe

Woher beziehen Sie Antibiotika in Ihrem Haushalt?
MEHRFACHNENNUNG MÖGLICH.

- ☐ Ich habe die Reste einer alten Packung benutzt
- ☐ Ein Verwandter/Bekannter hat es mir gegeben
- ☐ Von einem Arzt im Krankenhaus
- ☐ Von einem niedergelassenen Arzt
- ☐ Weiß nicht
- ☐ Keine Angabe

Wie lange wird ein Antibiotikum in Ihrem Haushalt angewandt?
MEHRFACHNENNUNG MÖGLICH.

- [ ] Bis die Packung vollständig aufgebraucht ist
- [ ] Bis ich mich besser fühle
- [ ] Nach Angaben der Packungsbeilage
- [ ] Nach Empfehlung des Apothekers
- [ ] Nach Anweisung des Arztes
- [ ] Keine Angabe

Was passiert mit den Antibiotikaresten in Ihrem Haushalt?
MEHRFACHNENNUNG MÖGLICH.

- [ ] Abgabe in der Apotheke
- [ ] Abgabe beim Sondermüll oder Abfall-/Schadstoffmobil
- [ ] Aufbewahrung
- [ ] Entsorgung über den Hausmüll
- [ ] Entsorgung über die Toilette
- [ ] Es wurde alles aufgebraucht
- [ ] Keine Angabe

Haben Sie in den vergangenen 12 Monaten ein Antibiotikum eingenommen?

- ○ Ja
- ○ Nein
- ○ Weiß nicht
- ○ Keine Angabe

Wie oft haben Sie in den vergangenen 12 Monaten ein Antibiotikum eingenommen?

____

In welchem Monat/in welchen Monaten haben Sie ein Antibiotikum eingenommen?

WENN ANZAHL EINNAHME >1, MEHRFACHNENNUNG MÖGLICH. JANUAR, FEBRUAR UND MÄRZ EXISTIEREN FÜR 2019 UND 2020.

- [ ] Januar 2019
- [ ] Januar 2020
- [ ] Februar 2019
- [ ] Februar 2020
- [ ] März 2019
- [ ] März 2020
- [ ] April 2019
- [ ] Mai 2019
- [ ] Juni 2019
- [ ] Juli 2019
- [ ] August 2019
- [ ] September 2019
- [ ] Oktober 2019
- [ ] November 2019
- [ ] Dezember 2019
- [ ] Weiß nicht
- [ ] Keine Angabe

Können Sie den Zeitraum eingrenzen?

WENN ANZAHL EINNAHME >1, MEHRFACHNENNUNG MÖGLICH.

- [ ] Frühling
- [ ] Sommer
- [ ] Herbst
- [ ] Winter
- [ ] Weiß nicht
- [ ] Keine Angabe

Wogegen haben Sie das Antibiotikum eingenommen?
WENN ANZAHL EINNAHME >1, MEHRFACHNENNUNG MÖGLICH.

- ☐ Angina
- ☐ Bronchitis
- ☐ Durchfall
- ☐ Erkältung
- ☐ Fieber
- ☐ Gelenk-/Sehnen-/Muskelentzündung
- ☐ Grippe
- ☐ Halsschmerzen
- ☐ Harnwegsinfekt (Blasenentzündung)
- ☐ Haut- oder Wundinfektion
- ☐ Kopfschmerzen
- ☐ Lungenentzündung
- ☐ Ohrenentzündung
- ☐ prophylaktisch gegen Sekundärinfektionen
- ☐ Rachenentzündung
- ☐ Scharlach
- ☐ Schnupfen
- ☐ Zahninfektion
- ☐ Andere Beschwerden und zwar...
- ☐ Weiß nicht
- ☐ Keine Angabe

Was für andere Beschwerden waren das?

____

Hat ein anderes Haushaltsmitglied in den vergangenen 12 Monaten ein Antibiotikum eingenommen?

- ○ Ja
- ○ Nein
- ○ Weiß nicht
- ○ Keine Angabe

Wie viele Haushaltsmitglieder - Sie selbst ausgeschlossen - haben in den vergangenen 12 Monaten ein Antibiotikum eingenommen?

____

» Bitte teilen Sie uns die folgenden Merkmale dieser Haushaltsmitglieder mit (beginnend mit der jüngsten Person).

Wie oft wurde in den vergangenen 12 Monaten ein Antibiotikum eingenommen?

____

In welchem Monat/in welchen Monaten wurde das Antibiotikum eingenommen?

WENN ANZAHL EINNAHME ODER PERSONEN >1, MEHRFACHNENNUNG MÖGLICH. JANUAR, FEBRUAR UND MÄRZ EXISTIEREN FÜR 2019 UND 2020.

- ☐ Januar 2019
- ☐ Januar 2020
- ☐ Februar 2019
- ☐ Februar 2020
- ☐ März 2019
- ☐ März 2020
- ☐ April 2019
- ☐ Mai 2019
- ☐ Juni 2019
- ☐ Juli 2019
- ☐ August 2019
- ☐ September 2019
- ☐ Oktober 2019
- ☐ November 2019
- ☐ Dezember 2019
- ☐ Weiß nicht
- ☐ Keine Angabe

Können Sie den Zeitraum eingrenzen?

WENN ANZAHL EINNAHME ODER PERSONEN >1, MEHRFACHNENNUNG MÖGLICH.

- ☐ Frühling
- ☐ Sommer
- ☐ Herbst
- ☐ Winter
- ☐ Weiß nicht
- ☐ Keine Angabe

Wogegen wurde das Antibiotikum eingenommen?
WENN ANZAHL EINNAHME ODER PERSONEN >1, MEHRFACHNENNUNG MÖGLICH.

- ☐ Angina
- ☐ Bronchitis
- ☐ Durchfall
- ☐ Erkältung
- ☐ Fieber
- ☐ Gelenk-/Sehnen-/Muskelentzündung
- ☐ Grippe
- ☐ Halsschmerzen
- ☐ Harnwegsinfekt (Blasenentzündung)
- ☐ Haut- oder Wundinfektion
- ☐ Kopfschmerzen
- ☐ Lungenentzündung
- ☐ Ohrenentzündung
- ☐ prophylaktisch gegen Sekundärinfektionen
- ☐ Rachenentzündung
- ☐ Scharlach
- ☐ Schnupfen
- ☐ Zahninfektion
- ☐ Andere Beschwerden und zwar...
- ☐ Weiß nicht
- ☐ Keine Angabe

Was für andere Beschwerden waren das?

Wissen Antibiotikanutzung und Antibiotikaresistenz

Nach der Einnahme und der Handhabung von Antibiotika, geht es im Folgenden um das vorhandene Wissen und Ihre Einstellung dazu.

Ich werde Ihnen nun 10 Aussagen vorlesen. Bitte geben Sie an, ob Sie den folgenden Aussagen zustimmen oder nicht.
SKALA 1 ZEIGEN.

Antibiotika sind effektiv gegen Erkrankungen verursacht durch Bakterien.

- ◯ richtig
- ◯ falsch
- ◯ Weiß nicht
- ◯ Keine Angabe

Antibiotika sind effektiv gegen Erkrankungen verursacht durch Viren.

- ◯ richtig
- ◯ falsch
- ◯ Weiß nicht
- ◯ Keine Angabe

Die Grippe und andere Erkältungskrankheiten sollten mit einem Antibiotikum behandelt werden.

- ◯ richtig
- ◯ falsch
- ◯ Weiß nicht
- ◯ Keine Angabe

Blasenentzündungen (Harnwegsinfekte) sollten mit einem Antibiotikum behandelt werden.

- ◯ richtig
- ◯ falsch
- ◯ Weiß nicht
- ◯ Keine Angabe

Antibiotika töten auch natürlich vorkommende Bakterien auf oder in dem Körper ab.

- ◯ richtig
- ◯ falsch
- ◯ Weiß nicht
- ◯ Keine Angabe

Wenn ein Antibiotikum zu oft oder falsch eingesetzt wird, kann es in Zukunft seine Wirksamkeit verlieren.

- ◯ richtig
- ◯ falsch
- ◯ Weiß nicht
- ◯ Keine Angabe

Der Mensch, der Antibiotika einnimmt, wird resistent gegen Antibiotika.

- richtig
- falsch
- Weiß nicht
- Keine Angabe

Der Einsatz von Antibiotika in der Landwirtschaft kann zu einer verminderten Wirksamkeit von Antibiotika bei Menschen führen.

- richtig
- falsch
- Weiß nicht
- Keine Angabe

Antibiotikaresistenzen gefährden medizinische Routine-Operationen.

- richtig
- falsch
- Weiß nicht
- Keine Angabe

Einstellung Antibiotikanutzung und Antibiotikaresistenz

Ich werde Ihnen nun weitere 10 Aussagen vorlesen. Bitte bewerten Sie die folgenden Aussagen auf einer Skala von "stimme gar nicht zu" bis "stimme voll und ganz zu".

SKALA 2 ZEIGEN.

Wenn ich mit einer Erkältungskrankheit oder Grippe zum Arzt gehe, erwarte ich ein Antibiotikum, damit es mir schnell besser geht.

- stimme gar nicht zu
- stimme nicht zu
- unentschieden
- stimme zu
- stimme voll und ganz zu
- Keine Angabe

Ich frage nach, wenn mein Arzt mir kein Antibiotikum verordnet.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

Wenn die Beschwerden nach der Einnahme des Antibiotikums abklingen und ich mich besser fühle, kann ich das Antibiotikum absetzen.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

Ich bevorzuge es, Antibiotika für einen Notfall zuhause im Schrank zu haben.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

Es ist in Ordnung, wenn ich aufbewahrte Antibiotika an Verwandte oder Freunde weitergebe oder selber nochmal einnehme, sofern es ähnliche Symptome sind.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

Antibiotikaresistenzen sind schon heute ein Problem auf der Welt.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

Antibiotikaresistenzen sind schon heute ein Problem in Deutschland.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

Antibiotikaresistenzen können die Gesundheit von mir und meiner Familie beeinträchtigen.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

Antibiotikaresistenz ist nur ein Problem für Menschen, die regelmäßig Antibiotika einnehmen.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

Ein Antibiotikum wird auch gegen die gleiche Krankheit in Zukunft noch effektiv sein.

- ◯ stimme gar nicht zu
- ◯ stimme nicht zu
- ◯ unentschieden
- ◯ stimme zu
- ◯ stimme voll und ganz zu
- ◯ Keine Angabe

» Durch was sind Antibiotikaresistenzen Ihrer Meinung nach am ehesten verursacht?

Bitte bringen Sie die folgenden fünf Kategorien in eine absteigende Reihenfolge (1=am ehesten bis 5 = am wenigsten).
LISTE 1 AUSHÄNDIGEN.

Auf natürliche Art und Weise

◯ 1	◯ 2	◯ 3
◯ 4	◯ 5	◯ Keine Angabe
◯ Keine Angabe	◯ Keine Angabe	◯ Keine Angabe
◯ Keine Angabe		

Einsatz von Antibiotika in der Landwirtschaft (ohne Tierhaltung)

◯ 1	◯ 2	◯ 3
◯ 4	◯ 5	◯ Keine Angabe
◯ Keine Angabe	◯ Keine Angabe	◯ Keine Angabe
◯ Keine Angabe		

Einsatz von Antibiotika beim Menschen

◯ 1	◯ 2	◯ 3
◯ 4	◯ 5	◯ Keine Angabe
◯ Keine Angabe	◯ Keine Angabe	◯ Keine Angabe
◯ Keine Angabe		

Einsatz von Antibiotika in der Nutztierhaltung

◯ 1	◯ 2	◯ 3
◯ 4	◯ 5	◯ Keine Angabe
◯ Keine Angabe	◯ Keine Angabe	◯ Keine Angabe
◯ Keine Angabe		

Sonstiges (u.a. mangelnde Hygiene)

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ Keine Angabe
- ◯ Keine Angabe
- ◯ Keine Angabe
- ◯ Keine Angabe

Ist Antibiotikaresistenz Ihrer Meinung nach in Zukunft ein eher abnehmendes, gleichbleibendes, oder zunehmendes Problem?

- ◯ abnehmend
- ◯ gleichbleibend
- ◯ zunehmend
- ◯ Weiß nicht
- ◯ Keine Angabe

Persönliche Angaben

Damit wir die bereits gesammelten Informationen so genau wie möglich auswerten können, benötigen wir von Ihnen im Folgenden noch ein paar Angaben.

» Individuelle Persönlichkeitsstruktur

Inwieweit treffen die folgenden Aussagen auf Sie zu? Bitte bewerten Sie die folgenden Aussagen auf einer Skala von "trifft überhaupt nicht zu" bis "trifft voll und ganz zu".

SKALA 3 ZEIGEN.

Ich bin eher zurückhaltend, reserviert.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich schenke anderen leicht Vertrauen, glaube an das Gute im Menschen.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich bin bequem, neige zur Faulheit.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich bin entspannt, lasse mich durch Stress nicht aus der Ruhe bringen.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich habe nur wenig künstlerisches Interesse.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich gehe aus mir heraus, bin gesellig.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich neige dazu, andere zu kritisieren.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich erledige Aufgaben gründlich.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich werde leicht nervös und unsicher.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

Ich habe eine aktive Vorstellungskraft, bin fantasievoll.

- ◯ trifft überhaupt nicht zu
- ◯ trifft eher nicht zu
- ◯ teils-teils
- ◯ trifft eher zu
- ◯ trifft voll und ganz zu
- ◯ Keine Angabe

» Demographische Standards

Nun noch ein paar Angaben zu Ihrer Person.

In welchem Jahr wurden Sie geboren?

____

In welchem Monat wurden Sie geboren?

- ◯ Januar
- ◯ Februar
- ◯ März
- ◯ April
- ◯ Mai
- ◯ Juni
- ◯ Juli
- ◯ August
- ◯ September
- ◯ Oktober
- ◯ November
- ◯ Dezember
- ◯ Keine Angabe

Haben Sie die deutsche Staatsangehörigkeit?

- ◯ Ja
- ◯ Nein

Haben Sie zusätzlich eine andere Staatsangehörigkeit?

- ◯ Ja und zwar...
- ◯ Nein
- ◯ Keine Angabe

Um welche Staatsangehörigkeit handelt es sich?

In welchem Land sind Sie geboren?

- ◯ Deutschland
- ◯ Anderes und zwar...
- ◯ Keine Angabe

Bitte geben Sie Ihr Geburtsland an.

In welchem Land wurde ihr Vater geboren?

- ◯ Deutschland
- ◯ Anderes und zwar...
- ◯ Keine Angabe

Bitte geben Sie das Geburtsland Ihres Vaters an.

In welchem Land wurde Ihre Mutter geboren?

- ◯ Deutschland
- ◯ Anderes und zwar...
- ◯ Keine Angabe

Bitte geben Sie das Geburtsland Ihrer Mutter an.

Welchen höchsten allgemeinbildenden Schulabschluss haben Sie?
LISTE A ZUR UNTERSTÜTZUNG HERANZIEHEN.

- ◯ Schüler/-in
- ◯ Abschluss nach höchstens 7 Jahren Schulbesuch
- ◯ Haupt-/ Volksschulabschluss oder gleichwertiger Abschluss
- ◯ Realschulabschluss (Mittlere Reife) oder gleichwertiger Abschluss (z.B. Polytechnische Oberschule der DDR)
- ◯ Fachhochschulreife
- ◯ Abitur/Allgemeine oder fachgebundene Hochschulreife
- ◯ Nicht zutreffend
- ◯ Weiß nicht
- ◯ Keine Angabe

Welchen höchsten beruflichen Ausbildungs- oder Hochschul-/Fachhochschulabschluss haben Sie?
LISTE B ZUR UNTERSTÜTZUNG HERANZIEHEN.

- ◯ Noch in beruflicher Ausbildung (Berufsvorbereitungsjahr, Auszubildende/r, Praktikant/-in, Student/-in)
- ◯ Schüler/-in und besuche eine berufsorientierte Aufbau-, Fachschule oder Ähnliches
- ◯ Keinen beruflichen Abschluss und bin nicht in beruflicher Ausbildung
- ◯ Beruflich-betriebliche Ausbildung (Lehre) abgeschlossen
- ◯ Beruflich-schulische Ausbildung (Berufsfachschule, Kollegschule) abgeschlossen
- ◯ Fachschulabschluss (Meister/-in, Techniker/-in oder gleichwertiger Abschluss)
- ◯ Berufsakademie, Fachakademie
- ◯ Abschluss einer Verwaltungsfachhochschule
- ◯ Fachhochschulabschluss, auch Ingenieurabschluss
- ◯ Abschluss einer Universität, wissenschaftlichen Hochschule, Kunsthochschule
- ◯ Anderes und zwar...
- ◯ Keine Angabe

Wie ist die Bezeichnung Ihres höchsten Abschlusses?

- ◯ Bachelor
- ◯ Master
- ◯ Diplom, Lehramtsprüfung, Staatsprüfung, Staatsexamen, Magister, künstlerischer Abschluss und vergleichbare Abschlüsse
- ◯ Promotion
- ◯ Keine Angabe

Bitte nennen Sie uns Ihren höchsten Abschluss.

____

Welche Erwerbssituation passt aktuell für Sie?
LISTE C ZUR UNTERSTÜTZUNG HERANZIEHEN.

- ◯ Vollzeiterwerbstätig
- ◯ Teilzeiterwerbstätig
- ◯ Altersteilzeit
- ◯ Geringfügig erwerbstätig, 450-Euro-Job, Minijob
- ◯ "Ein-Euro-Job" (bei Bezug von Arbeitslosengeld II)
- ◯ Gelegentlich oder unregelmäßig beschäftigt
- ◯ In einer beruflichen Ausbildung/Lehre
- ◯ In Umschulung
- ◯ Freiwilliger Wehrdienst
- ◯ Bundesfreiwilligendienst oder Freiwilliges Ökologisches/Soziales/Kulturelles Jahr
- ◯ Mutterschafts-, Erziehungsurlaub, Elternzeit oder sonstige Beurlaubung
- ◯ Nicht erwerbstätig
- ◯ Keine Angabe

Zu welcher dieser Gruppen gehören Sie?
LISTE C1 ZUR UNTERSTÜTZUNG HERANZIEHEN.

- ◯ Schüler/-innen an einer allgemeinen Schule
- ◯ Studenten/-innen
- ◯ Rentner/-innen, Pensionäre/-innen, im Vorruhestand
- ◯ Arbeitslose
- ◯ Dauerhaft Erwerbsunfähige
- ◯ Hausfrauen/Hausmänner
- ◯ Keine Angabe

Welche berufliche Stellung haben oder hatten Sie in Ihrer hauptsächlich ausgeübten Erwerbstätigkeit?
LISTE D ZUR UNTERSTÜTZUNG HERANZIEHEN.

- ◯ Angestellte/r
- ◯ Arbeiter/in
- ◯ Beamtin/Beamter, Richter/-in, Berufssoldat/-in
- ◯ Landwirt/in im Haupterwerb
- ◯ Selbstständig erwerbstätig und habe Mitarbeiter
- ◯ Selbstständig erwerbstätig ohne Mitarbeiter
- ◯ Mithelfende/r Familienangehörige/r
- ◯ Auszubildende/r
- ◯ Freiwilliges soziales/ökologisches Jahr
- ◯ Freiwillig Wehrdienst- oder Bundesfreiwilligendienstleistende/r
- ◯ Keine Angabe

Bitte ordnen Sie den Betrieb, in dem Sie tätig sind, einer Branche/einem Wirtschaftszweig zu.
LISTE D1 ZUR UNTERSTÜTZUNG HERANZIEHEN.

- ◯ Land- und Forstwirtschaft, Fischerei
- ◯ Verarbeitendes Gewerbe/Herstellung von Waren
- ◯ Bergbau und Gewinnung von Steinen und Erden
- ◯ Sonstige Industrie (Reparatur und Installation von Maschinen und Ausrüstung; Energie-, Wasserversorgung, Abfallentsorgung)
- ◯ Baugewerbe, Hoch- und Tiefbau
- ◯ Handel, Verkehr und Lagerei
- ◯ Gastgewerbe/Beherbergung und Gastronomie
- ◯ Information und Kommunikation
- ◯ Banken/Finanz- und Versicherungsdienstleistungen
- ◯ Grundstücks- und Wohnungswesen
- ◯ Freiberufliche, wissenschaftliche und technische Dienstleistungen sowie sonstige wirtschaftliche Dienstleistungen
- ◯ Öffentliche Verwaltung, Verteidigung, Sozialversicherung
- ◯ Erziehung und Unterricht
- ◯ Gesundheits- und Sozialwesen
- ◯ Sonstige überwiegend personenbezogene Dienstleistungen; allgemeine Reparaturen von Waren und Geräten
- ◯ Kunst, Unterhaltung, Sport und Erholung
- ◯ Gewerkschaften, Verbände, Parteien und sonstige Interessenvertretungen, kirchliche und religiöse Vereinigungen
- ◯ Konsulate, Botschaften, internationale und supranationale Organisationen
- ◯ Private Haushalte mit Beschäftigten
- ◯ Keine Angabe

Welcher Buchstabe aus der Liste trifft auf Ihr eigenes durchschnittliches monatliches Nettoeinkommen zu?

LISTE E AUSHÄNDIGEN.

- ○ C
- ○ D
- ○ E
- ○ F
- ○ G
- ○ H
- ○ K
- ○ L
- ○ M
- ○ N
- ○ O
- ○ P
- ○ R
- ○ S
- ○ U
- ○ V
- ○ Keine Angabe

Welcher Buchstabe aus der Liste trifft auf das durchschnittliche monatliche Nettoeinkommen Ihres Haushalts zu?

LISTE E AUSHÄNDIGEN.

- ◯ C
- ◯ D
- ◯ E
- ◯ F
- ◯ G
- ◯ H
- ◯ K
- ◯ L
- ◯ M
- ◯ N
- ◯ O
- ◯ P
- ◯ R
- ◯ S
- ◯ U
- ◯ V
- ◯ Keine Angabe

Zu welcher der folgenden Religionen, Glaubensrichtungen oder Weltanschauungen würden Sie sich zuordnen?

- ◯ Christentum
- ◯ Judentum
- ◯ Islam
- ◯ Buddhismus
- ◯ Hinduismus
- ◯ Sonstige Religion, Glaubensrichtung oder Weltanschauung
- ◯ Keiner Religion, Glaubensrichtung oder Weltanschauung
- ◯ Keine Angabe

Können Sie das näher benennen?

- ◯ Evangelisch
- ◯ Katholisch
- ◯ Keine Angabe

Können Sie das näher benennen?

- ○ Sunnitischer Islam
- ○ Schiitischer Islam
- ○ Alevitischer Islam
- ○ Keine Angabe

Welche Krankenversicherung bzw. -versorgung haben Sie?

- ○ Gesetzliche Krankenversicherung (GKV)
- ○ Private Krankenversicherung
- ○ Anderer Anspruch auf Krankenversorgung
- ○ Keine Krankenversicherung, Selbstzahler
- ○ Keine Angabe

Kontaktaufnahme

Das war's! Sie haben es geschafft. Wir möchten uns hiermit herzlich Ihre Teilnahme an der Haushaltsbefragung der Universität Bonn bedanken! Bitte erlauben Sie mir abschließend noch zwei kurze Fragen bezüglich der weiteren Kommunikation.

FALLS TEILNEHMENDE/R ZUSTIMMT, KONTAKTDATEN BITTE IN DIE EXTERNE TABELLE EINTRAGEN.

Möchten Sie nach Abschluss der Studie die Ergebnisse erhalten?

- ○ Ja
- ○ Nein

Stünden Sie für ein weiteres Gespräch zur Verfügung?

GEMEINT SIND HIERMIT QUALITATIVE INTERVIEWS.

- ○ Ja
- ○ Nein

Wir möchten Ihnen herzlich für Ihre Teilnahme an der Haushaltsbefragung danken. Ihr Beitrag ist für uns von enormer Bedeutung! Ich wünsche Ihnen noch einen angenehmen Tag! Auf Wiedersehen!

Identifikationsnummer

f. All statements, questions and corresponding reply options

The following document was submitted as supporting information 2 supporting the publication that constitutes chapter 5 of this doctoral thesis: Schmiege et al. (*under review*): Associations between socio-spatially different urban areas and knowledge, attitudes, practices and antibiotic use: a cross-sectional study in the Ruhr Metropolis, Germany.

Supporting information 2

Part A. All statements, questions and corresponding reply options (in German and English language)

Knowledge statements

Study participants were asked to indicate whether the following statements are (i) correct, (ii) wrong, (iii) “Don’t know” or (iv) could refuse to reply.

Antibiotics

English	***German***
Antibiotics are effective against infections caused by bacteria.	*Antibiotika sind effektiv gegen Erkrankungen verursacht durch Bakterien*
Antibiotics are effective against infections caused by viruses.	*Antibiotika sind effektiv gegen Erkrankungen verursacht durch Viren.*
The flu and other common colds should be treated with an antibiotic.	*Die Grippe und andere Erkältungskrankheiten sollten mit einem Antibiotikum behandelt werden.*
Urinary tract infections should be treated with an antibiotic.	*Blasenentzündungen (Harnwegsinfekte) sollten mit einem Antibiotikum behandelt werden.*
Antibiotics kill naturally occurring bacteria on or in the body.	*Antibiotika töten auch natürlich vorkommende Bakterien auf oder in dem Körper ab.*

Antibiotic resistance

English	***German***
If an antibiotic is used too often or incorrectly, it can lose its effectiveness in the future.	*Wenn ein Antibiotikum zu oft oder falsch eingesetzt wird, kann es in Zukunft seine Wirksamkeit verlieren.*
The person that takes antibiotics will become resistant against antibiotics.	*Der Mensch, der Antibiotika einnimmt, wird resistent gegen Antibiotika.*
The use of antibiotics in agriculture can lead to lower effectiveness of antibiotics in humans.	*Der Einsatz von Antibiotika in der Landwirtschaft kann zu einer verminderten Wirksamkeit von Antibiotika bei Menschen führen.*
Antibiotic resistance threatens medical routine operations.	*Antibiotikaresistenzen gefährden medizinische Routine-Operationen.*

Attitude statements

Study participants were asked to agree or disagree with the following statements on a five-point Likert scale: (i) strongly disagree, (ii) rather disagree, (iii) neutral, (iv) rather agree, (v) strongly agree or (vi) could refuse to reply.

English	*German*
When I go to the doctor with a cold or flu, I expect an antibiotic so that I can get better quickly.	*Wenn ich mit einer Erkältungskrankheit oder Grippe zum Arzt gehe, erwarte ich ein Antibiotikum, damit es mir schnell besser geht.*
I request further information from my doctor, when s/he does not prescribe me an antibiotic.	*Ich frage nach, wenn mein Arzt mir kein Antibiotikum verordnet.*
When the symptoms subside after taking the antibiotic and I feel better, I can stop taking the antibiotic.	*Wenn die Beschwerden nach der Einnahme des Antibiotikums abklingen und ich mich besser fühle, kann ich das Antibiotikum absetzen.*
I prefer to have antibiotics in my cupboard at home for an emergency.	*Ich bevorzuge es, Antibiotika für einen Notfall zuhause im Schrank zu haben.*
It if fine to pass on stored antibiotics to relatives or friends, or to take them again myself, if they are similar symptoms.	*Es ist in Ordnung, wenn ich aufbewahrte Antibiotika an Verwandte oder Freunde weitergebe oder selber nochmal einnehme, sofern es ähnliche Symptome sind.*

Risk awareness statements

Study participants were asked to agree or disagree with the following statements on a five-point Likert scale: (i) strongly disagree, (ii) rather disagree, (iii) neutral, (iv) rather agree, (v) strongly agree or (vi) could refuse to reply.

English	*German*
Antibiotic resistance is already a global issue today.	*Antibiotikaresistenzen sind schon heute ein Problem auf der Welt.*
Antibiotic resistance is already an issue in Germany today.	*Antibiotikaresistenzen sind schon heute ein Problem in Deutschland.*
Antibiotic resistance can affect my families' and my own health.	*Antibiotikaresistenzen können die Gesundheit von mir und meiner Familie beeinträchtigen.*
Antibiotic resistance is only an issue for people who take antibiotics regularly.	*Antibiotikaresistenz ist nur ein Problem für Menschen, die regelmäßig Antibiotika einnehmen.*
An antibiotic will remain effective against the same disease in the future.	*Ein Antibiotikum wird auch gegen die gleiche Krankheit in Zukunft noch effektiv sein.*

Handling practice questions

Study participants could choose multiple times from the pre-determined reply options.

English	*German*	Reply options
Has any antibiotic ever been used in your household?	*Wurde in Ihrem Haushalt jemals ein Antibiotikum genutzt?*	• Yes • No • Don't know • Not specified
From where do you get antibiotics in your household?	*Woher beziehen Sie Antibiotika in Ihrem Haushalt?*	• I used the leftovers from an old package • A relative/acquaintance gave it to me • From a doctor in the hospital • From a doctor in private practice • Don't know • Not specified
How long are antibiotics used in your household?	*Wie lange wird ein Antibiotikum in Ihrem Haushalt angewandt?*	• Until the package is completely used • Until I feel better • According to the package insert • As recommended by the pharmacist • According to the doctor's instructions • Not specified

What happens to the leftover antibiotics in your household?	*Was passiert mit den Antibiotikaresten in Ihrem Haushalt?*	• Disposal at the pharmacy • Delivery to hazardous waste or mobile waste/hazardous material • Storage • Disposal via household waste • Disposal via the toilet • Everything has been used • Not specified

Antibiotic use questions

English	***German***	**Reply options**
Have you taken an antibiotic in the past 12 months?	*Haben Sie in den vergangenen 12 Monaten ein Antibiotikum eingenommen?*	• Yes • No • Don't know • Not specified
How often have you taken an antibiotic in the past 12 months?	*Wie oft haben Sie in den vergangenen 12 Monaten ein Antibiotikum eingenommen?*	Number of treatments (integer)
In what month(s) did you take an antibiotic?	*In welchem Monat/in welchen Monaten haben Sie ein Antibiotikum eingenommen?*	• January 2019 • February 2019 • March 2019 • April 2019 • May 2019 • June 2019 • July 2019 • August 2019 • September 2019 • November 2019 • December 2019 • January 2020 • February 2020 • March 2020 • Don't know • Not specified
For "Don't know" only: Can you narrow down the time period?	*Können Sie den Zeitraum eingrenzen?*	• Spring • Summer • Autumn • Winter
What did you take the antibiotic for?	*Wogegen haben Sie das Antibiotikum eingenommen?*	• Angina • Bronchitis • Diarrhoea • Cold • Fever • Joint/ tendon/ muscle inflammation • Flu • Sore throat • Urinary tract infection (cystitis) • Skin or wound infection • Headache • Lung infection • Ear infection • Prophylactic against secondary infections • Pharyngitis

		• Scarlet fever • Sniff • Tooth infection • Other complaints • Don't know • Not specified
For other complaints only: What other health problems were they?	*Was für andere Beschwerden waren das?*	Write specific health issue (text)

Part B. All statements, questions and corresponding reply options (in German and English language)

Table B. Categorized coding of the outcome variables and covariates

Outcome variable	**Grouping**		**Remarks**
	0	**1**	
Low knowledge	Correct	False or "Don't know"	
Attitudes contrary to common recommendations	Rather or strongly disagree	Neutral, rather or strongly agree	
Low risk awareness[a]	Rather or strongly agree	Neutral, rather or strongly disagree	
Potential mishandling (index)[b]	No mishandling practice reported	Any mishandling practice reported	Using an old package, stopping treatment when feeling better and storage of antibiotics at home were included
Self-reported antibiotic use	No antibiotic use reported	Antibiotic use reported	
Covariates	**Reference**		
Area	Area C	Area A, Area B	
Age	NA		Continuous variable
Gender	Female	Male	One diverse person was removed
Immigration background	No	Yes	Defined as being an immigrant or descendant of immigrants
Family status	No partnership	In a partnership	Partner living in the same household
Education[c]	Secondary (2) or post-secondary non-tertiary (3,4)	Tertiary (6,7,8)	
Income	Below the national average	Equal to or above the national average	Average net income: 2,084 € per month in 2020 (statista, 2021)
Household income	Below the national average	Equal to or above the national average	Average net household income: 3,661 € per month in 2018 (Federal Statistical Office, 2020)
Occupational sector	Other	Health and social	
Previous antibiotic use	No	Yes	

[a] This grouping was reversed for the statements on antibiotic resistance as an individual problem and future effectiveness; [b] Mishandling practices were too rare to examine individually, therefore all mishandling practices were summarized into a single index for each participant; [c] The International Standard Classification of Education (ISCED) was used. Corresponding codes provided behind the level of education in parentheses.

g. Figures for self-reported antibiotic use and handling practices

The following document was submitted as supporting information 3 supporting the publication that constitutes chapter 5 of this doctoral thesis: Schmiege et al. (*under review*): Associations between socio-spatially different urban areas and knowledge, attitudes, practices and antibiotic use: a cross-sectional study in the Ruhr Metropolis, Germany.

Supporting information 3

Figures for self-reported antibiotic use and handling practices

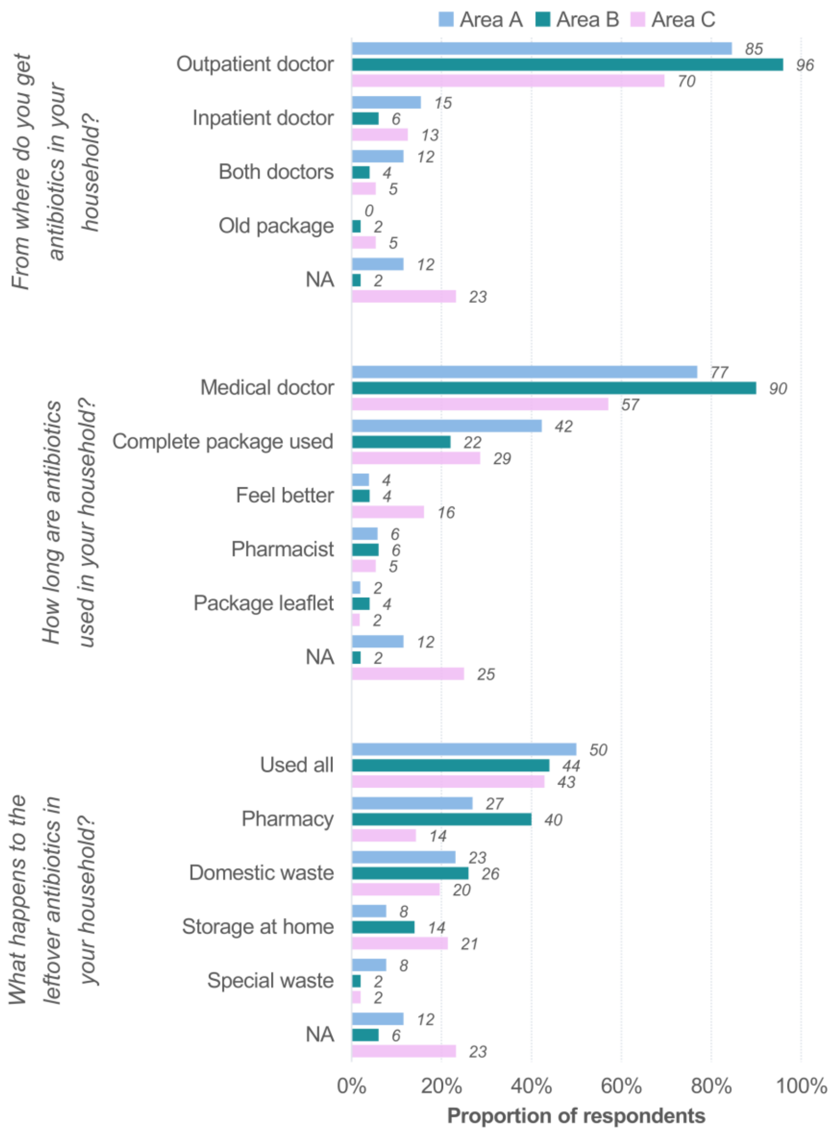


Figure A. Handling practices with antibiotics segregated by research areas

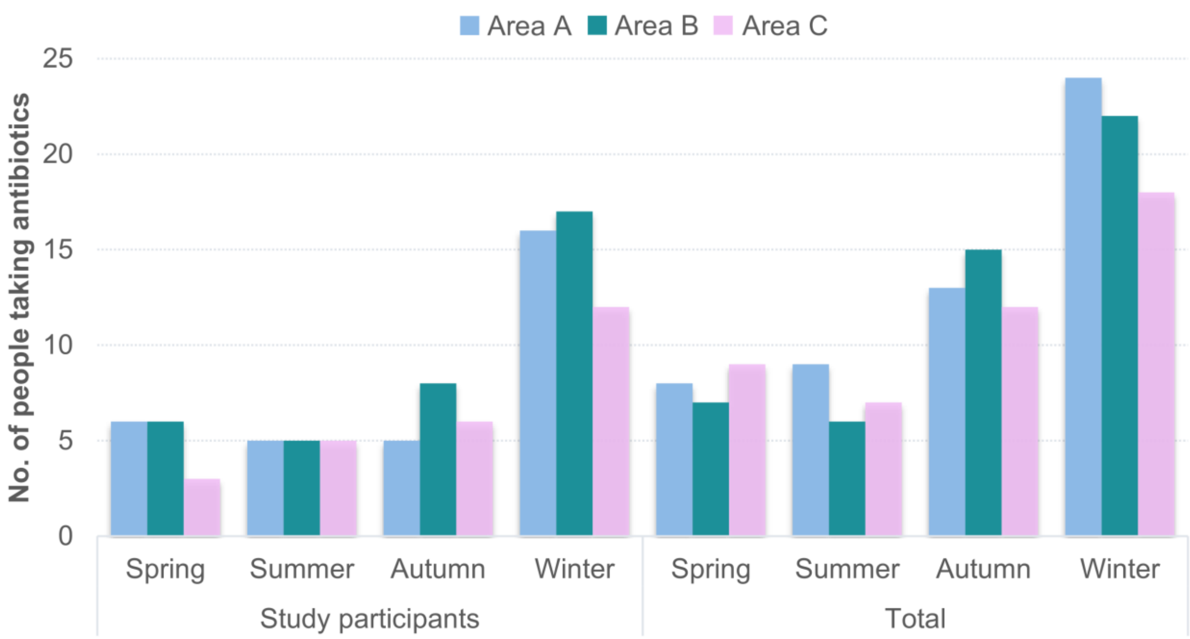


Figure B. Self-reported antibiotic use by the study participants (left) and total (right; study participants plus household members) segregated by research area and meteorological season

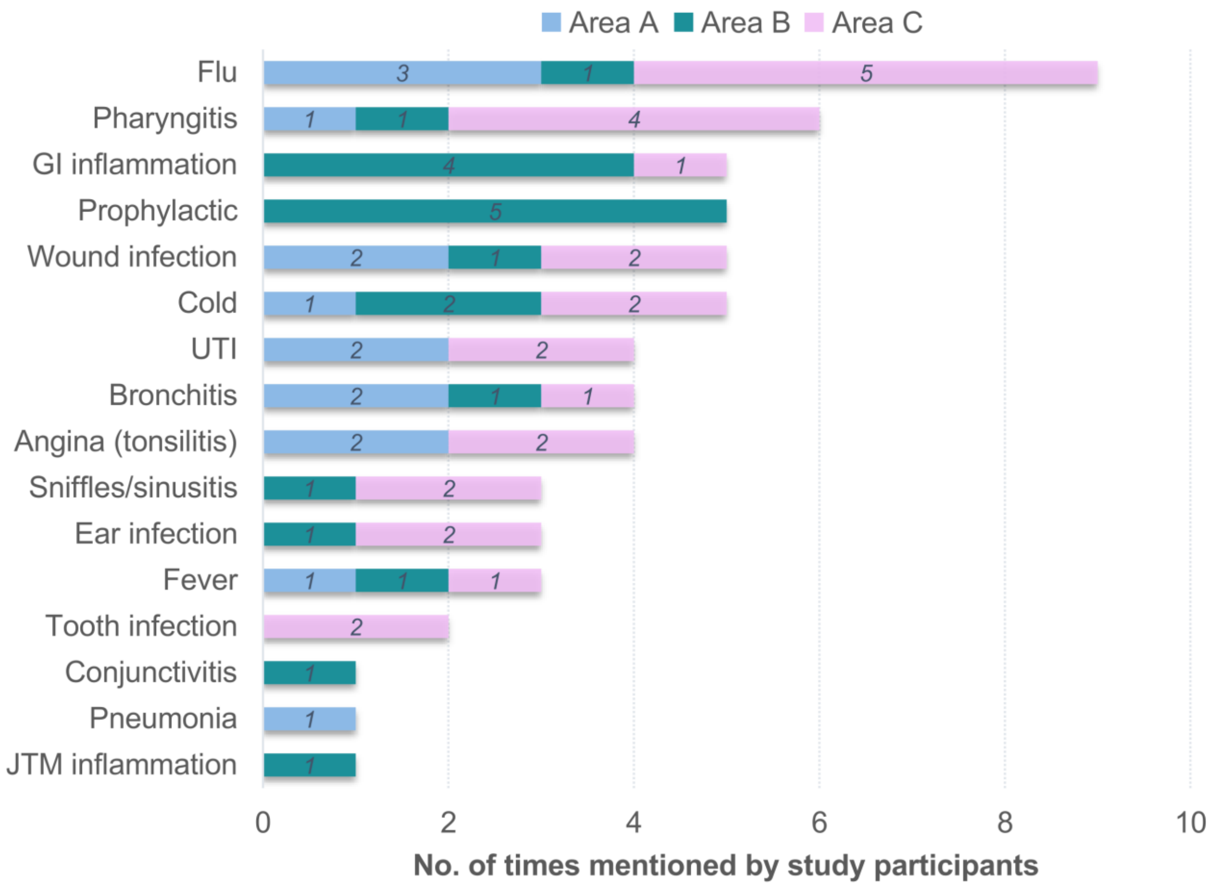


Figure C. Diseases mentioned by study participants against which an antibiotic was taken segregated by research area

iii. Supplementary material for chapter 6: Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing Escherichia coli in urban community wastewater

a. Definitions of indicators used for study area selection

The following document was submitted as supplementary material A supporting the publication that constitutes chapter 6 of this doctoral thesis: Schmiege et al. (2020): Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing *Escherichia coli* in urban community wastewater. https://doi.org/10.1016/j.scitotenv.2021.147269

It is available online under the following link: https://ars.els-cdn.com/content/image/1-s2.0-S0048969721023408-mmc1.docx

Supplementary material A

Table 1. Definitions of indicators used for study area selection

Indicator	Full name in reference	Pages	Additional information
Settlement and traffic area	Share of settlement and traffic area of the total area 2018 (%)	10-11	--
Inhabitants/ha	Inhabitants (main residential population) as of 31.12.2018 per hectare of settlement area	16-17	--
Living space/inhabitant	Living space per inhabitant (population entitled to reside) in buildings with residential space on 31.12.2016 (sqm)	94-95	--
Share of flats in one- or two-family houses	Share of apartments in one- and two-family houses in all apartments in residential buildings as of Dec. 31, 2016 (%)	90-91	--
Average age	Average age of the main resident population on 31.12.2018 (in years)	34-35	--
Share of persons below age 18	Percentage of 0- to under-6-year-olds in the main resident population as of Dec. 31, 2018 (%) + Percentage of 6- to under-18-year-olds in the main resident population as of Dec. 31, 2018 (%)	20-21 + 22-23	--
Share of persons above age 65	Percentage of 65- to under-80-year-olds in the main resident population as of Dec. 31, 2018 (%) + Percentage of 80-year-olds and older in the main resident population as of Dec. 31, 2018 (%)	30-31 + 32-33	--
Share of households with children	Share of households with children under 18 in all households as of 12/31/2018 (%)	84-85	--
Share of single-parent households	Percentage of single-parent households among all households with children under 18 on Dec. 31, 2018	86-87	--

Indicator	Full name in reference	Pages	Additional information
Mobility rate/1.000 inhabitants	Total number of changes of residence - in-migrants, out-migrants and relocations - per 1,000 inhabitants on average from 2014 to 2018	56-57	The sum of all residential changes is, in relation to the population, a measure of the local level of fluctuation.
Share with migration background	Persons with German citizenship and migration background as a percentage of the main resident population in 2018 (%)	64-65	Persons with a migration background include*: • Foreigners and their children • Naturalized persons and their children • (Late) emigrants and their children **Basis for the assignment is the MigraPro method in which migration background is approximately derived from the population register.*
Share of foreigners	Persons with exclusively non-German citizenship as a percentage of the main resident population in 2018 (%)	66-67	--
Share of employed population	Proportion of employees subject to social security contributions (at place of residence) in the population aged 18 to under 65 in December 2018 (%)	100-101	--
Share of unemployed population	Unemployed registered with the Federal Employment Agency as a percentage of the labor force (employed + unemployed) in December 2018 (%)	108-109	--
Share of recipients of state transfer payments	Recipients of state transfer benefits (social minimum income benefits) as a percentage of the main resident population in December 2018	118-119	Includes basic cover for jobseekers (code of social law (SGB II)), basic cover in old age or in the event of reduced earning capacity (code of social law (SGB XII)), assistance for living expenses, and standard benefits under the Asylum Seekers Benefits Act.

Reference

City Statistics. (2019). *Statistikatlas. Dortmunder Stadtteile* (Issue 215). https://www.dortmund.de/media/p/statistik/pdf_statistik/veroeffentlichungen/statistikatlas/215_-_Statistikatlas_-_2019.pdf

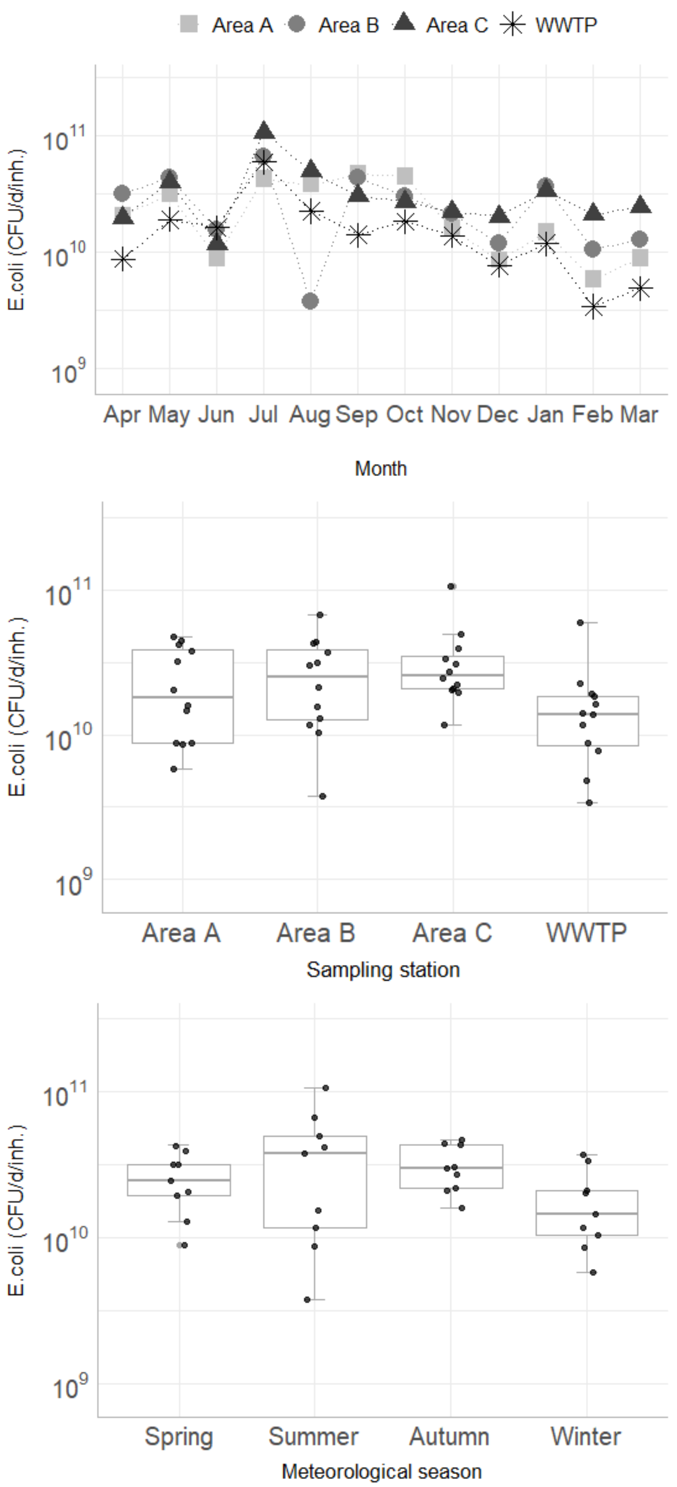
b. Figures of variation of the total number of *E. coli* and the ratio of ESBL-Ec to all *E. coli*

The following document was submitted as supplementary material B supporting the publication that constitutes chapter 6 of this doctoral thesis: Schmiege et al. (2020): Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing *Escherichia coli* in urban community wastewater. https://doi.org/10.1016/j.scitotenv.2021.147269

It is available online under the following link: https://ars.els-cdn.com/content/image/1-s2.0-S0048969721023408-mmc2.docx

Supplementary material B

3.1 Variation of the total number of *E. coli*



Note: The seasonal figure contains only the data points of the three peripheral sampling points (n=36).

Fig. A. Spatio-temporal (top), spatial (middle) and seasonal (bottom) distribution of *E. coli* in CFU per day per inhabitant (CFU/d/inh.) for all four sampling points between April 2019 and March 2020

3.2 Spatial and temporal variation of the ratio of phenotypic ESBL-Ec to all E. coli

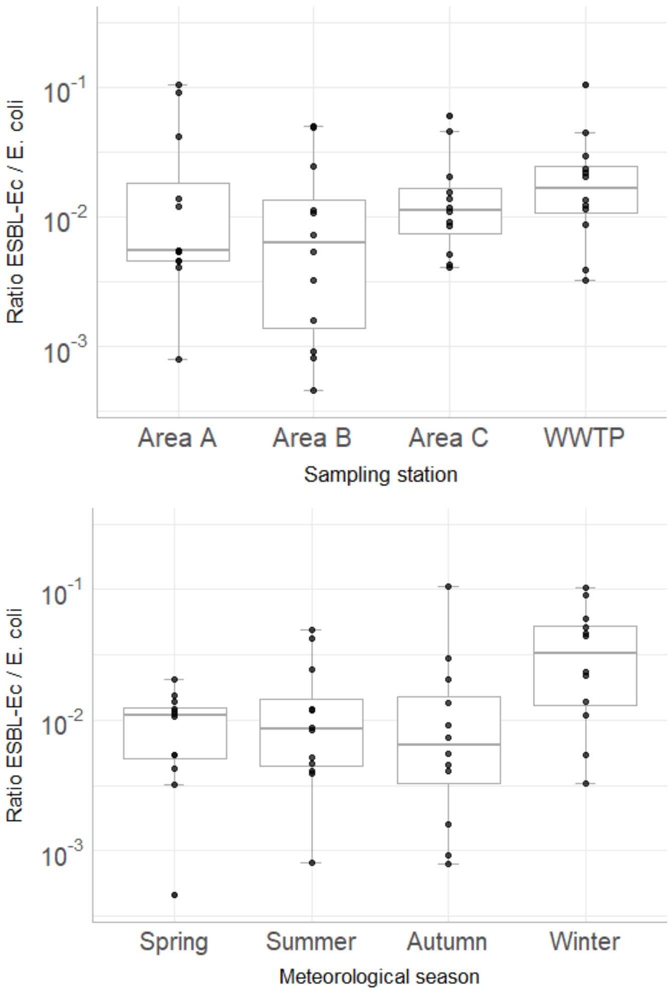


Fig. B. Spatial (top) and seasonal (bottom) distribution of the ratio of ESBL-producing *E. coli* to the total number of *E. coli* in CFU per day per inhabitant (CFU/d/inh.) for all four sampling points between April 2019 and March 2020

Publications and presentations

i. Peer-reviewed journal articles

Schmiege, D., Zacharias, N., Sib, E., Falkenberg, T., Moebus, S., Evers, M., & Kistemann, T. (2021). Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing Escherichia coli in urban community wastewater. Science of the Total Environment, 785, 147269. https://doi.org/10.1016/j.scitotenv.2021.147269

Schmiege, D., Perez Arredondo, A. M., Ntajal, J., Minetto Gellert Paris, J., Savi, M. K., Patel, K. Yasobant, S., Falkenberg, T. (2020): One Health in the context of coronavirus outbreaks: A systematic literature review. One Health, Vol. 10 (December), 100170. https://doi.org/10.1016/j.onehlt.2020.100170

Schmiege, D., Evers, M., Kistemann, T., & Falkenberg, T. (2020). What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. International Journal of Hygiene and Environmental Health, 226 (February), 113497. https://doi.org/10.1016/j.ijheh.2020.113497

Schmiege, D., Evers, M., Zügner, V., Rickert, B. (2020): Comparing the German enabling environment for nationwide Water Safety Plan implementation with international experiences: Are we still thinking big or already scaling up? International Journal of Hygiene and Environmental Health, 228 (July), 113553. https://doi.org/10.1016/j.ijheh.2020.113553

ii. Book chapters, policy briefs and other articles

Falkenberg, T., Paris, J.M.G., Patel, K., Arredondo Perez, A.M., **Schmiege, D.,** Yasobant, S. (*forthcoming*). Operationalising the One Health Approach in the Context of Urban Transformation. In: Gatzweiler, F. M. (eds.), Urban Health and Wellbeing Programme, Policy Briefs: Volume 3.

Yasobant, S., Arredondo Perez, A.M., Felappi, J.F., Ntajal, J., Paris, J.M.G., Patel, K., Savi, M.K., **Schmiege, D.**, Falkenberg, T. (2021). Integrating public services under One Health for the mitigation of future epidemics. In: Nima Rezaei, (eds.), Integrated Science of Global epidemics, Springer, UK (*In Print*)

Brückner, A., Paris, J.M.G., **Schmiege, D.**, Swoboda, P. (2020). Urban transformation and the need for One Health. Recommendations for Ruhr Metropolis. Center for Development Research (ZEF) One Health and Urban Transformation Policy Brief 1/2020. https://www.zef.de/project-homepages/one-health/template-following/policy-briefs.html

Schmiege, D. (2020): Don’t waste water: wastewater surveillance, antimicrobial resistance and One Health. WHO CC Newsletter, No. 30, August 2020. https://www.ukbonn.de/site/assets/files/16452/water_and_risk_vol30_high.pdf

Zügner, V., Rickert, B., **Schmiege, D.** (2019): Erfahrungen von Wasserversorgungen mit Risikomanagement in Deutschland. energie | wasser-praxis, Ausgabe 08/19. https://www.energie-wasser-praxis.de/heftarchiv/2019/8/

Schmiege, D., Schmoll, O., Demilechamps, C. (2019): Inequalities in access to basic drinking-water and sanitation services. In: Environmental health inequalities in Europe. Second assessment report. Copenhagen: World Health Organization Regional Office for Europe. https://www.euro.who.int/en/publications/abstracts/environmental-health-inequalities-in-europe.-second-assessment-report-2019

iii. Conference contributions

a. Oral presentations

Schmiege, D. (2021): "Multiresistente Bakterien im Abwassersystem einer Stadt in der Ruhr Metropole", oral presentation at the symposium on the occasion of the 40th anniversary of the BUKO Pharma-Kampagne, https://bukopharma.de/konferenz/part2.html

Schmiege, D., Perez Arredondo, A. M., Ntajal, J., Minetto Gellert Paris, J., Savi, M. K., Patel, K., Yasobant, S., Falkenberg, T. (2020): "One Health im Kontext von Coronavirus-Ausbrüchen –die zentrale Rolle der Geographie", oral presentation at the digital symposium „COVID-19 als Zäsur? Geographische Perspektiven auf Räume, Gesellschaften und Technologien in der Pandemie."

Schmiege, D., Kistemann, T., Evers, M. (2019): "Intra-urbane Verteilung von multiresistenten Bakterien in sozialräumlich gegensätzlichen Stadtbezirken der Stadt Dortmund, Ruhr Metropole", oral presentation at the German Congress for Geography, Kiel

Schmiege, D., (2018): "Status and tools for WSP implementation in small systems in Germany", oral presentation at the WHO sub-regional workshop on improving small-scale water supplies for better health, Dessau

Schmiege, D. (2018): "Risk assessment of source and dissemination of multidrug-resistant Enterobacteriaceae in the catchment area of a wastewater system in the Ruhr Metropolis, Germany", oral presentation at the 10th annual meeting of the Working Group Medical Geography, Remagen

b. Poster presentations

Schmiege, D., Zacharias, N., Sib, E., Falkenberg, T., Moebus, S., Evers, M., Kistemann, T. (2021): „Antibiotic resistance in wastewater from socio-spatially different communities", poster presentation at the 14th European Public Health Conference, online

Schmiege, D., Evers, M., Kistemann, T., Falkenberg, T. (2020): "What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector", poster presentation at the 6th World One Health Congress, online

Schmiege, D., Evers, M., Kistemann, T. (2019): "Risk assessment of intra-urban dissemination of multidrug-resistant bacteria in the Ruhr Metropolis (Germany)", poster presentation at the 20th International Symposium on Health-Related Water Microbiology (HRWM), Vienna, Austria

Schmiege, D., Evers, M., Kistemann, T. (2019): "Risk assessment of intra-urban dissemination of multidrug-resistant bacteria in the Ruhr Metropolis (Germany)", poster presentation at the 5th International Symposium on the Environmental Dimension of Antibiotic Resistance, Hong Kong

Eidesstattliche Erklärung

Hiermit versichere ich, Dennis Schmiege, an Eides statt, dass ich die vorgelegten Doktorarbeit mit dem Titel „Geographical perspective on antibiotic resistance in a metropolitan sewershed: Investigating socio-spatial hotspots of antibiotic use and antibiotic-resistant bacteria in Dortmund, Germany“ persönlich, selbstständig und ohne Benutzung anderer als der angegeben Hilfsmittel angefertig habe. Für die inhaltlich-materielle Erstellung der vorgelegten Arbeit habe ich keine fremde Hilfe insbesondere keine entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten in Anspruch genommen sowie keinerlei Dritte unmittelbar oder mittelbar geldwerte Leistungen für Tätigkeiten erhalten. Aus anderen Quellen direkt oder indirekt übernommene Daten und Konzepte sind unter Angabe der Quelle kenntlich gemacht. Die vorgelegten Arbeit ist nicht anderweitig als Dissertation eingereicht und ich habe keinen früheren Promotionsversuch unternommen. Die vorgelegte kumulative Dissertation ist auszugsweise bereits veröffentlicht worden (s. Hinweis).

Bonn, den 05.11.2021

Hinweis:

- Chapter 4 was originally published as: *Schmiege, D., Evers, M., Kistemann, T., Falkenberg, T. (2020): What drives antibiotic use in the community? A systematic review of determinants in the human outpatient sector. International Journal of Hygiene and Environmental Health, 226, 113497, https://doi.org/10.1016/j.ijheh.2020.113497*
- Chapter 6 was originally published as: *Schmiege, D., Zacharias, N., Sib, E., Falkenberg, T., Moebus, S., Evers, M., Kistemann, T. (2021): Prevalence of multidrug-resistant and extended-spectrum beta-lactamase-producing Escherichia coli in urban community wastewater. Science of the Total Environment, 785, 147269, https://doi.org/10.1016/j.scitotenv.2021.147269*