University of Applied Sciences Hamburg
Faculty of Life Sciences

Surveillance of vancomycin-resistant Enterococci and antibiotic consumption in German intensive care units from 2006 until 2020: A retrospective cohort study.

Master's thesis
Health Sciences

submitted by
Karras, Juliane
[redacted]

Hamburg, 08.12.2023

1st Supervisor: Prof. Dr. York Zöllner (Hochschule für angewandte Wissenschaften HH)
2nd Supervisor: Dr. Friederike Maechler (Charité Universitätsmedizin Berlin)

The thesis was supervised in the National Reference Center for Surveillance and nosocomial Infections (NRZ) in cooperation with Dr. rer. medic Frank Schwab at the Charité University hospital Berlin, Germany.

Abstract

Background Antibiotic resistance in bacteria is one of the top global public health topic and threat to human health. One sub-species that has shown increasing occurrence of resistances to multiple antibiotics is represented by *Enterococcus faecalis* and *Enterococcus faecium*. These pathogens can cause serious infections and are commonly found in intensive care units. The clinical significance of vancomycin-resistant enterococci led to the categorization as one of the global priorities among resistant bacteria. However, no current study is investigating the present trend of VRE, especially not in correlation to antibiotic consumption. Thus, the purpose of this retrospective cohort study is to examine the development of VRE in general and in relation to antibiotic substances.

Method Data from the German surveillance system SARI were used to analyze the distribution and the development of vancomycin-resistant enterococci and the antibiotic consumption rates in ICUs over the time from 2006 to 2020. Linear regression analyses and univariate generalized linear modeling (GLM) were conducted to examine linear trends in the resistance rate and resistance (incidence) density of VRE. *faecium* and VRE. *faecalis* and in antibiotic application densities. Multivariate GLM was performed to measure the influence of antibiotic consumption on increasing resistance rates and densities of VRE.

Results VRE. *faecium* resistance density showed a significantly increasing trend of 1.5% per year with no shift in VSE. *faecium*. The resistance rate of VRE. *faecium* showed an annual increase of 1.7% and a minimal decreasing trend in VSE. *faecium*. Results of VRE. *faecalis* and VSE. *faecalis* indicated a constant pathogen load. Multivariate GLM identified the application of glycopeptides, aminoglycosides and carbapenems as risk factors in relation with VRE. *faecium*. Increased aminoglycoside use was significant for increased pathogen resistance rates and increasing carbapenem density was associated with increasing incidence densities. In VRE. *faecalis* a protective effect was demonstrated for a high application density of beta-lactamase sensitive penicillin.

Conclusion The results of this study revealed significant changes in the trend of VRE. *faecium* and related influences of changing antimicrobial consumption densities on antimicrobial resistance of enterococci in German ICUs. These results underscore the high relevance of VRE in the context of nosocomial infections. Further biological and genetical understanding of the evolution of resistant enterococci is imperative and will contribute to improved prevention strategies to stop further resistance development.

Keywords Antibiotic resistance, ICUs, surveillance, VRE, resistance rate, resistance density, antibiotic consumption

Table of contents

I List of figures

I List of tables

III List of abbreviations

AD	Antibiotic application Density
AIC	Akaike Information Criterion
AMR	Antimicrobial Resistance
ARS	Antibiotic Resistant Surveillance
ATC	Anatomical Therapeutic Chemical Classification
AVS	Antibiotic Consumption System (Antibiotika-Verbrauchs-Surveillance)
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
CRE	Carbapenem Resistant Enterobacteriaceae
DDD	Defined Daily Dose
DNA	Desoxyribonucleic Acid
DIN	German Institute for Standards (Deutsches Institut für Normung)
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Center for Disease Prevention and Control
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GEE	Generalized Estimating Equation
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GLM	Generalized Linear Model
HAW	University of Applied Sciences Hamburg (Hochschule für Angewandte Wissenschaften Hamburg)
IBM	International Business Machines Corporation
ICU	Intensive Care Unit
ID	Incidence Density
IQR	Interquartile Range
IRR	Incidence Rate Ratio
KISS	Hospital Infection Surveillance System (Krankenhaus-Infektions-Surveillance-System)
MDR	Multidrug Resistance
NC	North Carolina
NCCLS	National Committee for Clinical Laboratory Standards
NRZ-F	National Reference Center Freiburg (Nationales Referenz Zentrum Freiburg)
NRZ	National Reference Center

	(Nationales Referenz Zentrum)
NY	New York
PBP	Penicillin Binding Protein
QIC	Quasi-likehood Information Criterion
RR	Resistance Rate
RD	Resistance Density
RDD	Prescribed Daily Dose
RKI	Robert Koch Institute
RNA	Ribonuclear Acid
SARI	Surveillance of Antibiotic Application and bacterial Pathogens in German Intensive Care Units (Surveillance der Antibiotikaanwendung und bakteriellen Resistenzentwicklung auf deutschen Intensivstationen)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis System
SE	Standard Error
SIR	Spread of Nosocomial Infections and Resistant Pathogens
SPSS	Statistical Package for Social Sciences
TESSy	The European Surveillance System
USA	United States of America
UV light	Ultraviolet light
VRE	Vancomycin Resistant Enterococci
VSE	Vancomycin Susceptible Enterococci
WHO	World Health Organization

1. Introduction

Antimicrobial resistance (AMR) is a commonly known problem in human medicine and public health that represents one of the most important public health topics. To be more precise, research findings have shown that, globally 4.95 million people die of infections associated with resistant pathogens per year, from which at least 1.27 million deaths are directly attributable to AMR [1].
The consequences of AMR on the healthcare system are massive. In addition to the general human suffering, the inability of antimicrobial substances to effectively treat bacterial infections has several consequences. Furthermore, antibiotic-resistant pathogens can spread rapidly within hospital wards, posing an additional risk to healthcare professionals and patients [2,3]. Beside these rapidly evolving resistance mechanism, there are no new antimicrobial active ingredients in the pipeline, what in turn makes it difficult to keep up with the emergence of new resistant strains and exacerbates the global public health problem additionally [4].

Vancomycin-resistant enterococci (VRE) are a subgroup of resistant pathogens causing hospital outbreaks worldwide. The two subspecies *Enterococcus faecalis* (E*. faecalis*) and *Enterococcus faecium* (E*. faecium*), which can cause enterococcal infections, have shown an increasing occurrence of resistances to multiple antibiotics in Germany and other European countries [5,6]. The rising prevalence has been accompanied by the dissemination of specific hospital-acquired strains, that indicate an alarming progress in the development of resistance mechanisms against Vancomycin [7].
Due to similar evidence in several countries and the clinical significance of VRE, global health authorities categorized the pathogen as one of the global priorities among antibiotic-resistant bacteria [8].

Despite different indicators of increasing trends in VRE [7], no study has investigated the present development of VRE compositions in Germany. Therefore, a retrospective cohort study, including data from the last 15 years, was conducted to address identified data gaps with a focus on epidemiological aspects in relation to antibiotic consumption on German intensive care units (ICUs). The resulting study project and data analysis, including background information, research questions, methods, results and significant limitations is presented in this Master's thesis.

1.2 Background

Global health crises, such as the SARS-CoV-2 pandemic, arise suddenly and require immediate action and response strategies, not only from physicians, scientists, health care professionals, and the health care system itself, but also from the society as a whole. Apart from viral pandemics, there is another microbial world that is slower to emerge, inconspicuous, and more intractable [1].

AMR occurs when bacteria, viruses, fungi or even parasites change their individual defense mechanisms and no longer respond to treatment. Although, AMR is a natural phenomenon, nowadays resistance mechanisms are developing more rapidly due to the misuse or overuse of broad-spectrum antibiotics. Thus, antibiotic resistance has significantly reduced the ability to treat common infections and can potentially lead to an increased risk of transmission to other patients or health care professionals, more severe disease, and a higher risk of death in affected patients [1,3].
To date, AMR has been identified as one of the top ten global public health issues and a serious threat to human health by the World Health Organization (WHO). To stress the seriousness of the situation, AMR has further been compared to the climate crisis because it is an internationally shared problem that does not respect national borders and is also hallmarked by an inconspicuously slow progression [2].

1.2.1 The antibiotic resistance crisis

The AMR crisis is the leading increasing global incidence of infectious disease that is significantly affecting the human population. Infections caused by multi-resistant bacteria are untreatable with any known antimicrobial substance. Consequently, the crisis will have devastating cost on public health and human society, as both debilitating and lethal disease will increase in frequency and range [9].

The microbial world, including bacteria, but also various types of multicellular organisms, is the basis of the global ecosystem, including every ecological niche, such as the surface, cavity, as well as animals and every human body. The direct ancestors of microbes were already present at the beginnings of life, approximately 3.5 billion years ago. Despite this long legacy of survival on this planet, microbes are both abundant and diverse, numbering over 10 billion individuals, including thousands of different subtypes [10]. The key to the

adaptive strength and the microbes' persistent mechanism lies in the immense numbers of individual microbes present in small volumes, and their rapid generation time. This rapid generation time is based on genetic variability, which is assured through mutation and reservoirs of adaptive genes. While mutation ensures responses to environmental changes, so-called mobile adaptive genes are available to enter different microbial communities through a mechanism called horizontal gene transfer [10,11].
Microbes of such communities are also invisible inhabitants of the external and internal milieu of the human body. Although, most microbial "passengers" are benign and at some point, beneficial for the human body, some of the bacteria serve as pathogens causing infections that eventually lead to lethal outcomes [3].

To combat bacterial infectious diseases, antibiotic treatments have been the main approach of modern medicine. The so-called "golden era" of antibiotics began in 1928, when Alexander Flemming discovered the first Penicillin, and ranged from the 1930s to the 1960s [3,9]. Since then, different antibiotic substances have been used to treat or prevented bacterial infections, for example during chemotherapy, or after major surgeries such as joint replacements, organ transplant, or cardiac interventions. Within that time, the average human life expectancy has changed from 56.4 years during the 1920s, to an average life expectancy of 80 years [10].
Unfortunately, the rapid progress in the development of many different compounds ended because scientists were unable to maintain the pace of antibiotic substance discovery, especially in the face of increase emergence of resistant pathogens. Hence, the persistent failure in the development and discovery of new antibiotic substances, in combination with the inconsiderate use of antibiotics and the microbial resilience introduced above, represent the predisposing factors associated with the increase in antibiotic resistance [9,10].

Additionally, AMR or multidrug-resistant (MDR) bacteria pose a serious global threat of growing concern to animals and the environment in general. The so-called "superbugs" exist across all environmental niches and share interlinked pathogens within this triad. Certain plausible causes of AMR include the overuse of antibiotic substances in humans, but also in animals, for instance in the agriculture and aquaculture industry for food processing. Especially in livestock, antibiotics are commonly used as therapeutics and prophylactics and have contributed to AMR hotspots across all continents. In fact, the European list of antibiotic substances which are marked as "critically important" for industrial agriculture includes representatives of all relevant classes of antibiotics, which are also used in human medicine [10,12].

Nevertheless, other human-caused drivers of the global resistome should not be underestimated, in particular the ever-increasing human population, rising global migration, as well as the increasing overuse of antibiotics in health care settings, and related rising selection pressure [10].

Today, as approximately 8 billion people are living on Earth, a large number of people are living in communities and in close proximity, providing significant opportunities for rapid proliferation of infectious diseases. Furthermore, in the modern world, individuals can travel to different places on the planet within a day or two and the microbes they carry are able to cross the planet rapidly without significant barriers. This allows pathogens to be distributed globally. What in turn, leads to the human population being exposed to both potential and existing pathogens from all environments that humanity encounters [11,13].

Another serious cause of rising AMR is the increased use of antibiotic treatments. The remarkable effectiveness of antibiotics to treat infectious disease without apparent side effects to the patient has led to a widespread use and a public belief that antimicrobials are universally effective and should therefore be applied in the first instance. The outcome of this belief resulted in an exuberant use and overuse of antibiotic substances and applied a widespread, strong, and polarized selective pressure on the microbial world [11]. In fact, this overuse of antibiotics as principal cause of pathogens' resistance evolution seen today, was already warned by Alexander Flemming in 1945: "The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism", and further "the public demand [the drug and] then will begin an era (…) of abuses" [13,14,15].

The problem is that antibiotics eliminate sensitive bacteria but allow resistant pathogens to remain, to reproduce and thrive through natural selection. Although, overuse of antibiotics is strongly discouraged, over prescription is a persistent issue across the globe. Several international studies have revealed that treatment indications, antibiotic therapy duration and agent choice are inappropriate in 30-50% of the cases [10].

The random application of antimicrobials is often due to practical shortcomings in rapid and accurate diagnostics when it comes to infectious disease. Especially, in detecting the causative pathogen and more importantly, the susceptibility of the pathogen to certain antibiotics. Such accurate diagnosis requires multiple laboratory-based tests that often take several days to complete. However, a patient suffering from life threatening symptoms requires immediate action that often includes various antimicrobials to treat the by then unidentified pathogen. This certain over-use typically takes place among hospitalized patients, especially in patients of ICUs [16].

Compared to that, the ambulant antimicrobial therapy is generally based on entrenched methodologies and guidelines, and further applied in fixed regimen. Usually, such regimens last for 5-7 days, although different antibiotics have been extended to 14 days or longer. The assumption behind prolongated application periods is that high dosages over prolonged periods will completely eradicate the pathogen from the human body. However, recent studies suggest that the relapse rates are not significantly higher in patients who discontinued therapy as soon as symptoms diminish, compared to those taking the full course of treatment [17,18].

Another important point that should not be neglected in the dynamic development of AMR is the so-called "antibiotic resistance pollution". The natural ecosystem provides various compartments that act as a reservoir for mobile genetic elements which in turn interact and spread to human or animal hosts. Resistant pathogens may occur in these compartments through the discharge of antibiotic substances, which enter the environment through several routes such as municipal and hospital waste, animal husbandry, manufacturing industries, as well as runoff from agricultural fields containing livestock manure [19].
While the half-life of antibiotic substances ranges from hours to hundreds of days, antibiotic residues are considered as persistent components in environmental compartments [20].

Adding all natural and human made factors together, it becomes clear that AMR is an international public health emergence and needs appropriate attention to control the "global resistome" in the future [21,22].

1.2.2 Vancomycin-resistant enterococci in Europe and Germany

One species of the most common antimicrobial pathogens that cause nosocomial infections is the vancomycin-resistant Enterococci (VRE). VRE are emerging worldwide and are associated with prolonged in-hospital stays and an excess in mortality rates. The WHO also deems VRE as a serious global health threat and classified the pathogen of high importance in the international priority list of antibiotic resistant bacteria [23,24].

Globally, VRE are commonly associated with hospital outbreaks of bacteremia and urinary tract infections. Especially the vancomycin-resistant *Enterococcus faecium* (VR*E. faecium*) has been identified as the leading multidrug enterococcus species in health care settings and results in high risk of fatal outcomes and exposing to further vulnerable patients. As

mentioned before, this challenge is also linked to treatment difficulties due to high-level resistances to several antibiotics [25,26].

In Europe, data on that resistance in several European countries has been assembled and processed by The European Surveillance System (TESSy) which is coordinated and presented by the European Center for Disease Prevention and Control (ECDC). Considering data over a range of 15 years, an increase of resistant isolates of both Enterococcus species is noticeable in several European countries. Although vancomycin-resistant E. *faecium* isolates (see Figure 1) indicate a more rising trend with higher percentages than vancomycin-resistant E. *faecalis* samples (see Figure 2), which shows a mixed trend among preselected European countries [27].

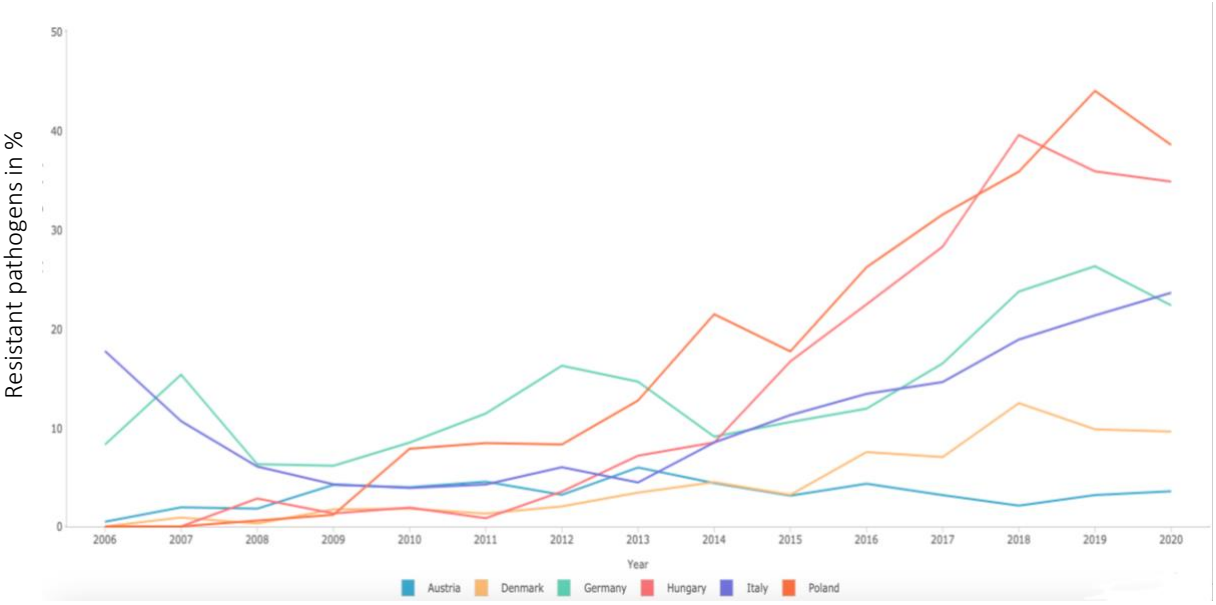


Fig. 1 Vancomycin-resistant E. *faecium* (isolates in %) in European countries from 2006 to 2020; TESSy by ECDC 2023 [27].

For E. *faecium* Poland, Hungary, Germany and Italy have shown the highest increase in vancomycin-resistant isolates, while Denmark showed a slight increase and Austria recorded steady fluctuations over time [27].

In comparison, E. *faecalis* isolates (see Figure 2) range between lower percentages in general but have clearly multiplied in Poland since 2012. While Italy shows a reverse trend from 2006 to 2014 with a minimal increase since then, all other countries indicate different shifts [27]. More detailed information and percentages for both graphs can be found in Appendix I.

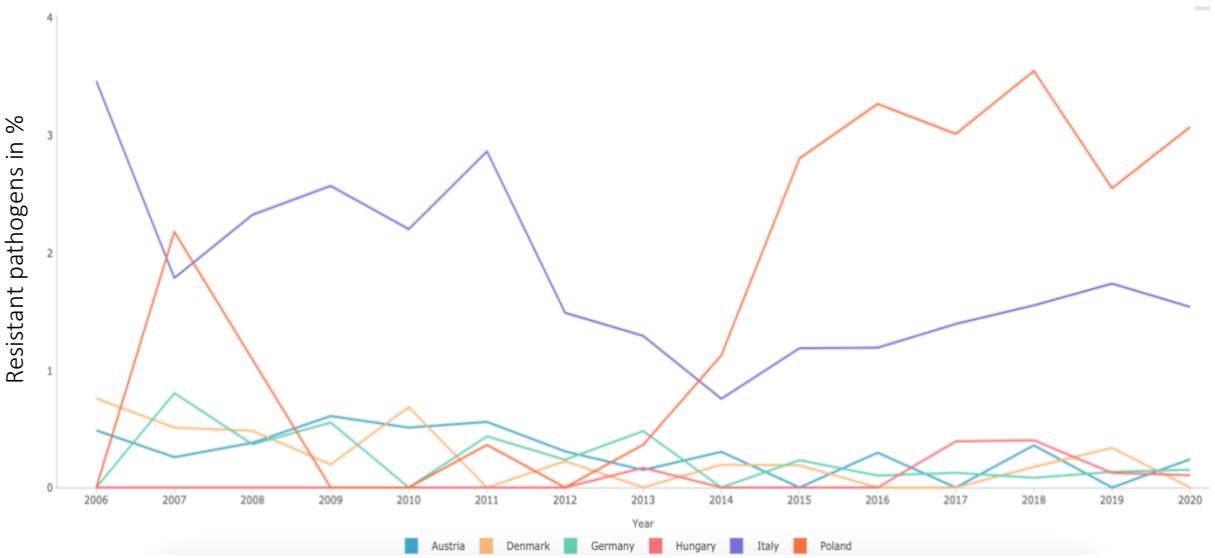


Fig. 2 Vancomycin-resistant E. *faecalis* (isolates in %) in European countries from 2006 to 2020; TESSy by ECDC 2023 [27].

Nevertheless, various research publications suggest that both species are among the most reported pathogens. The European Antimicrobial Resistance Surveillance Network (EARS-Net), which is also a part of ECDC, reported in 2018 a mean proportion of vancomycin-resistant *E. faecium* in invasive isolates of 17.3% (0.17-0.18 95%CI) compared to the mean value of 10.4%, 95% CI (0.10, 0.11 95%CI) in 2014, including countries of the European area. Similar increasing proportions have also been documented at different country levels (e.g., Germany, Italy, and Norway) [27,28]. Furthermore, between the years 2020 and 2021, there has been an increase in reported cases of +21% in *E. faecium,* and +14% in *E. faecalis* in European countries. Thus, the resistance profiles of both Enterococcus species under European surveillance continue to be of concern [29].

In Germany, resistance data is available from the Antibiotic Resistance Surveillance system (ARS), which is hosted by the Robert Koch Institute (RKI). The system provides data from university and hospital laboratories and additional commercial diagnostic companies as well as private laboratories. Additional data is provided through a surveillance system that determines antibiotic consumption and resistance development in German ICUs (SARI) [7]. In view of the resistance data of ARS, the development of VRE prevalence indicated a comparable trend on the national level in recent years (see Figure 3) [7].

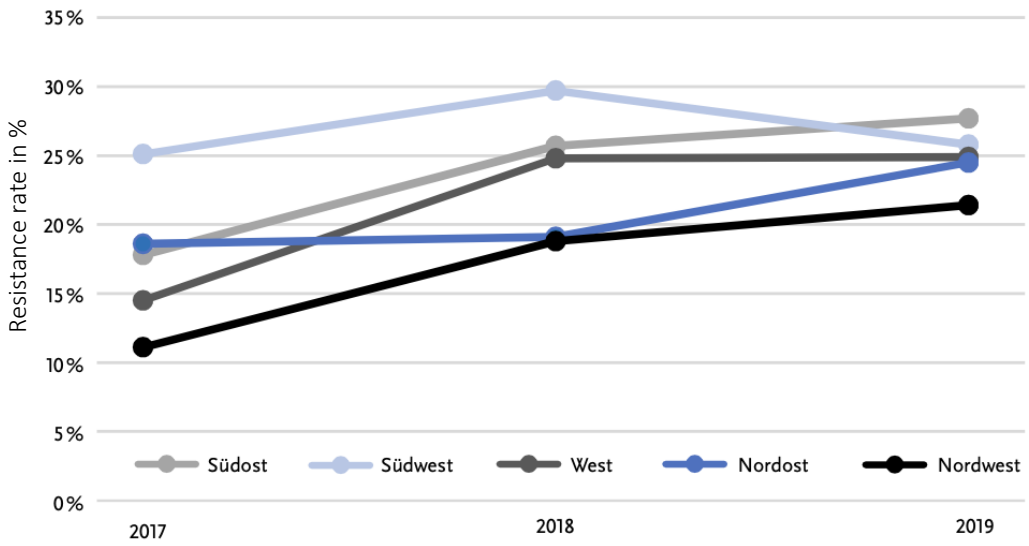


Fig. 3 Resistance rate (in %) of VRE. *faecium* blood cultures in Germany from 2017 to 2019 [7].

In 2017 the ratio of VRE in blood cultures of continuous participating hospitals was at 17.4%, (0.16-0.188 95%CI) and increased up to 23.4%, (0.219-0.25 95%CI) in 2018 and further to 25.1% (0.236-0.267 95%CI) in 2019. That year, the resistance proportions were clearly above 20% in all German regions [7].

Simultaneously, the German reference center (NRZ) also reported an increase in VRE cases between 2014 and 2018 [30]. Even after the exclusion of any selection bias when using data from contributing ICUs, it became clear that the increase in VRE bloodstream infections was substantial with rising results from 5.5% to 21.6% [31]. Accordingly, data from studies conducted by the Paul Ehrlich Society in 2010, 2013, and 2016 revealed a sustained increase in resistance rates among *E. faecium* isolates from 12.6% (n=301), 16.6% (n=320), up to 24.4% (n=316) [32].

In spite of this evidence, a comprehensive epidemiological picture of invasive VRE in Europe and Germany is still lacking. To deepen the understanding of the increasingly problematic situation, epidemiological trends of vancomycin-resistant *E. faecium* and *E. faecalis* and associated determining factors (e.g. antibiotic consumption) need to be strictly observed and studied on a national and international level [30,7].

1.3 Study purpose and research question

Due to incomplete epidemiological data the purpose of this master's thesis will be a detailed retrospective analysis of the available data of the last 15 years with respect to the German surveillance system SARI. The project will serve as a basis to examine specific trends, including the development among targeted pathogens, and furthermore in context to antibiotic consumption. What in fact, is relevant due to recent indicators of differences among rising incidences in VR*E. faecium* and stagnating incidences in VR*E. faecalis* [7].
Therefore, the data included is intended to examine differences in resistance rates and densities of the above pathogens and, as resistance mechanisms increase, to identify any changes in the load of resistant pathogens in relation to sensitive pathogens. Furthermore, the research project will examine whether there are analogous trends on the application densities of specific antibiotic groups, which are used for the treatment of VRE infections.
To investigate recent observations, the following two research questions are the essential content of the presented research project:

1. Are there differences in the development of resistance rates and resistance densities of the selected pathogens: Vancomycin-resistant *Enterococcus faecium*, vancomycin-resistant *Enterococcus faecalis*?
   In particular, as resistance mechanism increase, does the load of resistant pathogens increase with a constant load of sensitive pathogens, or does a switch from sensitive to resistant pathogens occur within a constant load of pathogen species?
2. Are there analogous trends on the application densities of specific antibiotic groups used for the treatment of vancomycin-resistant Enterococci infections?

Accordingly, the hypotheses of the planned thesis will include the following:

(1) The distribution of the antimicrobial resistant pathogen vancomycin-resistant *Enterococcus faecium* and vancomycin-resistant *Enterococcus faecalis* indicates changes over the past 15 years, especially regarding the load of sensitive and resistant pathogens among both species.
(2) There is a correlation between increasing resistance rates among both pathogens, vancomycin-resistant *Enterococcus faecium* and vancomycin-resistant *Enterococcus faecalis* and application densities of specific antibiotic drugs (e.g., glycopeptides).

1.4 Structure of thesis

First, a brief overview of relevant terms and definitions will be provided for a better understanding of the microbiological, medical, and epidemiological context. This includes background knowledge on pathogens, antibiotic resistance and VRE related epidemiology. The field of infectious disease epidemiology and the surveillance tool will then be introduced, which leads into the methods section of the thesis. Next, the research process, starting with the literature review, study design, and data collection beyond detailed statistical analyses is described. Following this, the research findings will be presented and critically reflected upon the discussion part. The thesis will finally be completed with the conclusion section and provides additional data in the appendix.

2. Terms and definitions

In order to understand the context and the subject of the presented research project, technical terms and definitions are first explained. For this purpose, specific definition approaches are used, as well as delimitations to similar terms are made.

2.1 Bacterial pathogens

Bacterial pathogens are responsible for about half of all human diseases. For example, more than 1 million people die each year of the lung disease tuberculosis, caused by a bacterium. And another 2 million people die each year from diarrhea, the result of various bacteria [33]. The group of pathogens that is studied within the presented research project belongs to prokaryotic cells, which are unicellular cells that contain desoxyribonucleic acid (DNA) and ribonucleic acid (RNA) at the same time. Prokaryotic cells are classified into two domains, including archaea and eubacteria and differ significantly in their structure and their variety of shapes [33,34]. Bacteria consist of a rigid cell wall (exoskeleton) and possess so-called locomotion organelles (flagellum). The cell wall is a significant key feature in bacteria, and contains peptidoglycan, which is a polymer composed of modified sugars that are cross-linked by short polypeptides [33,34].

The types of bacteria that are particularly relevant in the field of infectious disease medicine and infectious disease epidemiology are classified by their shape what leads to three groups including coccus, rod-shaped and spiral bacteria [35].

A further classification, which is particularly important for medical bacteriology, is based on the thickness and composition of the cell envelope of a bacterium. The different procurement of the cell walls divides them into the two groups of Gram-positive and Gram-negative bacteria. These groups were named after bacteriologist H.C.J. Gram, who first demonstrated the differentiation of cell wall composition by staining and washing out bacteria microscopically [33].
Gram-positive bacteria, that are present in this master's thesis, have a multilayered cell wall with a relatively large amount of peptidoglycan, which can considerably exceed the thickness of the cell wall of a Gram-negative bacterium [35,36]. At this point, Gram staining is a valuable tool in medicine to quickly determine if a patient's infection is due to Gram-negative or Gram-positive bacteria. This information has also treatment implications. In fact, the effectiveness of antibiotics depends on their inhibition of the previously introduced peptidoglycan cross-linking in bacterial cell walls [33,36].

Also different to animal or human cells is the internal organization of bacteria and bacterial DNA. The genome of prokaryotic cells is structurally different from the eukaryotic genome and has considerably less DNA [33]. The bacterial genome is equally important in the field of medicine and microbiology due to its ability of rapid reproduction, mutation, gene arrangement, and genetic diversity through activating and silencing mechanisms. Thus, even the smallest difference in the genetic recombination within a particular bacterial species can significantly influence the pathogenic potential of the species [37].

2.1.1 Enterococci

The bacteria that are relevant for the given research question are enterococci, which are Gram-positive, facultative an-aerobic, catalase-negative bacteria and form a genus of chain cocci, classified in the family of *Enterococcaceae*. They include over 17 different species and are usually colonized as natural commensals in the intestines of humans and animals. Only a few types of enterococci cause clinical infections and are relevant due to increasing antibiotic resistant strains. The species medically relevant include *Enterococcus faecium* and *Enterococcus faecalis* [38,39].

Infections caused by enterococci develop through an endogenous pathogenesis. Due to the anatomical proximity of the anus and urethra, a contamination with enterococci of the urogenital aera may occurs and leads to a urinary tract infection. In other cases, the bacteria can cause peritonitis via intestinal perforation. Further infections caused by enterococci may

be soft-tissue infections, sepsis, endocarditis, and respiratory infections, as well as nosocomial infections that are triggered by medical devices (e.g., catheters) [38]. Infectious diseases or blood stream infections caused by these pathogens are difficult to treat, as ordinary doses of antibiotics aren't strong enough to effectively treat the clinical disease pattern [39].

Enterococci are intrinsically resistant to many commonly used antimicrobial agents including most cephalosporins and semi-synthetic penicillin. They also exhibit a diminished susceptibility to ampicillin, even though the level of resistance to ampicillin does not preclude the clinical use of this agent for many strains. In fact, ampicillin remains the treatment of choice for enterococcal infections [40,41].

2.2 Antimicrobials and antimicrobial resistance

Antimicrobial substances that affect the growth process in bacteria are called antibiotics. These agents inhibit the reproduction of bacteria through different effects. A general distinction of the effects is made between reversible (bacteriostatic) and irreversible (bactericidal) inhibition [42].

Antimicrobials have been present in nature longer than they were used by humans; today's man-made antimicrobial substances are used as therapeutic treatments to prevent or treat infections caused by bacteria. Antibiotics are not effective in viral infections or mycosis. In bacterial infections they can kill the microorganisms and prevent their growth by targeting key steps in cellular metabolisms of the pathogen, such as the synthesis of biological macromolecules, the activity of enzymes, or cellular structures, including the cell wall and cell membrane [43].

The different types of substances are categorized into narrow, broad, or extended spectrum agents, and additionally classified by their mechanism of action. Antibiotic agents work by inhibiting the bacterial cell wall synthesis, the essential protein synthesis of the bacteria, or interfer with the bacterial RNA synthesis by binding to a certain subunit on a bacterial enzyme that is responsible for the RNA duplication (see Figure 4) [44].
The antimicrobial treatment that plays a decisive part in the present research project is vancomycin, which is a glycopeptide and usually used against infections caused by Gram-positive staphylococci [43,44].

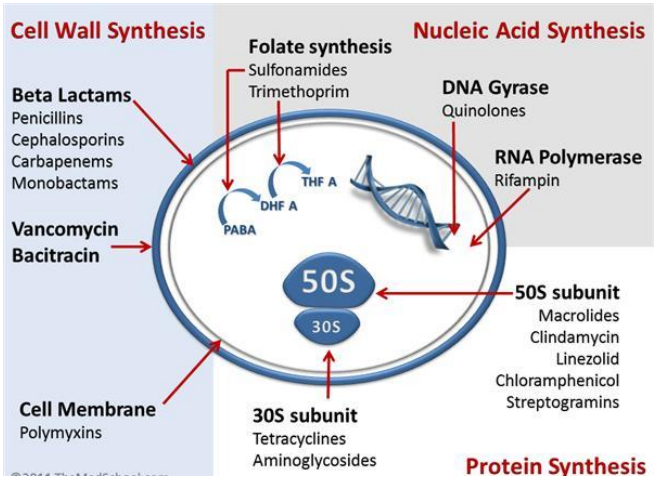


Fig. 4 Different resistance mechanism of action in bacterial cells [45].

Antimicrobial resistance, short AMR, is defined as the ability for microorganisms to survive and be viable under the influence of antimicrobial agents [46]. As such, antibiotic resistance is considered as existing when a microorganism shows reduced sensitivity to antibiotic substances. Pathogens that show reduced or complete insensitivity to several antibiotics or entire groups of antibiotics are referred to as multidrug resistant bacteria [47].

The development of resistance itself is a natural process that can occur in humans and animals, as well as the ecological environment or even in food. However, these resistances are becoming more common and are based on the evolutionary process of mutation and the transmission of resistance genes, between and across different bacterial species. Per definition, a bacterial pathogen is resistant to an antibiotic substance when the minimum inhibitory concentration is so high that therapeutic success fails to occur even with the maximum dosage used [42,48].

2.2.1 Vancomycin-resistant enterococci

The classification of resistant bacteria that is defined to describe the epidemiology of resistant germs, is based on the distinction between Gram-positive and Gram-negative groups, as well as on the corresponding groups of active substances to which a pathogen strain is resistant. Thus, the traditional naming occurs after leading antibiotic substances to which the concerned pathogen is resistant to (e.g., methicillin, vancomycin) [49,50].

Gram-positive enterococci have several factors that allow the pathogen to survive and multiply with a selective advantage in areas where antimicrobial substances are heavily used, such like the hospital environment. An essential factor is the extensive resistance to a wide range of antimicrobial agents. This advanced resistance of VRE includes intrinsic resistances to antimicrobial agents such like beta-lactams and aminoglycosides, as well as acquired mechanisms through plasmids[1] and mobile transposons[2] against glycopeptides, quinolones, tetracyclines, and macrolides, as well through horizontal transfer mechanisms of resistance genes [51,52].

The specific mode action of vancomycin and other glycopeptide antibiotics is to block the bacterial cell wall formation by targeting its building blocks. The substance binds to certain lipids and leads to the obstruction of penicillin binding protein (BPB) activity that is usually cross-linked to other lipids and supports the mature cell wall. Consequently, the integrity of the cell envelope is compromised, then leading to osmotic stress and bursting of the bacterial cell [55].
Vancomycin, what is known as drug of last resort for the treatment of severe infections caused by Gram-positive bacteria has long been considered immune to resistance. However, a complex resistance mechanism has emerged and is widely disseminated what now threatens the clinical efficiency of vancomycin [52,55]. The mechanism in VRE involves two different pathways: the replacement of the terminal D-Ala enzyme with D-lactate, which results in high-level resistance through the elimination of hydrogen bonds, leading then to a significant decrease in substance affinity, or with D-Ser amino acid, producing low-level resistance by decreasing the binding affinity of glycopeptides for peptidoglycan precursors [56].

From a medical point of view, VR*E. faecium* has emerged as the most therapeutically significant organism in the last 10 years. Microbial and a patient's host factors can lead the enterococcus from a second-rate pathogen to a first-rate clinical problem. This is caused by inherent anti-microbial agents and their capacity of acquiring additional determinants of antibiotic resistance [57]. Generally, enterococci related infections are treated with ampicillin, amoxycillin or similar penicillin substances, and in difficult cases in combination with aminoglycosides. In case of resistance against both combined substances, a

[1] Plasmid is a genetic structure that can replicate independently of the chromosomes, typically a small circular DNA strand in the cytoplasm of a bacterium or protozoan [53].

[2] Transposon is a genetic element that moves from one site in a chromosome to another site in the same or a different chromosome and thus alter the genetic constitution of the organism [54].

glycopeptide would be the product of choice. If then a glycopeptide resistance also occurs, the therapeutic options are severely limited [58].
Considering both enterococci, VR*E. faecium* shows higher resistance rates including additional substances that include cephalosporines, carbapenems, aminoglycosides and quinolones [58, 59].

2.2.2 Epidemiology of VRE

Among all VRE colonization, *E. faecalis* is the most common cause of infections, although *E. faecium* is intrinsically more resistant to antimicrobial substances including vancomycin and more often associated with nosocomial isolates [60,61]. Risk factors for such colonization involve the individual's characteristics, especially overall health and past or current exposure to antimicrobials, including oral or intravenous administration of vancomycin, cephalosporins, aminoglycosides and further anti-anaerobic agents. An increased risk is also given due to immunosuppression, hematological malignancies, organ transplantation, as well as increased hospital days in ICUs, residence in long-term care facilities, and exposures to other colonized or infected patients [60,61].

The transmission of VRE is affected by health care professionals that can transmit the pathogen between patients due to its long survival on even washed skin. VRE can persist on hands for up to 60 minutes and on other surfaces, such like beds, side tables or medical devices for up to four months [52]. Consequently, the common pathway for nosocomial infections with VRE begins with person-to-person contact or exposures to contaminated objects [62].

3. Infectious disease epidemiology

To observe the above-mentioned development of antibiotic resistance and its spread among different populations, the special field of infectious disease epidemiology provides various tools to study such trends and correlations. The field also includes the evaluation of different factors that lead to an infection, promote transmission, and exposures associated with clinically recognizable disease among those who are infected [63]. It also serves as a basis for the development of prevention strategies or to put an end to the spread of diseases [64].

For public health professionals, the most important features that come with epidemiological data are the prevalence, the incidence, as well as routes of transmission and susceptible populations. These aspects are of great importance in developing an action plan and control program [64,65]. Thus, (infectious disease) epidemiology is the basic science of preventive medicine, that understands the importance of causative agents, risk factors and transmission processes [64].

3.1 Surveillance of AMR

One major function tool in the field of infectious disease epidemiology is a monitoring system that collects relevant data and information for the purpose of health care and prevention. Such surveillance tool is also necessary to inform policies and guide responses during outbreak events [64].

In Europe, there are different tools and surveillance systems that are used to monitor and observe relevant data about infectious disease. Accordingly, information on antimicrobial resistance numbers is also recorded and evaluated through experts and published by the European Center for Disease Prevention and Control (ECDC) afterwards [66].
To participate in the European and global network for AMR, including the Global Antimicrobial Resistance Surveillance System (GLASS) of the WHO, Germany has established the Antibiotic Resistance Surveillance (ARS) covering both inpatient hospital care and the outpatient care sector [67]. In addition, Germany has another surveillance system that monitors data of resistance rates, densities, and antibiotic consumptions in German ICUs. The SARI system aims to represent actual-states and identify trends and developments in antibiotic consumption and resistant pathogens [68,69]. Furthermore, an separate antibiotic consumption surveillance system (AVS) records defined data of antibiotic application densities in German hospitals by the use of anatomical therapeutic chemical and defined daily doses (ATC/DDD) that are pre-specified in the WHO's classification system [70].

4. Method

In the following section, the methodological approach of the current thesis is presented, as well as the execution of the data analysis from the German surveillance system SARI. Beginning with a brief description of the initial literature review, an explanation of the used surveillance technology, including specific definitions, for understanding the data analysis is provided. Finally, an explanation of the statistical data analysis and an assessment of the techniques used will follow.

4.1 Literature review

Initially, a literature research and review of related scientific articles and publications was conducted. For the purpose of understanding terms and definitions, the medical library at the Charité Campus Berlin Mitte and the medical library at the medical university of Brandenburg were used for relevant literature and reference books. Moreover, a computer-based literature search was conducted including online libraries of the Charité university and the Hamburg University of Applied Sciences (HAW). In addition, published articles and research findings considering the same data base were reviewed. Regarding international databases, PubMed, Free Medical Journals, Springer Link, Elsevier and, in certain cases, Google Scholar were used for online research. Official websites of health institutions or governmental offices including the WHO, the RKI, the EDCD and the German Ministry of Health were also considered for public health related information. In addition, individual articles were provided by the responsible team and cooperating colleagues of the NRZ.

The following literature investigation contained definitions in specific educational books, national and international study reports, publications in scientific journals, and systemic review articles. The research considered German and English specialist literature.
For the purpose of the background writing and discussion part central terms were used for the online literature search. These terms included "antimicrobial resistance", "resistant pathogens", "antibiotic resistance", "enterococci", "vancomycin resistant enterococci", "nosocomial infection", "infectious disease epidemiology", "transmission of antimicrobial resistant bacteria", "VRE", "VRE mechanism", "surveillance", "surveillance of resistant pathogens", "AMR", "AMR in Europe", "AMR in Germany", "VRE in Germany", "AMR surveillance", "AMR in ICUs". Furthermore, terms including "AMR", "resistant pathogens", "VRE" and synonyms mentioned previously were linked to different other terms including "epidemiology", "surveillance", "nosocomial infection", "public health", and "health crisis",

by using "AND" as operator in PubMed and Google Scholar (e.g., "VRE AND resistance mechanism", "antibiotic resistance AND surveillance", or "resistance AND enterococci"). Results from queries for the purpose of this background writing have been limited to a ten-year period, beginning with literature from the year 2013 and up to 2023. Further technical literature that was perused for the purpose of definitions or the explanation of subject-specific terms, including microbiological techniques and medical terms, was expanded to a 23-year period, starting with book sources and biomolecular papers from 2000.

After excluding duplicates, the subsequent review of the titles and abstracts was performed via a skim-through reading of titles, abstracts and, when indicated, of section headings for content related to VRE, nosocomial infections, epidemiological information on VRE, surveillance of VRE and or AMR in general, AMR and public health and topics related to the evolution and spreading of VRE in Europe and Germany. Following that step, remaining articles and reviews were read and screened for relevant context and information about the topic of interest. Articles that contained other additional pathogen species and/or different variables irrelevant for the presented research question were excluded at this point.
The entire process resulted in a significant shortlist of the most relevant articles, reviews, and study findings, including 68 resources for the background writing and a total of 87 results as the basis for the entire thesis. A detailed process chart can be found in Appendix II.

4.2 Study design and data collection

In order to investigate the epidemiology of VRE and the related load of sensitive and resistant pathogens among both species and the consumption of antimicrobial substances, a retrospective cohort study was conducted to analyze data from the SARI database from 2006 to 2020.
The study includes data from German ICUs that participate on a voluntary basis and report their data on a monthly basis. Due to the voluntary nature of the participation, the available data from individual units in SARI can change over time, potentially altering the set of ICUs that provided clinical data throughout the time period that was determined for the presented cohort study. Nevertheless, the information that is gained from this retrospective study can be helpful to plan further prospective studies to follow up the development of resistance rates.

4.2.1 Retrospective cohort study

For the purpose of the presented research question, a retrospective cohort study design was applied and conducted. A cohort study refers to groups of individuals with characteristics who are followed up over time to determine incidence, mortality and morbidity rates and other outcomes [71]. Particularly in clinical research, cohort studies are appropriate to examine evidence of a link between an exposure and an outcome [71], as it is also assumed within the second present hypothesis regarding the antibiotic consumption and increasing resistance rates in VRE.
Due to the longitudinal design of a cohort study, many different variables can be examined either over time or retrospectively, as it is the case in this research project. From this retrospective study design, conclusions shall be drawn about resistance rates, densities, and ratios of pathogen densities. Although statistical causality cannot be established through the chosen study design, the resulting data are useful to provide evidence that suggests information regarding the strength of the association between antibiotic application densities and increasing resistance rates.

The retrospective time period was determined for 15 years, starting from January 2006 and including all available data up to December 2020. This time period was chosen due to an increased participation among German ICUs and more extensive available data.

4.2.2 Surveillance system SARI

To fulfill the purpose of the retrospective cohort study a comprehensive data acquisition was ensured through the German surveillance system SARI.
The SARI project was first implemented in February 2000 and initially tested for one year. Since then, the monitoring tool has continuously recorded resistance rates of different pathogens and antibiotic application densities from various German ICUs [72,73]. The surveillance system was established and is still run by the NRZ at the Institute for Hygiene and Environmental Medicine Charité in Berlin and the National Reference Center for Hospital Hygiene (NRZ-F) at the university hospital in Freiburg, Germany [74]. Thus, SARI is an important part of the network of infectious disease epidemiology (SIR – Spread of Nosocomial Infections and Resistant Pathogens) that aims to record the antimicrobial application and MDR on ICUs and to correlate both variables with one another.

The participation in SARI is voluntary, although different requirements have to be fulfilled, e.g., the official compliance of responsible head physicians, the readiness for the implementation of external and internal quality processes, as well as available laboratories that can determine antibiotic susceptibility according to DIN 58940 (Deutsches Institut für Normung), NCCLS (National Committee for Clinical Laboratory Standards), CLSI (Clinical & Laboratory Standards Institute) or EUCAST (European Committee on Antimicrobial Susceptibility Testing) guidelines. Furthermore, available data needs to be transmitted online on a monthly basis via a computer-based system. In return, the NRZ evaluates the data and assists with professional advices and expertise. In addition, participating units receive information on their own data, as well as current frequency distributions of resistance densities and antibiotic consumption trends [74].
Each participating SARI-hospital has a contact person who is responsible for the digital data transfer. The monthly submitted data include the following:

- Patient days/ units
- Pharmacy/ units
- Resistance data/ units.

Pharmacy data includes oral or parenteral antimicrobial consumption (in g), and laboratory data provides information on resistant pathogens, although screening samples and copy strain[3] are not included. All relevant pathogens and associated antimicrobial substances that are captured in SARI are pictured in Table 1.

Pathogen	**Antimicrobial agent**
Staphylococcus aureus	Oxacillin, vancomycin, teicoplanin, gentamicin, ciprofloxacin/ ofloxacin, quinupristin/dalfopristin, linelozid
Staphylococcus pneumoniae	Oxacillin, cefotaxime, vancomycin, erythromycin, ciprofloxacin/ ofloxacin, levofloxacin, moxifloxacin
Coagulase-negative *staphylococci*	Vancomycin, teicoplanin
Enterococcus faecalis	Ampicillin, vancomycin, teicoplanin, ciprofloxacin, levofloxacin, moxifloxacin,
Enterococcus faecium	see E. *faecalis*, linezolid
Escherichia coli, Klebsiella pneumoniae	Cefotaxime/ ceftazidime/ ceftriaxone, imipenem,

[3] Repeated sample of the same bacterial strain with the same resistance within 30 days [74].

Pathogen	Antimicrobial agent
	meropenem, ciprofloxacin, amikacin, piperacillin/tazobactam, ampicillin/ sulbactam, amoxicillin/ clavulanic acid
Enterobacter cloacae, Citobacter, Serratia marcescens	Imipenem, meropenem, amikacin, ciprofloxacin, levofloxacin
Acinetobacter baumannii	Ceftazidime, cefuroxime, piperacillin/ tazobactam/ sulbactam, imipenem, meropenem, amikacin, ciprofloxacin
Stenotrophomonas maltophilia	Ceftazidime/ cefotaxime, ciprofloxacin, piperacillin/ tazobactam, amikacin, levofloxacin, cotrimoxazol

Source: Own representation following the SARI Protocol [74].

Table 1: Antibiotic pathogens and collected data of associated susceptibility.

Relevant data from the hospital pharmacies are first sent to Freiburg, where the data are converted into so-called defined daily doses (DDDs) according to the Anatomical Therapeutic Chemical Classification system (ATC). The DDDs are predetermined by the WHO and defined as "The assumed average maintenance dose per day for a drug used for its main indication in adults" [74,76]. Despite this definition, it is important to mention that the DDDs do not reflect the actual recommended or prescribed daily dose (RDD). For the presented study method and in the purpose of international interpretation of hospital surveillance data the DDDs are referred to 1000 patient days [74,77].

For further data processing, the antibiotic use density and incidence density of pathogens are calculated for each individual ICU. For comparability, resistance rates are collected per 1000 patient days [77].

4.3 Statistical analysis

To answer the research questions of the thesis, relevant variables and different mathematical and statistical analyses are described in the following chapter. The data were extracted from SARI and transposed into Microsoft Excel Version 16.76. The following analyses were conducted also using Microsoft Excel Version 16.76, as well as SPSS Statistics Version 29.0. [IBM SPSS statistics, Somer, NY, USA] and SAS Version 9.4 [SAS Institute, Cary, NC, USA] supported by the NRZ.

A detailed listing of relevant data records, example commands and outputs can be found in Appendix III, VII.

4.3.1 Relevant variables

For the analysis of the captured data multiple variables are determined to investigate trends and differences in the distribution of VRE. Following, these variables and their definitions are explained, including the description of the variables in context of the distribution of VRE. *faecium* and VRE. *faecalis* and coherent resistance densities, as well as antibiotic consumption densities in German ICUs. The definitions are specified in the official SARI protocol [74].

The variables are calculated to obtain appropriate data on resistance densities, resistance rates, and antibiotic use densities. The resistance density corresponds to a number of resistant pathogens in relation to 1000 patient days. 1000 patient days refer to an annualized number of hospital days that are used in a year for each thousand covered patients. The resistance density (RD) is defined as:

$$\mathbf{RD} = \frac{\text{Number of resistant pathogen x 1000}}{\text{Patient days.}}$$

The resistance rate refers to numbers of resistant isolates of a pathogen from a certain species in relation to all tested pathogens of this species. The resistance rate (RR) is defined as:

$$\mathbf{RR} = \frac{\text{Number of resistant isolates of a species}}{\text{Number of all tested pathogens of this species}} \text{ x 100.}$$

The antibiotic use density (AD) is calculated as the DDD per 1000 patient days. The formula is defined as follows:

$$\mathbf{AD} = \frac{\text{Antibiotic consumption (g)}}{\text{Defined daily dose (g)}} \text{ x } \frac{1000}{\text{Patient days.}}$$

Next, variables targeting the pathogen species of interest were identified from the extracted SARI data set and specified (see Table 2).

E. *faecium* and E. *faecalis* cases are differentiated into total tested, total resistant to vancomycin and vancomycin resistances of both species per 100 patient days what equals the resistance density per 100 patient days.

Variable name	**Label**	**Characteristic of variable**
tB13i	Total E. *faecium*	-
tG13A4	Total tested E. *faecium*	Number E. *faecium*
tR13A4	Total resistant VRE. *faecium*	Number VRE. *faecium*
tB6l	Total E. *faecalis*	-
tG6A4	Total tested E. *faecalis*	Number E. *faecalis*
tR6A4	Total resistant VRE. *faecalis*	Number VRE. *faecalis*
RR13A4	RR VRE. *faecium*	Resistance rate VRE. *faecium* (per 100 *E. faecium*)
RR6A4	RR VRE. *faecalis*	Resistance rate VRE. *faecalis* (per 100 *E. faecalis*)
RP13A4	RD VRE. *faecium*	Resistance density VRE. *faecium* per 1000 patient days
RP6A4	RD VRE. *faecalis*	Resistance density VRE. *faecalis* per 1000 patient days

Table 2: Overview of variables included in statistical analysis (pathogens).

In order to examine the increasing resistance rates and densities in relation to assumed higher antibiotic use densities, further variables addressing multiple substances needed to be identified. With the help of a medical specialist enterococci-related antimicrobial substances were gated and determined (see Table 3). For this analysis relevant antibiotic substances were analyzed in sub-groups related to their ATC-classifications. Individual associated compounds of each substance group and associated application forms can be found in Appendix IV.

Variable name	Label/ Substance group = DDD ATC per 1000 patient days	ATC code
g1	Beta-lactamase sensitive penicillin	J01CE
g2	Broad-spectrum penicillin	J01CA
g3	Beta-lactamase resistant penicillin	J01CF
g4	Penicillin + lactamase inhibitors (antipseudomonal penicillin excluded)	J01CR
g5	Cephalosporins (1st generation)	J01DB
g6	Cephalosporins (2nd generation)	J01DC
g7	Cephalosporins (3rd generation)	J01DD
g7a	Cephalosporins (4th generation)	J01DD
g8	Carbapenems	J01DH
g9	Monobactams	J01DF
g10	Glycopeptides	J01XA
g11	Fluoroquinolones	J01MA
g12	Sulfonamides and trimethoprim	J01E
g14	Tetracyclines	J01AA
g16	Macrolides	J01FA
g18	Aminoglycosides	J01G
g21	Imidazole derivates	J01XD
g22	Other antibiotics	J01XX

Table 3: Overview of variables of antibiotic substances included as antibiotic use density in statistical analyses.

For the analyses, matched data were included from all ICUs that delivered separated information regarding the selected pathogens and the use of antibiotic substances. Data was collected from separate data bases regarding ICU and months. If either information was missing, the concerned ward was excluded from the data set.

The data level of all pathogen and antibiotic application associated variables is metric. The resulting values depend on calculated variables due to varying characteristics of resistance rates and densities.

4.3.2 Descriptive analyses

Initially, a descriptive analysis of the whole data set with the attention to the variables identified above was conducted by creating tables and visual graphs in Microsoft Excel. To get an overview of the participating ICUs and the completeness of available data on pathogen rates and densities, as well as antibiotic application densities, the data were scanned for missing and unreasonable values.
Next, the variables "Total tested E. *faecium*", "Total resistant VRE. *faecium*", "Total tested E. *faecalis*", "Total resistant VRE. *faecalis*", "RR VRE. *faecium*", "RR VRE. *faecalis*", "RD VRE. *faecium*", and "RD VRE. *faecalis*" were checked for calculated numbers, percent and pooled means of the investigated parameters. The same procedure was applied for the pooled variables of antibiotic substances, including "g1 – g12", and "g14, g16, g18, g21, g22". All variables of interest were first analyzed descriptively, which includes absolute frequencies, minimum and maximum values. Additionally, graphs were generated to demonstrate the individual distribution of different ICUs over time and the differences among both pathogen subspecies, as well as the application density of antibiotic substances.
Due to the relevance of glycopeptides in the context of vancomycin-resistant enterococci, an exemplary trend analysis was conducted to get an impression of the retrospective and predictable development of the glycopeptide application density by calculating linear trends.

Additionally, in the generalized model for the descriptive analysis number and percent's for categorial parameters were calculated and median and interquartile range (IQR) were calculated for continuous parameters. After this, differences were compared using Chi-square or Kruskal-Wallis test. Next

4.3.2 Linear regression analyses

Next, a linear regression model was calculated to test the existing linearity of the pooled rates per year for both pathogen-related variables and antibiotic use density per year. This model was conducted to get an initial estimation of how the variables have changed in 15

years and whether a general linear trend is identifiable. This analysis was not yet assessed for individual observations or patient days per year and served as initial test for linearity in the pooled rate.

The independent variable of all models is the year, measured in one year each including data from 2006 to 2020. For the depending variables, there are "Total resistant VRE. *faecium*", "Total resistant VRE. *faecalis*", "RR VRE. *faecium*", "RR VRE. *faecalis*", "RD VRE. *faecium*", and "RD VRE. *faecalis*". In addition, the pooled variables for all antibiotic substance groups were analyzed, including "g1 – g12", and "g14, g16, g18, g21, g22".
For the goodness of fit of the model, the correlation coefficient R, the R^2 and adjusted R^2 are rated to provide an understanding of the percentage of variation of the dependent variable that can be explained by each year. Furthermore, the F-statistics of the analysis of variance (ANOVA) will be reported to check the overall significance of the model. The effect size of the year on the outcome will be given by the unstandardized coefficient (B) and its standard error (SE). Significance is indicated by the p-values of the t-statistics with a significance level of $p \leq 0.05$ [79].

4.3.4 Generalized linear model

Due to the mathematical limitations of the simple linear regression model, the next step was to perform a more flexible regression analysis that allows changes in unconstrained inputs to affect the output variable on an appropriately constrained scale. For this, a generalized linear model (GLM) was performed [79]. The model was first built for the univariate analyses and then for a multivariate linear analysis.

4.3.4.1 Univariate analysis

First, univariable, and multivariable regression using GLM was performed to estimate the association of the frequency of the pathogens VRE. *faecium* and VRE. *faecalis* per month with different antimicrobial groups in the current month and the month before the current month and further confounding parameters such as trend, year, season, and type and size of ward and hospital.
For the analysis of resistance rates, including the variables "RR VRE. *faecium*", "RR VRE. *faecalis*", a GLM with response equal to the binomial proportion of resistant pathogens per

tested pathogens was calculated. For this the variables "Total tested E. *faecium*", "Total resistant VRE. *faecium*", "Total tested E. *faecalis*", "Total resistant VRE. *faecalis*" were used. For the calculated model the probability distribution was binomial, and the link function was logit.

For the analysis of incidence densities including the variables "RD VRE. *faecium*" and "RD VRE. *faecalis*" (pathogens per 1000 patient days), a GLM with negative-binomial distribution was calculated instead of Poisson distribution, because the variance exceeds the mean and an overdispersion was observed. Following, the Lagrange multiplier test was used to test whether the negative binomial model significantly differs from the Poisson model. In addition, the log number of patient days during each month was used as an offset in the model.

Since observations within a ward are not statistically independent due to diagnostic and management policies, in particular the frequency of microbiological tests and screenings, and the timely development, adjusted incidence rate ratios (IRR) with 95% confidence intervals (CI) were estimated. The IRRs were based on generalized estimating equation (GEE) models that account for such clustering effect by using an autoregressive correlation structure [80].

4.3.4.2 Multivariate analyses

Multivariable regression models were calculated to examine independent risk factors in relation to the presented research question. For this model building all parameters with $p < 0.2$ in the univariable regression model were included in a full model and then non-significant parameters excluded by variable selection stepwise backward. The selection criteria were the smallest Chi-square value and $p \geq 0.05$ in the type III score statistic. The quasi-likelihood information criterion (QIC) as a modification of the Akaike information criterion (AIC) was used as goodness-of-fit measure in the GEE model.

Two models were calculated afterwards. The models considered all identified isolates on the ICUs. Antimicrobial agents that are relevant for the treatment of VRE (e.g., daptomycin, linezolid and tigecycline) were excluded from the analysis [23]. For better interpretation, the antibiotic application density in the statistical models was calculated by 100 patient days, consequently the estimated effects in the model can interpreted as per 1 DDD per 100 patient days.

In the sensitivity analysis, to validate the effect of type of ICU and hospital and where ICUs are located, the final models were adjusted according to these parameters. The following

categories were used: interdisciplinary ICU versus medical ICU versus surgical ICU; and hospital of maximum care (university/ maximum care) versus other. Additionally, for analyze longer effects of antibiotic use on the ICUs, the models were expanded by the antibiotic use one month before the current month, in which the isolates were observed. All results with values of $p \leq 0.05$ were considered as significant.

5. Results

The following chapters present the results of the analyses of the research question. First, the results of the descriptive analysis of the initial SARI data set, including all relevant variables are presented. Second, the results of the initial linear regression will be given, and following the descriptive and analytical outcome of the univariate GLM is explained. Finally, additional results from the multivariate modelling are presented to finally answer the research questions. Extensive outputs, comprehensive data tables and modelling codes can be found in the appendix.

5.1 Descriptive analyses

In the following, the raw data set that was derived from the SARI system is described and relevant variables are presented. In addition, the variables are visualized in graphs to give a better impression of the assumed trends.

5.1.1 Sample description

Overall, 79 ICUs delivered data on pathogen counts and antibiotic consumption. The structure of ICUs is shown in Table 4.

The descriptive analyses resulted in valid data of a total of n = 79 participating ICUs, from three different categories and four different hospital types (see Table 4). The ICU categories include interdisciplinary wards, internal and chirurgical wards. As such, the results include data from 35 interdisciplinary ICUs (44.3%), 19 internal ICUs (24.1%) and 25 surgical ICUs (31.6%). Furthermore, 62 out of 79 ICUs (78.5%) are part of university hospitals or hospitals that offer all available disciplines. And 17 (21.5%) of the ICUs belong to smaller hospital facilities or specialized institutions. The ICUs consist of various types of hospitals that differ in size and specialty. Thus, 65.8% of the ICUs are located in hospitals with ≥ 600 beds, and 34.2% are located in smaller hospitals with fewer than 600 beds. The ICU size ranges from 33 wards (41.8%) with fewer than 12 patient beds to 46 wards (58.2%) with 12 patient beds or more.

Overall, the ICUs have collected data from a median value of 34038 patient days per ward and have participated for a median value of 103 months, with an interquartile range of 1486 and 48 months out of 180 possible months over 15 years. Thus, less than 25% of the ICUs delivered continuous data for this time period between 2006 and 2020.

Parameter	Category	Number	Percent (%)
ICU type	Interdisciplinary	35	44.3
	Internal	19	24.1
	Surgical	25	31.6
Hospital type	University/maxi	62	78.5
	Other	17	21.5
Hospital size	≥ 600 beds	52	65.8
	<600 beds	27	34.2
ICU size	≥ 12 beds	46	58.2
	<12 beds	33	41.8
Parameter	**Category**	**Number**	**Sum**
Patient days	Median (IQR)	34038 (16353-57903)	6147142
Participation months	Median (IQR)	103 (146-48)	79.5

Table 4: Distribution of participating ICUs (n=79); IQR = interquartile range.

5.1.2 Description of relevant variables

Next, the variables of vancomycin-resistant enterococci, total counts of tested E. *faecium* and E. *faecalis* are available for each of the 15 years (see Table 5). The maximum value of reported E. *faecium* isolates reached 1832 counts in 2018, and for E. *faecalis* at 1781 counts in 2017. The lowest count of E. *faecium* was documented in 2008 with 1168 reported isolates and for E. *faecalis* in 2020 with 1064 reported cases in total. Continuing, the highest count of total tested E. *faecium* was reported in 2018 with 1818 isolates tested, of which 563 isolates were resistant to vancomycin. The year with the lowest amount of tested E. *faecium* isolates was 2008 with 1149 counts and 92 vancomycin resistant cases. For E. *faecalis* the highest value of tested isolates was reported in 2017 with 1751 tested isolates in total, and the minimum value in 2014 with 1209 isolates tested.

Among the available data of vancomycin-resistant enterococci, the highest value of total VRE. *faecium* isolates was reported in 2019 with a total of 693 isolates and the lowest value with 38 isolates in 2006. The highest value of VRE. *faecalis* isolates was reported in 2013 with a total of 11 isolates, while in year 2006, 2009, and 2015 no isolates were reported at all.

Label	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Total E. *faecium*	1320	1406	1168	1223	1310	1509	1385	1624	1395	1534	1771	1819	1832	1780	1325
Total resistant VRE. *faecium*	38	47	92	84	95	175	134	215	133	231	361	399	563	693	478
Total tested E. f*aecium*	1306	1384	1149	1211	1300	1495	1376	1613	1364	1503	1756	1804	1818	1773	1308
Total E. *faecalis*	1707	1602	1360	1388	1313	1381	1620	1542	1245	1456	1559	1781	1510	1425	1064
Total resistant VRE. *faecalis*	0	1	3	0	4	3	5	11	8	0	1	1	7	3	1
Total tested E. *faecalis*	1682	1579	1337	1375	1291	1362	1539	1516	1209	1405	1542	1751	1480	1405	997

Table 5: Overview of pathogen rates of VRE. faecium and VRE. faecalis from 2006 to 2020.

Label	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
VRE. *faecium* per 100 E. *faecium* (RR)	2.9	3.4	8.0	6.9	7.3	11.7	9.7	13.3	9.8	15.4	20.6	22.1	31.0	39.1	36.5
VRE. *faecalis* per 100 E. *faecalis* (RR)	0.0	0.1	0.2	0.0	0.3	0.2	0.3	0.7	0.7	0.0	0.1	0.1	0.5	0.2	0.1
VRE. *faecium* / 1000 patient days (RD)	0.18	0.23	0.49	0.43	0.49	0.86	0.56	0.91	0.66	1.07	1.58	1.79	2.55	3.29	2.61
VRE. *faecalis* / 1000 patient days (RD)	0.00	0.00	0.02	0.00	0.02	0.01	0.02	0.05	0.04	0.00	0.00	0.00	0.03	0.01	0.01

Table 6: Overview of resistance rates (/100 pathogens) and resistance densities (/1000 patient days) of VRE. faecium and VRE. faecalis from 2006 to 2020.

Resistance rates and resistance densities of both pathogen species are available for the entire study period (see Table 6). The resistance rate of VRE. *faecium* was the highest in 2019 with 39.1 per 100 pathogens and the lowest in 2006 with 2.9. The resistance rate of VRE. *faecalis* had the highest values of 0.7 in the year 2013 and 2014. The lowest rate, with a value of 0, was documented in 2006 and 2015.
For the pathogen density of VRE. *faecium* is a maximum value of 3.29 per 1000 patient days documented in year 2019 and a minimum value of 0.18 in 2006. The density of VRE. *faecalis* isolates ranges from zero findings in 2006, 2007, 2008 and 2015 to 2017 to a maximum value of 0.05 in 2013.

Continuing with the antibiotic consumption, application densities for all antibiotic substances are also available for the whole period of the study (see Table 7).
The pooled application density of all included antimicrobial substances varies over the years and within their different subgroups. For example, the application density of beta-lactamase sensitive penicillin ranges from a minimum value of 15.1 in 2013 to the high of 26.4 in 2015. In contrast, the group of penicillin with lactamase inhibitors ranges between a minimum value of 135.9 in year 2009 and a maximum value of 354.3 in 2019.
Another substance class with high use densities is present in the group of carbapenems, as the lowest value of 120.2 was documented in 2006 and has since increased to a maximum value of 339.9 in 2020.
The antibiotic substance class with the least application frequencies is represented by the monobactams with a minimum value of 0.1 in 2014 and a maximum value of 0.6 in 2007 and 2010.
The group of glycopeptides, which plays a special role in the context of vancomycin-resistant pathogens, showed the lowest application density in 2008 with a value of 36.2 and ranged up to a maximum value of 89.3 in 2020. Another group of fluoroquinolones ranged from a antibiotic use density of 88.9 in 2019 to 184.5 in 2011. Whereas the group of aminoglycosides ranges from a minimum value of 24.4 in year 2013 to a maximum value of 39.3 in 2020.
The summarized group of other antibiotic substances shows minimal consumption values of 38.2 in 2007 and has since then increased to a maximum value of 105.4 in 2020.

All explicit results of the individual antibiotic substances included in the pooled groups and their application densities over the entire study period are available in Appendix IV.

Antibiotic group (ATC code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Beta-lactamase sensitive penicillin (J01CE)	23.0	20.0	17.2	19.4	20.2	18.7	18.3	15.1	23.0	26.4	22.9	20.7	23.8	26.1	25.5
Broad-spectrum penicillin (J01CA)	100.9	103.4	81.6	89.2	66.6	60.7	47.5	33.6	36.5	38.9	39.6	64.4	57.7	60.0	65.6
Beta-lactamase resistant penicillin (J01CF)	37.3	45.2	40.7	41.7	25.0	32.5	34.3	33.4	49.7	53.1	75.5	86.2	85.7	90.6	98.5
Penicillin + lactamase inhibitors (J01CR) (pseudomonas efficacy excluded)	157.6	160.2	145.2	135.9	160.9	193.8	227.1	262.8	267.8	276.4	273.0	284.4	328.6	354.3	353.0
Cephalosporines (1st Generation) (J01DB)	39.2	32.8	28.5	34.1	28.6	35.5	38.1	35.3	36.7	33.5	32.2	35.4	40.2	40.9	37.0
Cephalosporines (2nd generation) (J01DC)	93.6	97.9	95.3	95.3	92.9	92.7	88.4	89.7	74.0	93.5	71.8	62.3	46.7	44.0	36.6
Cephalosporines (3rd generation) (J01DD)	124.0	111.8	111.6	122.6	117.7	115.1	109.2	98.8	91.2	99.3	92.1	99.3	83.3	81.6	75.6
Cephalosporines (4th generation) (J01DE)	10.8	10.2	4.1	4.0	4.3	4.8	14.8	14.6	6.3	8.6	10.7	16.4	16.3	16.1	21.5
Carbapenems (J01DH)	120.2	132.8	142.9	167.7	184.1	213.5	230.7	233.1	248.3	244.7	266.4	245.2	278.1	304.3	339.9
Monobactams (J01DF)	1.2	0.6	0.4	0.4	0.6	0.2	0.4	0.5	0.1	0.3	0.2	0.2	0.5	0.3	0.2
Glycopeptides (J01XA)	40.3	37.9	36.2	45.6	61.5	54.3	56.6	59.2	62.4	58.2	64.7	58.6	64.1	77.2	89.3
Fluoroquinolones (J01MA)	172.3	168.7	164.6	170.7	171.6	184.5	183.6	160.5	152.2	172.1	167.3	157.2	128.9	88.9	90.2
Sulfonamides + trimethoprim (J01E)	17.1	19.8	26.0	24.5	22.5	20.3	34.4	33.5	42.6	44.6	42.3	37.6	33.2	32.7	31.9
Tetracyclines (J01AA)	13.6	24.2	21.8	28.0	35.8	25.5	26.7	25.6	24.0	31.9	33.2	24.2	24.8	22.3	22.7
Macrolides (J01FA)	74.7	83.1	89.1	106.4	107.9	111.4	105.8	109.9	99.8	113.8	91.6	90.3	89.0	82.9	92.5
Aminoglycosides (J01G)	29.8	28.1	25.2	27.6	32.6	29.2	28.8	24.4	26.1	29.0	33.7	29.8	35.6	35.7	39.3
Imidazolderivates (J01XD)	66.6	59.6	51.4	48.3	46.4	47.3	48.0	45.2	41.2	48.2	39.8	36.5	32.7	29.1	24.6
Other antibiotics (J01XX)	39.8	38.2	45.3	50.5	60.8	60.8	73.0	72.0	58.8	67.7	77.1	71.7	82.9	91.4	105.4

Table 7: Overview frequencies of pooled antibiotic use densities (AD) from 2006 to 2020 (AD = DDDs / 1000 patient days).

5.1.2 Visualization of relevant variables

To understand these results in the context of the research question presented, the data for all relevant variables are visualized in the following graphs.

Starting with the number of all tested E. *faecium* isolates compared to all VRE. *faecium* isolates documented, a clear difference between both variables appears (see Figure 5). Seasonal fluctuations are visible in both variables, although peaks and lows are more distinctive in the prevalence of all E. *faecium* isolates. After a slight decrease between 2007 and 2008 the data rose to 1832 isolates until the year of 2018 and again dropped down to 1325 isolates in 2020.
Continuing with the data of all VRE. *faecium* isolates identified, the numbers marginally increased from 2006 to 2014, when the count of total resistant isolates again increased from 133 to a peak of 693 resistant isolates out of 1773 total tested E. *faecium* isolates in 2019. In the last year of observation, the numbers dropped down to 478 resistant isolates.

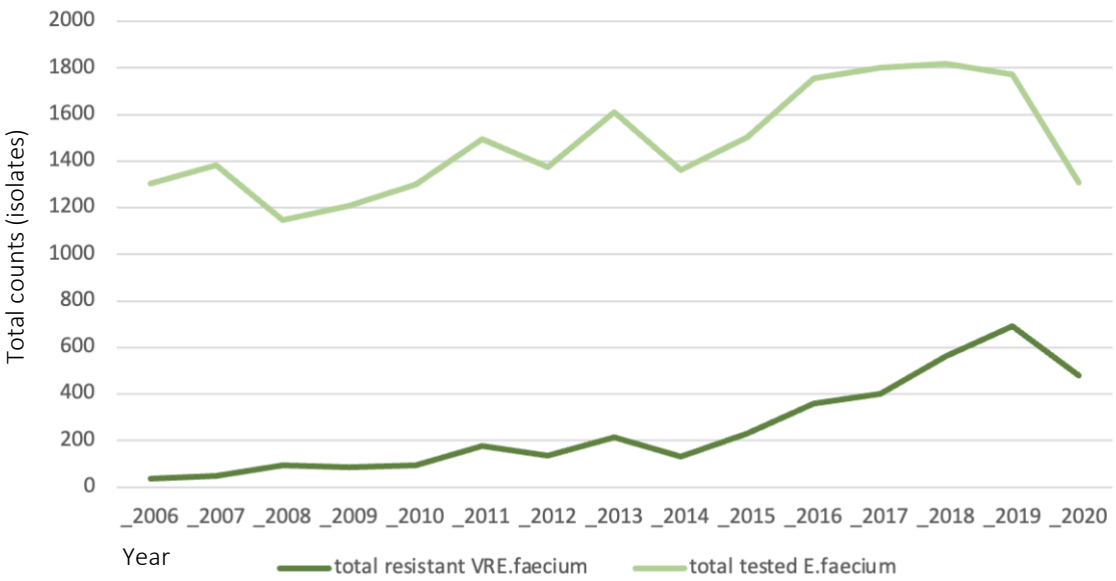


Fig. 5 Yearly total tested E. *faecium* and total resistant VRE. *faecium*.

Compared to that, the total tested E. *faecalis* and total resistant VRE. *faecalis* show a different trend in both variables over the selected time period (see Figure 6). The count of total tested E. *faecalis* was at 1682 isolates in 2006 in which no isolate showed any resistance to vancomycin. After some fluctuations between the year 2008 and 2013, there was the first drop in 2014 with 1209 tested E. *faecalis* isolates from which 8 isolates tested as resistant to vancomycin.

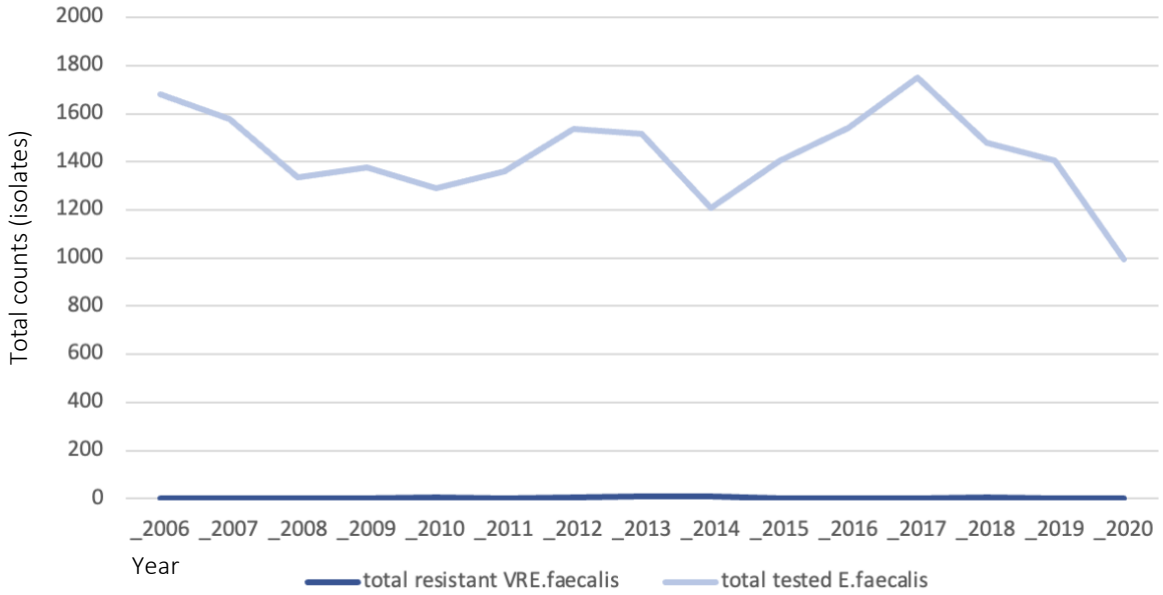


Fig. 6 Yearly total tested E. *faecalis* and total resistant VRE. *faecalis*.

In 2017 was the highest count documented with 1751 total tested isolates, after which the amount dropped to 997 E. *faecalis* isolates in 2020. Although, it is not clearly identifiable in the graph, the highest count of VRE. *faecalis* isolates was in 2013 with 11 resistant cases among 1516 total tested E. *faecalis* isolates.

Continuing with the resistance rates of both pathogens, the differences between VRE. *faecium* and VRE. *faecalis* that are already present in the total counts presented above are also reflected in the resistance rates (see Figure 7).

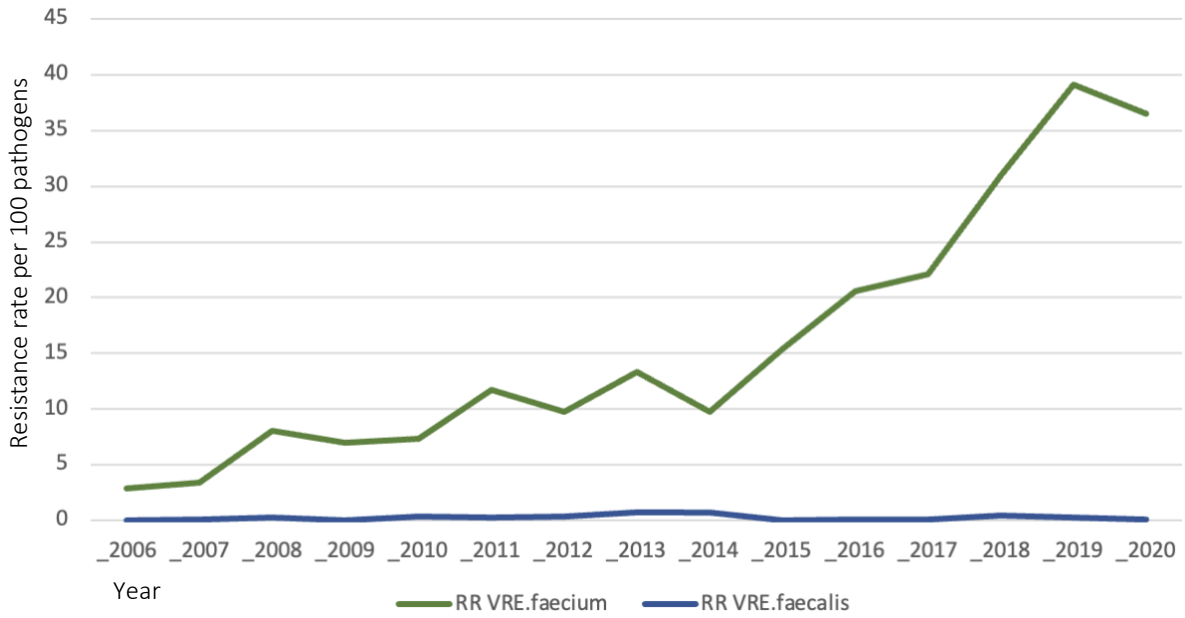


Fig. 7 Yearly resistance rates of VRE. *faecium* and VRE. *faecalis* (per 100 pathogens).

While the resistance rate for VRE. *faecalis* fluctuates between 0 in 2006 and 0.2 in 2019 and 0.1 in 2020, with its highest peaks of 0.7 in 2013 and 2014. The resistance rate of VRE. *faecium* started with a rate of 2.9 in 2006 and continued with increasing undulations between the year 2008 and 2014. Over the next 5 years the resistance rate of VRE. *faecium* has increased from 9.8 in 2014 to 39.1 in 2019. During the last year between 2019 and 2020 the rate decreased again to a resistance rate of 36.5.

For the resistance densities, a similar trend is visible in both variables, including VRE. *faecium* and VRE. *faecalis* per 1000 patient days (see Figure 8).

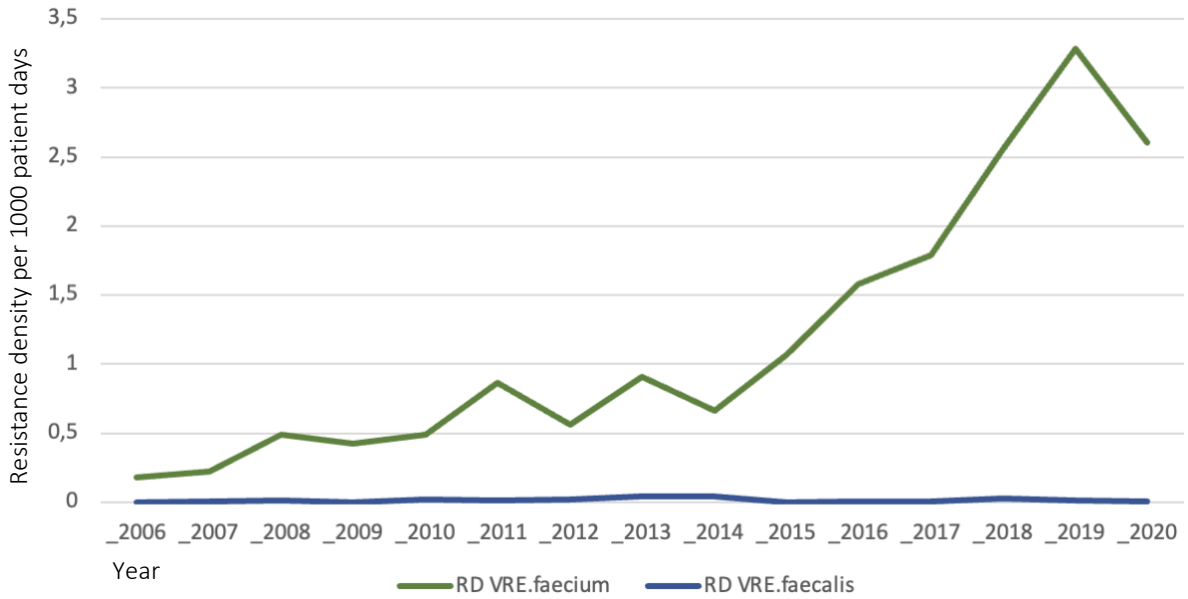


Fig. 8 Yearly resistance density of VRE. *faecium* and VRE. *faecalis* (per 1000 patient days).

The graph of VRE. *faecalis* shifts again from 0 in 2006 to 0.01 in 2020. The peak in VRE. *faecalis* density was documented in 2013 with a value of 0.05 and 0.04 in 2014.
For the density of VRE. *faecium* a rising trend is clearly noticeable over the 15-year period. The first two peaks were reported in 2011 with a density of 0.86 and 0.91 in 2013. Afterwards, the VRE. *faecium* density increased over the next 5 years until it reached a peak of 3.29 in year 2019. A slight drop then appears, as the data decreased to 2.61 in 2020.

Next, the variables of all grouped antibiotics were separated and visualized in three different graphs. Starting with the first graph, the variables g1-g6 including beta-lactamase sensitive penicillin, beta-lactamase resistant penicillin, broad-spectrum penicillin, combination preparation with penicillin and lactamase inhibitors, as well as cephalosporines of the 1st and 2nd generation (see Figure 9).

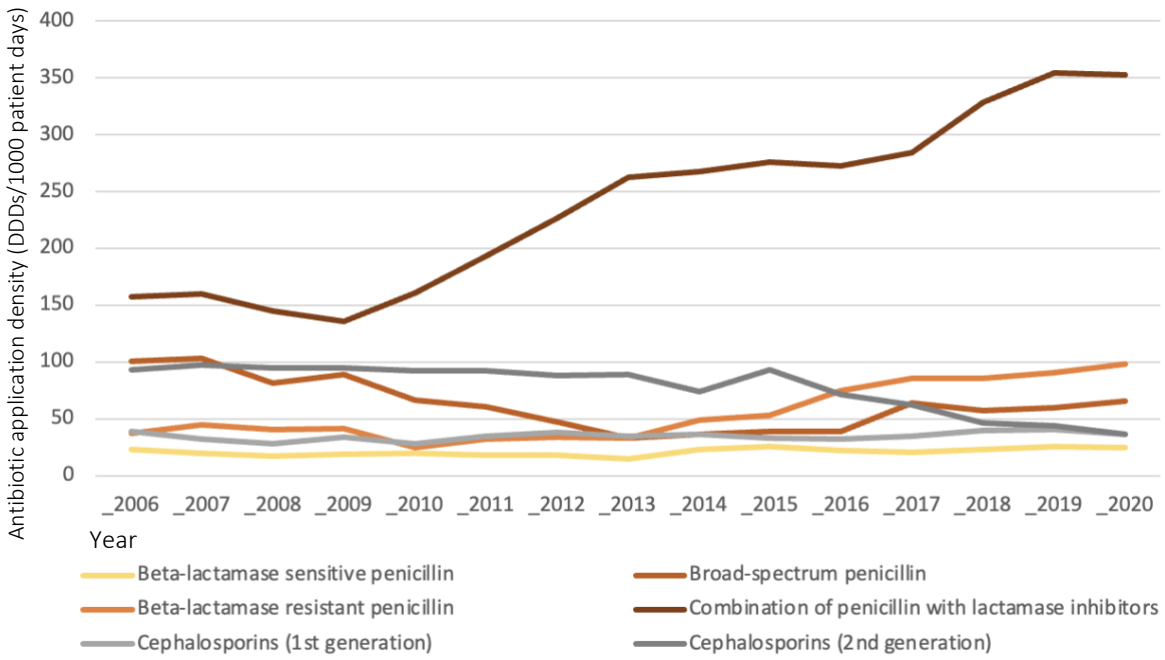


Fig. 9 Yearly antibiotic use densities (DDDs/1000 patient days) from 2006 to 2020 (g1-g6).

As it is clearly visible the combination substance of penicillin and lactamase inhibitor was the most commonly used one, with an increasing trend since 2009 and peak values of 354.3 in 2019 and 353.0 in 2020. The least used substance among the six groups of antibiotics is the standard beta-lactamase sensitive penicillin with a highest application density of 26.4 in year 2015. The groups of beta-lactamase resistant penicillin and broad-spectrum penicillin also show relatively low application densities with seasonal variation before and after 2013. The group of 1st generation cephalosporines indicates a stagnant trend over the whole time period, while the group of 2nd generation cephalosporines have decreased from an application density of 97.9 in 2007 to 36.6 in 2020.

The second graph of the divided antibiotic groups presents the variables g7-g11 including the 3rd and 4th generation of cephalosporins, as well as carbapenems, glycopeptides, monobactams, and fluoroquinolones (see Figure 10). Following up on the cephalosporines of the first graph, the 3rd generation indicates the highest application density among all generations, especially in 2006 with a value of 124, and between 2009 with a value of 122.6 and 2010 with a value of 117.7. The curve then decreases to 75.6 in 2020. By contrast, the 4th generation of cephalosporines is less used on participating ICUs with a peak value of 21.5 in 2020.

Carbapenems show the highest application density among these groups presented. They started with a consumption density of 120 in 2006 and increased to an application density

of 339.9 in 2020. In contrast to that, fluoroquinolones indicate a decreasing trend over time and reached the lowest level of application density in 2019 with a value of 88.9.

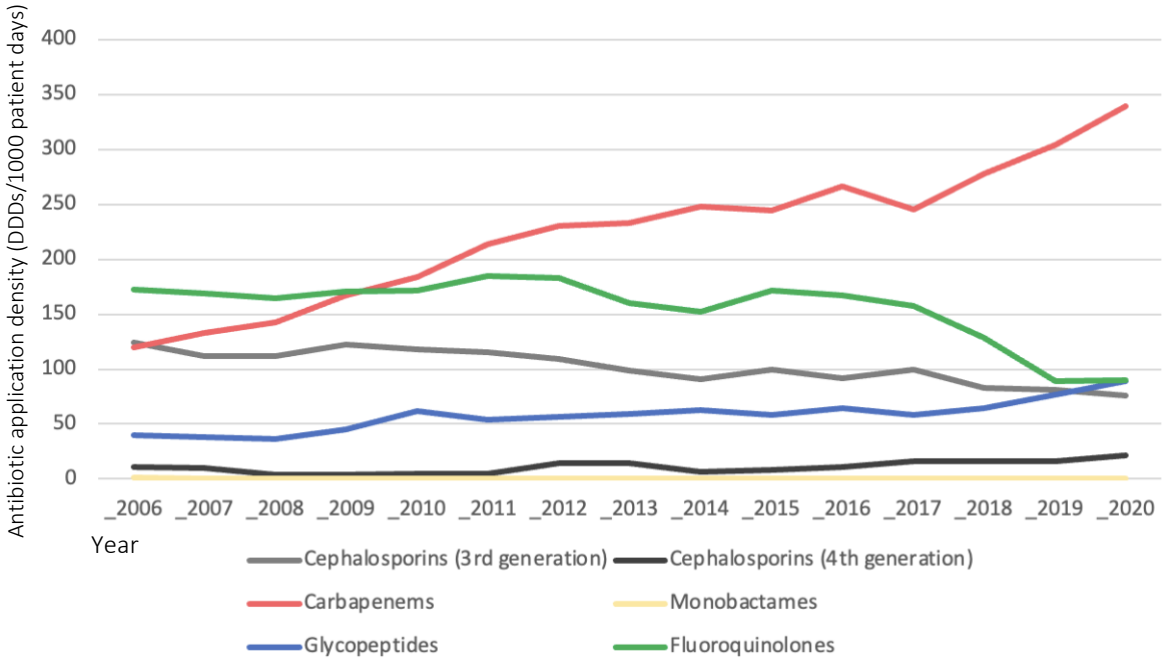


Fig. 10 Yearly antibiotic application use (DDDs/1000 patient days) from 2006 to 2020 (g7-g11).

The curve of monobactams is hardly observable, which reflects the low levels of application densities. The highest point of monobactam consumption was documented in 2006 with a value of 1.2. Afterwards, the data shows a steady application density of roughly 0.5 with imperceptible differences. The last antibiotic group are the glycopeptides, which are analyzed in a separate graph further down.

The third graph with the remaining antibiotic groups includes the variables g12, g14, g16, g18, g21 and g22, which stand for sulfonamides and trimethoprim, tetracyclines, macrolides, aminoglycosides, imidazole derivates and other antibiotic groups that are not otherwise specified (see Figure 11).

The subgroups of sulfonamides, tetracyclines and aminoglycosides show the lowest overall trend in this graph with the highest values in sulfonamide consumption with a peak value of 44.6 in the year 2015. The tetracyclines and aminoglycosides are similar in their trend, with the difference of rising application densities for aminoglycosides and decreasing densities for tetracyclines since 2017.

Continuing with the imidazole derivates a downward trend is visible from 2006 onward and the application density has dropped from 66.6 in 2006 to 24.6 in 2020. Whereas the group

of macrolides indicates higher consumption densities in general, starting with a value of 74.7 in 2006, up to with a consumption density of 113.8 in 2015, followed by a decreasing trend to values of 82.9 in 2019 and 92.5 in 2020.

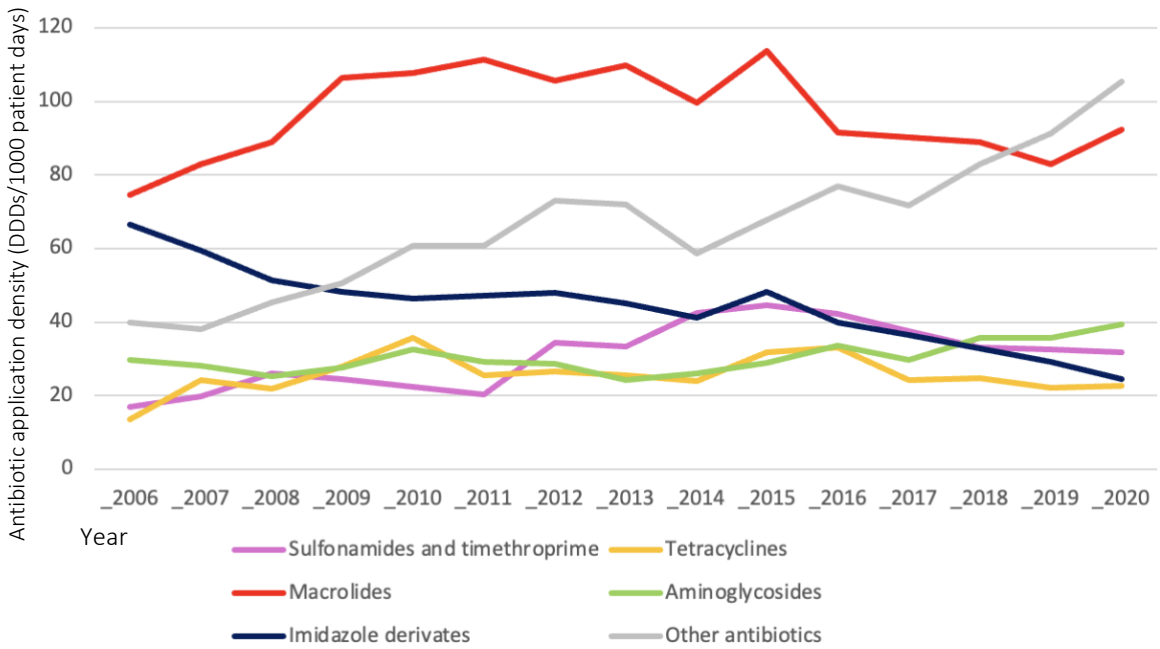


Fig. 11 Yearly antibiotic use densities (DDDs/1000 patient days) from 2006 to 2020 (g12, g14, g16, g18, g21-g22).

The last group, that gathers all remaining antibiotic substances, such as fosfomycin, linezolid or daptomycin, indicates an increasing trend over the whole time period of 15 years. The application density was the lowest in 2006 with a value of 39.8 and fluctuated with a constantly rising trend over time. The highest application density was documented at 105.4 in 2020.

In context of the vancomycin resistance of enterococci, the pooled group of glycopeptides was analyzed separately and visualized in an additional graph (see Figure 12). Extensive values of each year and all glycopeptide related supplements can be found in Appendix IV and are analyzed more accurately in chapter 5.3.
As seen above, the application density of glycopeptides ranged generally from 40.3 in 2006 up to 89.3 in 2020. The lowest application density with a peak value of 0.4 in 2006 is visible for oral applied vancomycin. A similar trend is noticeable for the parenteral application of teicoplanin, which shows low consumption densities between the years 2006 and 2017, but have since then increased from 1.6 to 22.5 in 2019 and decreased again to a value of 18.8 in 2020.

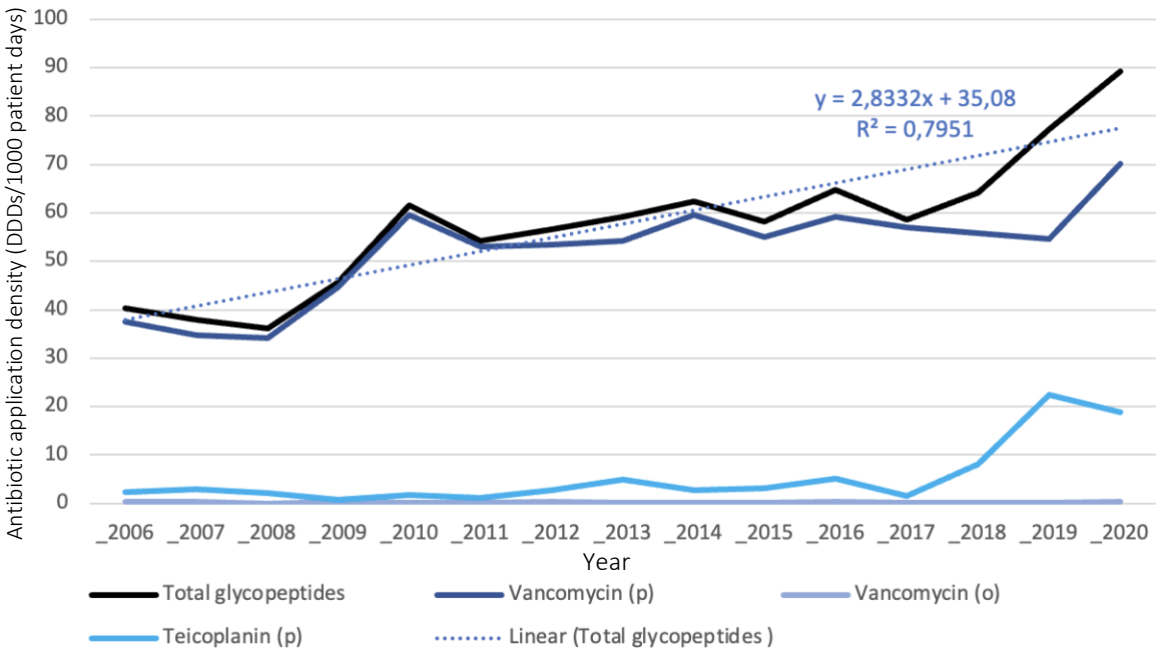


Fig. 12 Yearly antibiotic use densities (DDDs/1000 patient days) of different glycopeptides from 2006 to 2020.

Parenteral vancomycin application densities show a similar high trend to total glycopeptide consumption. The overall trend increased over the 15 years with a first peak in 2010 with a consumption density of 59.7 and increased again in 2019 to a value of 70.2 in 2020. The added glycopeptide curve shows an analogous trend with values of 40.3 in 2006 and 61.5 in 2010. Afterwards, a slight increase is visible with two more peaks in 2014 and 2016. Finally, the application density has again risen from 58.6 in 2017 to 89.3 in 2020.

To test for an assumed linear trend in the increasing antibiotic use density of glycopeptides a linear trend line was calculated and superimposed. The resulting trend line indicates an intersection point on the y-axis at 35.08 and an annual increase in application density of 2.83. For the goodness of fit the proportion of variances of the dependent variable was calculated and resulted in $R^2 = 0.79$. Due to inaccuracy and missing p-values of the trend analysis in Microsoft Excel the remaining variables were analyzed via SPSS and SAS.

5.2 Linear regression analyses

The results of the linear regression analyses are presented below (see Table 8). The independent variable is given by the time period of 15 years, from which one year represents one unit of change in the regression model.

Dependent variable	R	R^2	B	SE	p*
Total resistant VRE. *faecium*	0.90	0.81	41.0	5.42	**<0.001**
Total resistant VRE. *faecalis*	0.15	0.02	0.11	0.20	0.59
Resistance rate VRE. *faecium*	0.92	0.85	2.40	0.27	**<0.001**
Resistance rate VRE. *faecalis*	0.15	0.02	0.00	0.01	0.58
Resistance density VRE. *faecium*	0.90	0.81	0.19	0.02	**<0.001**
Resistance density VRE. *faecalis*	0.14	0.02	0.00	0.00	0.614

*Significance level of 5%; p=0.05

Table 8: Results of linear regression analysis (total resistant, RR, RD of VRE).

The results indicate that there is a linear trend between time and the amount of total resistant E. *faecium* isolates ($F(1,13) = 57.13$, $p < 0.001$; $R^2 = 0.81$; $B = 41.0$; $t(13) = 7.5$, $p < 0.001$), the resistance rate of VRE. *faecium* ($F(1,13) = 75.13$, $p < 0.001$; $R^2 = 0.85$; $B = 2.4$; $t(13) = 8.6$, $p < 0.001$), and the resistance density in VRE. *faecium* ($F(1,13) = 58.35$, $p < 0.001$; $R^2 = 0.81$; $B = 0.19$; $t(13) = 7.6$, $p < 0.001$). For the variables total resistant VRE. *faecalis*, resistance rate VRE. *faecalis* and resistance density VRE. *faecalis,* time did not show any significant influence.

For the antibiotic application density and time (see Table 9), a positive linear trend is displayed in the groups of beta-lactamase sensitive penicillin ($F(1,13) = 6.1$, $p = 0.02$; $R^2 = 0.32$; $B = 0.42$; $t(13) = 2.4$, $p = 0.02$), beta-lactamase resistant penicillin ($F(1,13) = 32.3$, $p < 0.001$; $R^2 = 0.84$; $B = 4.68$; $t(13) = 5.6$, $p < 0.001$), combination substance penicillin and lactamase inhibitor ($F(1,13) = 168.9$, $p < 0.001$; $R^2 = 0.92$; $B = 16.3$; $t(13) = 12.9$, $p < 0.001$), cephalosporines of the 4^{th} generation ($F(1,13) = 11.6$, $p = 0.005$; $R^2 = 0.47$; $B = 0.85$; $t(13) = 3.4$, $p = 0.005$), carbapenems ($F(1,13) = 234.7$, $p < 0.001$; $R^2 = 0.94$; $B = 13.85$, $t(13) = 15.3$, $p < 0.001$), glycopeptides ($F(1,13) = 50.4$, $p < 0.001$; $R^2 = 0.79$; $B = 2.83$;

t(13) = 7.1, p < 0.001), sulfonamides (F(1,13) = 12.3, p = 0.004; R^2 = 0.48, B = 1.37, t(13) = 3.5, p = 0.004), aminoglycosides (F(1,13) = 9.63, p = 0.008; R^2 = 0.42, B = 0.61; t(13) = 3.1, p = 0.008), and in the group of other antibiotics (F(1,13) = 88.1, p < 0.001; R^2 = 0.87; B = 3.92; t(13) = 9.38, p < 0.001).

Dependent variable	**R**	**R^2**	**B**	**SE**	**p***
Beta-lact. sensitive penicillin (J01CE)	0.56	0.32	0.42	0.17	**0.02**
Broadspect. penicillin (J01CA)	0.61	0.37	-3.07	1.10	**0.01**
Beta-lact. resistant penicillin (J01CF)	0.84	0.73	4.68	0.82	**<0.001**
Penicillin + lact. inhibitor (J01CR)	0.96	0.92	16.3	1.26	**<0.001**
Cephalosporines 1st gen. (J01DB)	0.43	0.19	0.36	0.20	0.10
Cephalosporines 2nd gen. (J01DC)	0.88	0.78	-4.18	0.61	**<0.001**
Cephalosporines 3rd gen. (J01DD)	0.92	0.84	-3.14	0.36	**<0.001**
Cephalosporines 4th gen. (J01DE)	0.68	0.47	0.85	0.25	**0.005**
Carbapenems (J01DH)	0.97	0.94	13.85	0.90	**<0.001**
Monobactams (J01DF)	0.60	0.36	-0.03	0.01	**0.01**
Glycopeptides (J01XA)	0.89	0.79	2.83	0.39	**<0.001**
Fluoroquinolones (J01MA)	0.72	0.52	-4.83	1.28	**0.002**
Sulfonamides + trimethoprim (J01E)	0.69	0.48	1.37	0.39	**0.004**
Tetracyclines (J01AA)	0.16	0.02	0.19	0.32	0.56
Macrolides (J01FA)	0.01	0.00	0.03	0.75	0.967
Aminoglycosides (J01G)	0.65	0.42	0.61	0.20	**0.008**
Imidazolderivates (J01XD)	0.93	0.87	-2.29	0.24	**<0.001**
Other antibiotics (J01XX)	0.93	0.87	3.92	0.41	**<0.001**

*significance level of 5%; p=0.05

Table 9: Results of linear regression analysis (antibiotic sub-groups).

In the groups of broad-spectrum penicillin ($F(1,13) = 7.74$, $p = 0.01$; $R2 = 0.37$; $B = -3.07$; $t(13) = -2.78$, $p = 0.016$), cephalosporines 2nd ($F(1,13) = 45.9$, $p < 0.001$; $R2 = 0.78$; $B = -4.18$; $t(13) = -6.78$, $p < 0.001$) and 3rd generation ($F(1,13) = 72.5$, $p < 0.001$; $R2 = 0.84$; $B = -3.14$; $t(13) = -8.51$, $p < 0.001$), as well as in monobactams ($F(1,13) = 7.5$, $p = 0.017$; $R2 = 0.36$; $B = -0.03$; $t(13) = -2.74$, $p = 0.017$), fluroquinolones ($F(1,13) = 14.2$, $p = 0.002$; $R2 = 0.52$; $B = -4.83$; $t(13) = -3.77$, $p = 0.002$) and in imidazolderivates ($F(1,13) = 91.6$, $p < 0.001$; $R2 = 0.87$; $B = -2.29$; $t(13) = -9.57$, $p < 0.001$) and time significance is given for a negative linear trend.

Among the remaining antibiotic groups, including 1st generation cephalosporines, tetracyclines and macrolides, proceeding time had no significance influence.

5.3 Generalized linear model

In the following chapter, results of the linear model are presented for the univariate and multivariate analysis. The univariate analysis includes detailed results on both characteristics, including resistance rates and resistance densities. However, parallel analyses conducted in the background in collaboration with the institute have shown that correlating antibiotic substance groups differ in their influence among the pathogen resistance rate and the density. In these background analyses additional substances, that were not included in the context of this thesis (e.g., tuberculostatic drugs), showed a significant influence on resistance rates but not on incidence densities. Additionally, the variables resistance density and resistance rate differ in their specificity as the density is calculated with counts and the rate with ratios. Consequently, the calculation of the resistance rate depends on available resistance data in all months and does not work with blank values. Thus, additional results of the resistance rates and excluded antibiotic consumption densities can be found in the Appendix VII but will not further be included in the multivariate results part.

5.3.1 Univariate analysis

Continuing with the univariate trend analysis of the pathogen incidence densities (ID), the significance for an increasing linear trend is shown for VRE. *faecium*, but not for VRE. *faecalis* (see Table 10).

Year	ID VRE. *faecium*		ID VRE. *faecalis*	
	IRR (95%CI)	p*	IRR (95%CI)	p*
Model with time as linear trend				
lin. trend	**1.015** (1.013-1.018)	**< .0001**	1.0027 (0.99-1.00)	0.274
Model with year as categorial parameter				
2006	1 = Reference		Not estimable	
2007	1.42 (0.64-3.14)	0.376	1.09E+10	-
2008	2.48 (1.13-5.41)	**0.022**	3.07E+10	-
2009	2.84 (1.40-5.75)	**0.003**	5.29E-10	-
2010	2.80 (1.35-5.8)	**0.005**	4.75E+10	-
2011	4.80 (2.47-9.32)	**<.0001**	3.51E+10	-
2012	3.39 (1.68-6.87)	**0.000**	5.23E+10	-
2013	5.38 (2.64-10.9)	**<.0001**	1.07E+10	-
2014	4.06 (2.09-7.87)	**<.0001**	8.08E+10	-
2015	6.37 (3.21-12.6)	**<.0001**	4.85E-10	-
2016	9.55 (5.08-17.9)	**<.0001**	8.86E+09	-
2017	11.1 (5.71-27.9)	**<.0001**	9.42E+09	-
2018	14.3 (7.32-27.9)	**<.0001**	6.31E+10	-
2019	19.8 (9.73-40.3)	**<.0001**	2.93E+10	-
2020	15.3 (7.58-31.0)	**<.0001**	1.19E+10	-

*Significance level of 5%; p=0.05

Table 10: Trend analysis of incidence densities of VRE. *faecium* and VRE. *faecalis*; ID = incidence density, IRR = incidence rate ratio, CI = confidence interval.

The VRE. f*aecium* incidence density shows a generally rising trend of 1.5% per year. Individual coefficients of VRE. *faecium* densities also show that the incidence density has increased by a factor of 15 since 2006. Starting with a ratio of 1.015 (1.013-1.018 95%CI)

in 2006, the rate has ranked up to 15.3 (7.58-31.0 95%CI) in 2020. The increasing trend is statistically significant in all years, except the year of 2007 where the trend of 1.42 (0.64-3.14 95%CI) showed no significance p = 0.376.

As for the incidence density of VRE. *faecalis* no individual quantity per year could be calculated due to blank values in 2006, 2007, and 2015-2017. Consequently, this model is not able to estimate valid counts and resulting values would be adulterated. However, a general trend could be tested and resulted in a ratio of 1.00 (0.99-1.00 95%CI); p = 0.274. Thus, no significant increase or decrease in the incidence density of VRE. *faecalis* could be determined for the study period of 15 years.

To answer the research question regarding the complexity in the load of sensitive and resistant pathogens in both species, the trend was parallelly analyzed for vancomycin-susceptible E. *faecium* and E. *faecalis* (VSE) in the background (see "VSEKM" and "VSEKS" in Appendix VI) Comparing both pathogen loads, a difference is noticeable between VRE. *faecium* and the remaining species. While the rates of vancomycin susceptible E. *faecium* indicate a slight regressive trend, vancomycin-susceptible E. *faecalis* results display a constant trend. However, in both additional variables, no significant trend could be identified.

For the resistance rates of VRE. *faecium* and VRE. *faecalis* the GLM calculated similar trends to the results of the incidence densities of both pathogen species (see Table 11). The trend of VRE. *faecium* rate significantly (p < 0.0001) increased from a ratio of 1.017 (1.015-1.019 95%CI) in 2006 to 16.8 (8.26-34.27 95%CI) in 2020, which mirrors a rising trend of 1.7% per year. Comparing each year with one another, a significant linear trend could be identified in 2006, and the period of 2009-2020. In 2007 (p = 0.812) and 2008 (p = 0.968), the trend showed no significant influence on the resistance rate.

Year	**RR VRE. *faecium***		**RR VRE. *faecalis***	
	IRR (95%CI)	p*	IRR (95%CI)	p*
Model with time as linear trend				
lin. trend	1.017 (1.015-1.019)	**<.0001**	1.003 (0.997-1.008)	0.233
Model with year as categorial parameter				
2006	1 = Reference		Not estimable	
2007	1.10 (0.47-2.55)	0.812	1.13E+10	-

2008	2.11 (0.94-4.76)	0.068	3.91E+10	-
2009	2.51 (1.21-5.2)	**0.013**	1.08E+10	-
2010	2.26 (1.08-4.72)	**0.028**	5.49E+10	-
2011	3.77 (1.88-7.53)	**.0002**	3.83E+10	-
2012	3.31 (1.63-6.70)	**.0009**	5.54E+10	-
2013	4.48 (2.40-9.74)	**<.0001**	1.22E+10	-
2014	3.63 (1.88-7.53)	**0.0001**	1.11E+10	-
2015	5.46 (2.71-10.9)	**<.0001**	1.19E+10	-
2016	7.76 (4.12-14.64)	**<.0001**	1.08E+10	-
2017	8.96 (4.72-17.0)	**<.0001**	9.54E+10	-
2018	12.85 (6.86-24.06)	**<.0001**	7.93E+10	-
2019	20.01 (10.24-39.07)	**<.0001**	3.57E+10	-
2020	16.8 (8.26-34.27)	**<.0001**	1.68E+10	-

*Significance level of 5%; p=0.05

Table 11: Linear trend analysis of resistance rates of VRE. *faecium* and VRE. *faecalis*; ID = incidence density, IRR = incidence rate ratio, CI = confidence interval.

For the trend analysis of the resistance rates in VRE. *faecalis,* there was an observational limitation due to previously identified blank values in 2006, 2007, and 2015-2017. However, a general trend analysis resulted in a value of 1.003 (0.997-1.008 95%CI) with a non-significant (p = 0.233) trend, corresponding to a constant VRE. *faecalis* density over the period of 15 years. A summary overview of the trend can be found in Appendix V.

To reinforce the significant observation in the distribution of VRE. *faecium,* the additional consideration of the included hospital wards results in a trend that is observed in all units, although the variance of resistance rates differs between individual wards (see Figure 13). As it is visible, the pooled mean value of all ICUs (bold red line) slightly rises from 2006 to 2014 and shows another strong increase between 2015 and 2019. However, the variance (green marked area, interquartile range, 25th and 75th percentile) and the median (dotted green line) show differences, as e.g., in 2006 less than 25% of the ICUs have recorded a

single resistant E. *faecium*, while between 2013 and 2014 some units had a resistance rate of 26 per 100 pathogen and others had a resistance rate of 0. In comparison, the resistance rate was at 20 in over 75% out of all ICUs in 2020. Thus, the increasing trend not only affects individual wards but all participating ICUs in Germany.

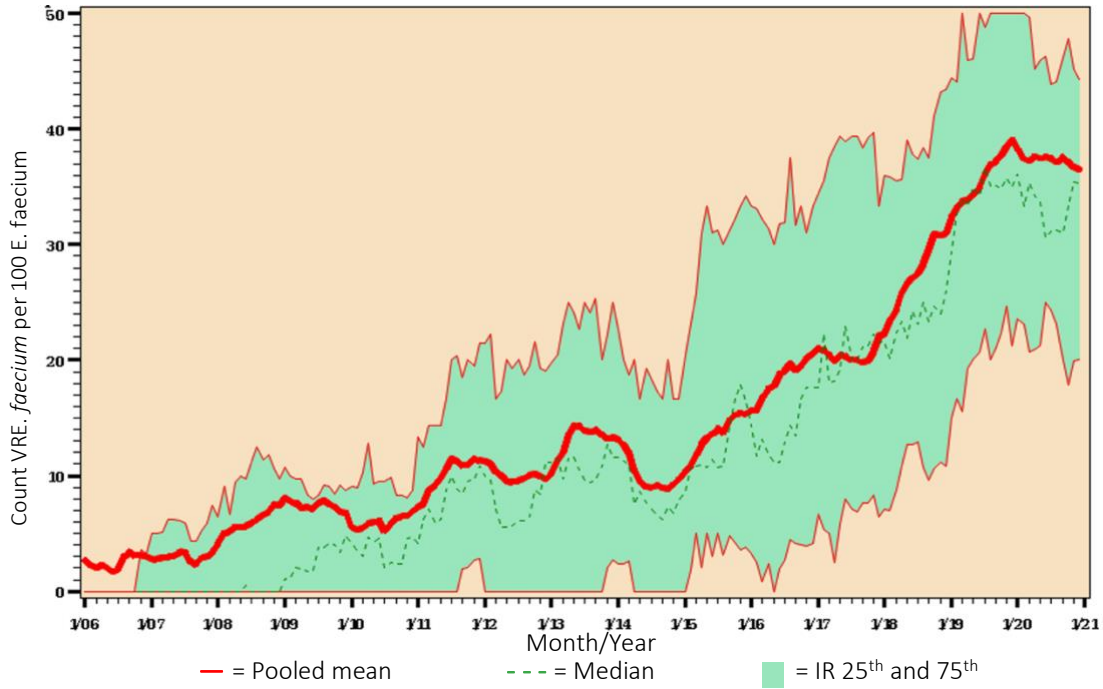


Fig. 13 Trend resistance rate of VRE. *faecium* in SARI ICUs (n=79) from 2006 to 2020.

The subsequent analysis intended to examine possible associations between VRE. *faecium* and VRE. *faecalis* and various antimicrobial substance groups (see Table 12). The GLM calculated the antibiotic consumption density with a reference value of ref = 1, what results in values above 1.0 indicate a positive association while values below 1.0 indicate a negative association between pathogen densities and rates and antibiotic substances.
Overall, a significant positive association was found for all antibiotic groups in incidence densities of VRE. *faecium* (IRR 1.003 (1.002-1.004 95%CI), p < .0001), and VRE. *faecalis* (IRR 1.003 (1.00-1.007 95%CI), p = 0.02), as well as in VSE. *faecium* (IRR 1.0008 (1.00-1.001 95%CI), p = 0.001). The results for VSE. *faecalis* and resistance rates in VRE. *faecium* showed no significant association with all summarized antibiotic substances. Between resistance rates of VRE. *faecalis* and all substance groups (IRR 0.917 (0.87-0.96 95%CI), p = 0.0012), a significant negative association was found. However, these general results differ among their individual sub-groups of different antibiotic substances, as some substances have a negative influence on pathogen incidence densities and rates and other substances have protecting effects.

Antibiotic group	ID VRE. *faecium*		ID VSE. faecium		ID VRE. *faecalis*		ID VSE. *faecalis*		RR VRE. *faecium*		RR VRE. *faecalis*	
	IRR (95%CI)	p*	IRR (95%CI)	p*	IRR (95%CI)	p*	IRR (95%CI)	p*	IRR (95%CI)	p*	IRR (95%CI)	p*
All groups	1.003 (1.002-1.004)	**<.0001**	1.00 (1.00-1.001)	**0.001**	1.003 (1.00-1.007)	**0.02**	1.003 (0.99-1.00)	0.296	1.003 (0.99-1.01)	0.386	0.917 (0.87-0.96)	**0.0012**
Beta-lact. sensitive penicillin (J01CE)	1.004 (0.99-1.01)	0.288	0.999 (0.995-1.00)	0.795	0.882 (0.81-0.95)	**0.0031**	0.997 (0.99-1.00)	0.063	0.975 (0.93-1.01)	0.258	0.875 (0.61-1.25)	0.46
Broadspect. penicillin (J01CA)	0.999 (0.99-1.005)	0.77	1.001 (0.998-1.00)	0.344	0.988 (0.92-1.05)	0.736	1.001 (1.00-1.005)	**0.0006**	0.984 (0.94-1.02)	0.484	0.832 (0.7-0.98)	**0.0281**
Beta-lact. resistant penicillin (J01CF)	1.004 (0.999-1.01)	0.083	0.997 (0.993-1.00)	0.123	0.996 (0.954-1.04)	0.875	0.997 (0.99-1.00)	0.137	0.000	-	0.447 (0.19-1.03)	0.06
Penicillin + lact. inhibitor (J01CR)	1.005 (1.001-1.008)	**0.002**	1.00 (0.99-1.00)	0.908	0.964 (0.91-1.01)	0.191	1.009 (0.99-1.00)	0.562	0.992 (0.97-1.01)	0.531	1.002 (0.96-1.04)	0.891
Cephalosporines 1st gen. (J01DB)	0.998 (0.986-1.01)	0.78	1.002 (0.995-1.01)	0.506	1.00 (0.94-1.063)	0.983	1.005 (0.99-1.01)	0.069	0.924 (0.72-1.18)	0.528	1.304 (0.78-2.16)	0.30
Cephalosporines 2nd gen. (J01DC)	0.989 (0.98-0.998)	**0.016**	0.997 (0.993-1.00)	0.306	1.014 (1.00-1.02)	**0.0459**	1.004 (1.00-1.007)	**0.0324**	0.981 (0.97-0.99)	**0.0011**	1.008 (0.98-1.03)	0.518
Cephalosporines 3rd gen. (J01DD)	0.997 (0.993-1.002)	0.33	1.00 (0.998-1.00)	0.74	0.024	-	1.005 (0.99-1.00)	0.612	0.989 (0.97-1.00)	**0.0497**	0.975 (0.88-1.07)	0.631
Cephalosporines 4th gen. (J01DE)	1.01 (0.996-1.02)	0.14	0.995 (0.989-1.00)	0.236	1.013 (0.95-1.07)	0.64	0.998 (0.99-1.00)	0.751	1.01 (1.00-1.01)	**<.0001**	1.015 (0.99-1-03)	0.061
Carbapenems (J01DH)	1.013 (1.009-1.017)	**<.0001**	1.005 (1.00-1.007)	**<.0001**	1.022 (1.00-1.03)	**0.0092**	0.999 (0.99-1.00)	0.949	1.014 (1.01-1.018)	**<.0001**	1.00 (0.97-1.02)	0.875
Monobactams (J01DF)	0.94 (0.855-1.03)	0.202	0.985 (0.93-1.04)	0.624	0.301	-	0.981 (0.96-0.99)	**0.0151**	0.958 (0.78-1.16)	0.674	0.97 (0.86-1.08)	0.61

Antibiotic group	ID VRE. *faecium*		ID VSE. faecium		ID VRE. *faecalis*		ID VSE. *faecalis*		RR VRE. *faecium*		RR VRE. *faecalis*	
	IRR (95%CI)	p*	IRR (95%CI)	p*	IRR (95%CI)	p*	IRR (95%CI)	p*	IRR (95%CI)	p*	IRR (95%CI)	p*
Glycopeptides (J01XA)	1.02 (1.014-1.027)	**<.0001**	1.001 (0.997-1.00)	0.461	1.013 (0.98-1.04)	0.418	0.993 (0.98-0.99)	**0.0061**	0.951 (0.77-1.17)	0.064	0.04 (0.01-0.09)	**<.0001**
Vancomycin (p) (J01XA01)	1.023 (1.01-1.03)	**<.0001**	1.00 (0.99-1.00)	0.46	-	-	0.99 (0.98-0.99)	**0.0243**	1.011 (1.00-1.02)	**0.03**	1.04 (1.00-1.08)	0.05
Vancomycin (o) (J01XA01)	0.96 (0.77-1.19)	**0.74**	0.96 (0.88-1.04)	0.75	-	-	1.02 (0.94-1.11)	0.5526	0.99 (0.98-1.00)	0.05	1.00 (0.98-1.02)	0.56
Teicoplanin (p) (J01XA02)	1.01 (1.00-1.02)	**0.03**	1.00 (1.00-1.008)	0.05	-	-	0.98 (0.98-0.99)	**0.03**	0.99 (0.99-1.00)	0.48	1.01 (0.98-1.04)	0.39
Fluoroquinolones (J01MA)	0.996 (0.991-1.00)	0.088	1.00 (0.99-1.002)	0.326	1.009 (0.99-1.02)	0.334	1.00 (0.99-1.00)	0.542	1.001 (0.98-1.01)	0.812	0.998 (0.94-1.05)	0.958
Sulfonamides + trimethoprim (J01E)	1.003 (0.997-1.012)	0.264	0.998 (0.995-1.00)	0.358	0.926 (0.83-1.02)	0.129	0.995 (0.99-0.999)	**0.02**	1.00 (1.00-1.00)	-	1.00 (1.00-1.00)	**-**
Tetracyclines (J01AA)	1.01 (1.006-1.014)	**<.0001**	1.003 (1.00-1.006)	**0.0018**	0.999 (0.96-1.03)	0.979	1.001 (0.99-1.00)	0.915	1.007 (0.99-1.01)	0.169	1.00 (0.93-1.07)	0.99
Macrolides (J01FA)	1.002 (0.997-1.007)	0.302	1.00 (0.99-1.003)	0.753	1.002 (0.95-1.04)	0.918	0.999 (0.99-1.00)	0.831	1.036 (1.00-1.06)	**0.01**	0.572 (0.47-0.68)	**<.0001**
Aminoglycosides (J01G)	1.014 (1.008-1.021)	**<.0001**	0.999 (0.994-1.00)	0.831	1.003 (0.97-1.03)	0.835	1.00 (0.99-1.00)	0.816	1.032 (1.01-1.04)	**0.0002**	1.00 (0.91-1.09)	0.99
Imidazolderivates (J01XD)	1.01 (0.997-1.024)	0.109	1.014 (1.00-1.02)	**0.0001**	1.042 (0.97-1.10)	0.187	1.01 (1.01-1.02)	0.061	0.9462 (0.89-1.00)	0.065	1.083 (0.88-1.32)	0.429
Other antibiotics (J01XX)	1.021 (1.013-1.029)	**<.0001**	1.01 (1.00-1.01)	**<.0001**	1.006 (0.96-1.05)	0.787	1.002 (0.99-1.00)	0.204	1.039 (0.9-1.19)	0.585	0.422 (0.03-4.47)	0.474

*bold if p<0.05

Table 12: Univariate trend analysis for the outcome incidence densities of VSE/VRE. *faecium* and VSE/VRE. *faecalis* and resistance rates VRE. *faecium* and VRE. *faecalis* with the antibiotic use densities; ID = incidence density, IRR = incidence rate ratio, CI = confidence interval.

In VRE. *faecium,* an increase in incidence density is significantly associated with the consumption of penicillin with lactamase inhibitors (IRR 1.005 (1.001-1.008 95%CI), p = 0.002), carbapenems (IRR 1.013 (1.009-1.017 95%CI), p < .0001), glycopeptides (IRR 1.02 (1.014-1.027 95%CI), p < .0001), tetracyclines (IRR 1.01 (1.006-1.014 95%CI), p < .0001), and aminoglycosides (IRR 1.014 (1.008-1.021), p < .0001).

By contrast, the consumption of 2nd generation cephalosporines (IRR 0.989 (0.98-0.998 95%CI), p = 0.016) showed a negative association, suggesting that a higher application density of 2nd generation cephalosporines is associated with a lower incidence density of VRE. *faecium.*

As for the VSE. *faecium,* isolated antibiotic substances showed significant associations with the pathogen species, although sensitive enterococci should not be increasing in respond to antibiotic treatments. However, in the calculated model outlying enterococci are selected through the higher application densities in carbapenems (IRR 1.005 (1.002-1.007 95%CI), p < .0001), tetracyclines (IRR 1.003 (1.001-1.006 95%CI), p = 0.001) and imidazolderivates (IRR 1.014 (1.007-1.022 95%CI), p = 0.0001).

For the analysis of VRE. *faecalis* and antibiotic use densities, the same issue previously mentioned occurred during the model calculation. Due to insufficient pathogen surveillance and resulting blank values, an association between VRE. *faecalis* densities and antibiotic application significant results are difficult to determine. However, the GLM calculated a significant negative association between VRE. *faecalis* and beta-lactamase sensitive penicillin (IRR 0.981 (0.96-0.99 95%CI), p = 0.01). On the contrary the positive association between the pathogen species and carbapenems (IRR 1.02 (0.95-1.04 95%CI), p = 0.009) indicates a possible selection pressure.

Similar to VSE. *faecium*, VSE. *faecalis* should theoretically not respond to increased antibiotic consumption with increasing pathogen densities. Nonetheless, the results suggest a selective pressure in broad-spectrum penicillin (IRR 1.001 (1.00-1.005 95%CI), p = 0.0006) and 2nd generation cephalosporines (IRR 1.004 (1.00-1.007 95%CI), p = 0.032).

Despite that, a negative association is found in VSE. *faecalis* that are treated with monobactams (IRR 0.98 (0.96-0.99 95%CI), p = 0.01), glycopeptides (IRR 0.993 (0.98-0.99 95%CI), p = 0.006), and sulfonamides plus trimethoprim (IRR 0.99 (0.990-0.999 95%CI), p = 0.02) which equates an appropriate antimicrobial therapy.

Further calculations of the pathogens' resistance rates reflect corresponding results, especially in VRE. *faecium* as the 2nd generation cephalosporines (IRR 0.981 (0.97-0.99 95%CI), p = 0.001) and 3rd generation cephalosporines (IRR 0.989 (0.97-1.00 95%CI), p = 0.04) prevent resistance rates from increasing. According to this model, the resistance rate of VRE. *faecalis* also seems to be protected by the application of broad-spectrum penicillin

(IRR 0.832 (0.7-0.98 95%CI), p = 0.0281), glycopeptides (IRR 0.04 (0.01-0.09 95%CI), p < .0001), and macrolides (IRR 0.572 (0.47-0.68 95%CI), yet these results can be neglected due to invalid values as previously demonstrated and rarely detectable pathogens.

Due to the targeted vancomycin resistance in enterococci, an exemplary separated analysis of glycopeptides (see blue labeled groups in Table 12) shows a significant association between rising VRE. *faecium* incidence densities and high consumption densities in parenteral applied vancomycin (IRR 1.023 (1.01-1.03 95%CI), p < .0001) and teicoplanin (IRR 1.01 (1.00-1.02 95%CI), p = 0.03). The significance is also manifest for an association of the resistance rate of VRE. *faecium* and parenteral applied vancomycin (IRR 1.01 (1.00-1.02 95%CI), p = 0.03). Additionally, parenteral vancomycin application is significant (IRR 1.01 (1.00-1.02 95%CI), p = 0.03) when associated with an increased resistance rate in VRE. *faecium,* although no significant association is shown in glycopeptides in general.

5.3.2 Multivariate analysis

The following multivariate analysis intended to examine the trend of the incidence density and the resistance rate of VRE. *faecium* and VRE. *faecalis* and correlating antibiotic substances adjusted by the different confounders, including time, type of ICU, type of hospital, and, additionally, the lag of antibiotic use (see Table 13). A summarized overview of the pooled antibiotic groups and related trends can additionally be found in Appendix VI. Overall, the parsimonious model for the incidence density analysis shows significant results in VRE. *faecium* for the linear time trend (IRR 1.015 (1.012-1.017 95%CI), p < .0001), carbapenems (IRR 1.009 (1.006-1.013 95%CI), p < .0001), and glycopeptides (IRR 1.009 (1.002-1.015 95%CI), p = 0.009). After adjusting the model with above mentioned confounders, the incidence density of VRE. *faecium* still shows an increasing linear trend of 1.5% per month (IRR 1.015 (1.012-1.017 95%CI), p < .0001) and a positive correlation in carbapenems (IRR 1.009 (1.005-1.012 95%CI), < .0001) and glycopeptides (IRR 1.007 (1-1.013 95%CI), p = 0.04) with no influence of ICU type or hospital type.
For the second sensitivity analysis, the additional antibiotic consumption of the month before was included and results in a monthly increasing linear trend of 1.4% (IRR 1.014 (1.012-1.016 95%CI), p < .0001), as well as significant correlations with the consumption density of glycopeptides in the current month (IRR 1.007 (1.001-1.013 95%CI), p = 0.021) and, for carbapenems, not only in the current month (IRR 1.008 (1.005-1.012), p < .0001) but also the previous month (IRR 1.006 (1.002-1.009 95%CI), p = 0.001).

Parameter	Category	ID VRE. *faecium*	
		IRR (95%CI)	p*
Parsimonious model			
Time trend (linear)	per month	1.015 (1.01-1.01)	**<.0001**
Carbapenems (J01DH)	per 1DDD/100 pd	1.009 (1.00-1.01)	**<.0001**
Glycopeptides (J01XA)	per 1DDD/100 pd	1.009 (1.00-1.01)	**0.009**
Model adjusted by confounders			
Time trend (linear)	per month	1.015 (1.01-1.01)	**<.0001**
Type of ICU	Medical	0.949 (0.65-1.37)	0.784
	Surgical	1.061 (0.96-1.62)	0.785
	Interdisciplinary	1 = reference	
Type of hospital	Maximum care	1.46 (0.856-2.49)	0.164
	Other	1 = reference	
Carbapenems (J01DH)	per 1DDD/100 pd	1.009 (1.00-1.01)	**<.0001**
Glycopeptides (J01XA)	per 1DDD/100 pd	1.007 (1-1.01)	**0.04**
Model with lag of AB use			
Time trend (linear)	per month	1.014 (1.01-1.01)	**<.0001**
Carbapenems (J01DH) in current month	per 1DDD/100 pd	1.008 (1.00-1.01)	**<.0001**
Carbapenems (J01DH) before current month	per 1DDD/100 pd	1.006 (1.00-1.00)	**0.002**
Glycopeptides (J01XA) in current month	per 1DDD/100 pd	1.007 (1.00-1.01)	**0.002**

*Significance level of 5%; p=0.05

Table 13: Multivariate analysis of the incidence density for VRE. *faecium* adjusted by ICU type, hospital type, lag of AB use; ID = incidence density, IRR = incidence rate ratio, CI = confidence interval, pd = patient days.

Next, for the incidence density of VRE. *faecalis* (see Table 14) no significant trend could be shown, neither in the parsimonious model (IRR 1.003 (0.998-1.008 95%CI), p = 0.216), nor in the adjusted model (IRR 1.003 (0.997-1.008 95%CI), p = 0.3308). However, the results of the included antibiotic consumption density indicate that beta-lactamase sensitive penicillin (IRR 0.880 (0.81-0.956 95%CI), p = 0.002) has a protecting effect on the incidence density of VRE. *faecalis* that depends neither on hospital nor the type of ICU (IRR 0.888 (0.822-0.96), p = 0.002).

Parameter	Category	ID VRE. *faecalis*	
		IRR (95%CI)	p*
Parsimonious model			
Time trend (linear)	per month	1.003 (0.99-1.00)	0.216
Beta-lactamase penicillin (J01CE)	per 1DDD/100 pd	0.880 (0.81-0.95)	**0.002**
Model adjusted by confounders			
Time trend (linear)	per month	1.003 (0.99-1.00)	0.338
Type of ICU	Medical	0.831 (0.29-2.32)	0.725
	Surgical	1.215 (0.47-3.08)	0.681
	Interdisciplinary	1 = reference	
Type of hospital	Maximum care	0.508 (0.12-2.01)	0.335
	Other	1 = reference	
Beta-lactamase sensitive penicillin (J01CE)	per 1DDD/100 pd	0.888 (0.88-0.96)	**0.0028**

*Significance level of 5%; p=0.05

Table 14: Multivariate analysis of the incidence density for VRE. *faecalis* adjusted by ICU type, hospital type, lag of AB use; ID = incidence density, IRR = incidence rate ratio, CI = confidence interval, pd = patient days.

The multivariate analysis that was conducted to examine the resistance rate of VRE. *faecium* and VRE. *faecalis* showed significant results for different antibiotic groups than for the resistance density (see Table 15 and 16). This is attributable to the differences previously mentioned in the available data, since the resistance rate depends on integral numbers.

However, the parsimonious model shows a significant rising linear trend of 1.7% per month in VRE. *faecium* resistance rate (IRR 1.017 (1.015-1.019 95%CI), p < .0001) and a positive correlation for the application density of glycopeptides (IRR 1.015 (1.004-1.028 95%CI), p = 0.0112) and aminoglycosides (IRR 1.014 (1.004-1.024 95%CI), p = 0.0045). After adjusting the model by the confounding variables of ICU and hospital type, no significant differences could be identified between medical and surgical ICU, nor between maximum care and other types of hospital.

Furthermore, the adjusted model with the additional lag of antibiotic use shows, that the VRE. *faecium* resistance rate increases significantly with a rising application density of glycopeptides (IRR 1.013 (1.004-1.022 95%CI), p = 0.0045), and aminoglycosides (IRR 1.012 (1.003-1.021 95%CI), p = 0.0106) in the current month, and the use of glycopeptides in the previous month (IRR 1.015 (1.008-1.023 95%CI), p < .0001). Additionally, the

application of broad-spectrum penicillin in the month before also showed a significant correlation (IRR 1.005 (1-1.01 95%CI), p = 0.033) in the increasing VRE. *faecium* resistance rate.

Parameter	Category	RR VRE. *faecium*	
		IRR (95%CI)	p*
Parsimonious model			
Time trend (linear)	per month	1.017 (1.01-1.01)	**<.0001**
Glycopeptides (J01XA)	per 1DDD/100 pd	1.015 (1.00-1.02)	**0.0112**
Aminoglycosides (J01G)	per 1DDD/100 pd	1.014 (1.00-1.02)	**0.0045**
Model adjusted by confounders			
Time trend (linear)	per month	1.017 (1.01-1.01)	<.0001
Type of ICU	Medical	1.295 (0.73-2.29)	0.376
	Surgical	1.079 (0.60-1.93)	0.798
	Interdisciplinary	1 = reference	
Type of hospital	Maximum care	1.78 (0.588-2.35)	0.643
	Other	1 = reference	
Glycopeptides (J01XA)	per 1DDD/100 pd	1.014 (1.00-1.02)	**0.015**
Aminoglycosides (J01G)	per 1DDD/100 pd	1.014 (1.00-1.02)	**0.004**
Model with lag of AB use			
Time trend (linear)	per month	1.017 (1.01-1.01)	**<.0001**
Glycopeptides (J01XA) in current month	per 1DDD/100 pd	1.013 (1.00-1.02)	**0.004**
Glycopeptides (J01XA) before current month	per 1DDD/100 pd	1.015 (1.00-1.02)	**<.0001**
Aminoglycosides (J01G) in current month	per 1DDD/100 pd	1.012 (1.00-1.02)	**0.01**
Broad-spectrum sensitive penicillin (J01CA) in current month	per 1DDD/100 pd	1.005 (1-1.01)	**0.033**

*Significance level of 5%; p=0.05

Table 15: Multivariate analysis of the resistance rate for VRE. *faecium* adjusted by ICU type, hospital type, lag of AB use; RR = resistance rate, IRR = incidence rate ratio, CI = confidence interval, pd = patient days.

In the analysis of the resistance rate of VRE. *faecalis* (see Table 16) no significant linear trend could be identified, neither in the parsimonious model (IRR 1.003 (0.998-1.009 95%CI), p = 0.218), nor in the adjusted model (IRR 1.003 (0.998-1.009 95%CI), p = 0.267). However, this model shows a significant protecting effect in the consumption of beta-lactamase sensitive penicillin (IRR 0.916 (0.869-0964 95%CI), p = 0.0008). This effect is

also replicated in the adjusted model (IRR 0.917 (0.874-0.961 95%CI), p = 0.0004) with a constant trend of VRE. *faecalis* resistance rate (IRR 1.003 (0.998-1.009 95%CI), p = 0.267). No differences could be identified among different types of hospital and ICU.

Parameter	**Category**	**RR VRE. *faecalis***	
		IRR (95%CI)	p*
Parsimonious model			
Time trend (linear)	per month	1.003 (0.99-1.00)	0.218
Beta-lactamase penicillin (J01CE)	per 1DDD/100 pd	0.916 (0.86-0.96)	**0.0008**
Model adjusted by confounders			
Time trend (linear)	per month	1.003 (0.99-1.00)	0.267
Type of ICU	Medical	1.107 (0.41-2.93)	0.838
	Surgical	1.267 (0.51-3.13)	0.607
	Interdisciplinary	1 = reference	
Type of hospital	Maximum care	0.449 (0.14-1.41)	0.171
	Other	1 = reference	
Beta-lactamase sensitive penicillin (J01CE)	per 1DDD/100 pd	0.917 (0.87-0.96)	**0.0004**

*Significance level of 5%; p=0.05

Table 16: Multivariate analysis of the resistance rate for VRE. faecalis adjusted by ICU type, hospital type, lag of AB use; RR = resistance rate, IRR = incidence rate ratio, CI = confidence interval, pd = patient days.

To sum up the presented results in relation to the constructed research question, it becomes clear, that there are significant differences in the development and distribution of VRE. *faecium* and VRE. *faecalis* during the selected 15-year period.

6. Discussion

The aim of this master's thesis was to investigate the development of resistance rates and densities of VRE and the relationship between pathogen species and antibiotic use density in German intensive care units between 2006 and 2020.

The first finding of the study was that since 2006, the resistance density of VRE. *faecium* has clearly increased with a linear trend of 1.7% per year, and an annual increase of the resistance rate of 1.5%. In the meantime, the load of vancomycin-susceptible E. *faecium* strains stagnated. For VRE. *faecalis* no significant rising or decreasing trend could be identified neither for the resistance density, nor for the resistance rate. This supports the findings from previous publications in different European countries and the most recent data that is available from the EARS-network. However, most surveillance data and studies focus on isolates in terms of percentage and not on the incidence density or the resistance rates. Nevertheless, VRE. *faecium* shows a concerning trend that has significantly increased since 2006. The increasing counts of resistant isolates observable in various European countries [27] reflect an identical situation in Germany. The variance clearly showed that an increasing resistance rate of VRE. *faecium* affects not just individual wards but all types of hospitals and ICUs. This observation is verified by a novel report that reviewed data and outbreak reports from Germany and the Netherlands and identified VRE. *faecium* as causal pathogen in all evaluated outbreak events [81].
Considering the individual development of the resistance rate and the incidence density, the results show an explicit increase until 2019, where the resistance rate of VRE. *faecium* has significantly increased to a ratio of IRR 15.72 (7.72-31.9 95%CI) that is 15 times higher than in 2006, while the resistance density has increased by a factor of 16 (IRR 16.73 (8.45-33-1 95%CI)) at the same time. However, this increasing trend seems to pause in 2019, as results for 2020 showed a minimal downward trend in Germany, although data from the EARS-network still captured rising trends in other European countries [29]. The reasons for this contrastive development might include the SARS-CoV-19 outbreak in 2020, and the consequential reorganization of German ICUs and resource allocation, due to different terms of admission, fewer surgeries, and different patients with numerous Covid-19 cases. These factors could not be captured by the SARI system. Additionally, an overburdening of the health care system and healthcare professionals needs to be considered at this point, which may have led to less data recording or even reduced pathogen screening. This assumption is backed up by the German RKI that reported a decline of transferred pathogen detection in ARS during the second quarter of the first pandemic year [81]. Based on the ARS surveillance the institute also reports a decrease in VRE. *faecium* isolates after a peak

ratio of 26.3% in 2019 that dropped to 21.6% in 2021. Yet, Germany lies still above the European average which was 17.2% in the same year [82].
Compared with other clinically relevant resistant bacteria e.g., methicillin-resistant *Staphylococcus aureus*, which has shown increasing rates for decades but has stagnated in recent years, the distribution of AMR varies widely among European countries. Despite north-to-south and west-to-east gradient evidence, with the lowest AMR percentage in the northern region and the highest incidences of several resistant pathogens in the south and the east, there is no distinct geographical pattern for VRE. *faecium* that can be identified [83].

The second aim of the study was to determine the relationship between increasing VRE and analogous trends of the application density of specific antibiotics. The multivariate analysis confirmed the linear rising trend of VRE. *faecium* with no evidence of differences among different types of hospitals and ICUs. Comparing this with antibiotic substances that are available to treat VRE, high resistance rates of VRE. *faecium* were involved with high application densities of glycopeptides and aminoglycosides. These substances are used for serious enterococci infections, although acquired resistances already exist in the species, and are especially known in E. *faecium* [58]. Indeed, the known intrinsic low-level resistance against aminoglycosides was enhanced by adding cell wall-active agents e.g., vancomycin in the past [57]. However, the occurrence of resulting high-level resistance against all aminoglycosides and correlated rising VRE. *faecium* resistance rates eliminates the potential for such synergetic treatments in the pictured development.

After adjusting the model and additionally including antibiotic consumption of the month before the original month, broad-spectrum sensitive penicillin was also identified as a risk factor for high resistance rates in VRE. *faecium*. The group of carbapenems, on the other hand, did not have an effect on the resistance rate but on the incidence density of the pathogen. The application of carbapenems in the current month and in the previous month was significantly correlated with the increasing resistance rate of VRE. *faecium,* although carbapenems are not connected with the treatment of enterococcal infections in the first place. Moreover, despite the susceptibility in the wild type, VRE are already known for their carbapenem resistance [59]. Furthermore, carbapenems are mainly used in gram-negative infections, or infections that are caused by bacteria that are already highly resistant against several antibiotic groups. In fact, carbapenem resistance is rather known in *Escheria coli* or *Klebsiella pneumonaie* which can also cause serious infections in hospitalized patients and are referred to carbapenem resistant *Enterobacteriaceae* (CRE) [83]. Beside several risk factors, that were not included in this study but are relevant for the development of infections

caused by enterococci, including medical devices, length of hospital stay, or a patient's comorbidity, the interaction between these different pathogen species needs to be taken in account as well. Especially the increasing number of hospitalized patients in critical care units that are immunosuppressed and receiving multiple antibiotic agents promote multiresistant germs to evolve [57]. Study findings from the United States suggest information that strains of CRE and VRE are capable of forming biofilms and show synergetic interactions between antibiotics and added virulence factors [84]. However, such biofilm formations are not well characterized and were in this specific study tested for VRE. *faecalis*, which is in fact the less relevant strain in the present report.

Despite that, the positive correlation of VRE. *faecium* and the use of carbapenems is supported by earlier study findings from Taiwan, where data were evaluated from 2010 to 2019, considering prevalence of VRE. *faecium* and antibiotic consumption. In this study, an increased consumption of carbapenems, which included meropenem, was found to be significant for the resistance rate of VRE. *faecium*, but also the increase in total rates of VRE. Although the study explored data from only one single hospital, the results clearly indicated that significant changes in antimicrobial use have affected antimicrobial resistance of enterococci in that hospital [85].

It is already known that various antimicrobial agents, especially broad-spectrum substances, may predispose patients to resistant enterococci, but another retrospective study indicated that longer exposures to vancomycin, fluroquinolones, or meropenem, which belongs to the group of carbapenems, were associated with VRE bacteremia. This is thought to be caused by longer occurrences of fluroquinolones and meropenem may promote intestinal colonization with hospital-adapted strains of E. *faecium* [86]. Furthermore, Harbarth et. al. published findings according to which an increased use of multiple antimicrobials in patients with VRE colonization inhibits other bacteria and promotes overgrowth with VRE. This happens especially due to the use of substances that are considered most active against gram-negative bacteria, which in turn would explain the atypical observed correlation of carbapenems and VRE. *faecium* in the present study [87,88].

In view of the increased glycopeptide use another point that needs consideration is that co-colonization or co-infection of VRE and MRSA can occur among hospitalized patients, as glycopeptides such as vancomycin and teicoplanin are the first choice of treatment of MRSA [84], what would explain the high glycopeptide consumption density and its positively association with the increased VRE. *faecium* incidence density. However, this assumption contradicts the reported stagnant or even decreasing trend of MRSA in recent years. The finding of positive correlations between increased teicoplanin use and decreased MRSA

incidence but increased VRE incidence may be contradictory but should not be neglected in the development of VRE. Therefore, MRSA should be considered as an additional pathogen species to serve as a co-factor or reference species in further analyses.

However, the limitations of the present study and method need to be discussed before drawing conclusions.

6.1 Limitations

The first limitation of the presented study is due to variations among the participating units, as not every ICU delivered continuous data in all 12 months of the year, and certainly not for the full 15-year period. In fact, more reliable data would be available if the count of participating hospitals and individual wards increased, which is difficult to implement on a voluntary basis. Furthermore, the heterogeneity regarding the type of patients need to be considered critically, due to a high representativeness of university hospitals and hospitals with maximum care. This may lead to biased data and an overestimation of the antibiotic application density and resistance rate [75]. Another important point regarding the data collection is that resistance testing depends on different laboratories with non-identical standards (DIN, CLSI and EUCAST) and diverse limiting values. In case of an adjustment in a certain laboratory or changes in test procedures in such long time period, resulting resistance rates may increase and can be difficult to interpret [75].

What additionally limits the interpretation of the presented results is that no differentiation between nosocomial and non-nosocomial infection is possible in SARI. Due to missing information as to when a patient got colonized or infected with the pathogen species, the captured data cannot be differentiated in a hospital acquired or brought pathogen. Based on that, there is also no information available of how long a patient stayed in a hospital and what procedures or devices were used in the context of the stay. In fact, there is evidence that the main risk factors for colonization and subsequent nosocomial infection with VRE include long periods of hospitalization, and the presence of urinary catheters [57]. These risk factors are associated with high densities of antibiotic use, but are not captured by SARI but by other surveillance systems. However, ICUs that participate in SARI are not necessarily included in other available surveillance data, e.g., hospital infections surveillance system (KISS). To compensate this limitation used isolates could be differentiated by genotypization. Genotyping the pathogen isolates would contribute to a

differentiation of two essential causes that are relevant in the context of correlations between resistance data and antibiotic application densities. Increasing resistances can occur due to selection pressure and antibiotic application induced resistances or the transmission and distribution of bacteria through insufficient hygiene measures. In case of a transmission caused pathogen accumulation the diversity of the strain would be less diverse compared to an antimicrobial induced resistance increase [68].

Another methodical limitation is due to the analysis of pooled antibiotic substance, as the random analysis of glycopeptides showed significant differences within the sub-group itself. In the univariate generalized linear model no significant result was shown between the resistance rate of VRE. *faecium* and the application density of the glycopeptide group. However, the individual analysis identified a significant positive correlation for parenteral applied vancomycin. Hence, evidence suggests that there could be other individual antibiotic substances overlooked in non-significant substance groups. This suspicion is confirmed by the parallel background analyses previously mentioned that included further substances such as tuberculostatics and showed significant results in correlation with rising resistance rates of VRE. *faecium*, which again led to altered results after excluding them from the model. In fact, those findings are not described in any available literature yet and again point out the complexity of AMR in general. Compared with high-level resistance to aminoglycosides, what eliminates the effectivity of antibiotic combination previously mentioned, VRE. *faecium* might be one of the most pressing issue clinicians are facing, as other therapeutics are not reliable, or have not been tested in prospective clinical trials [57].

Next, the statistical calculation of the more rarely VRE. *faecalis* needs to be discussed. The results of the study showed that the resistant pathogen did not change in appearance and that VSE. *faecalis* did not show a significant increase or decrease either. Although this stagnant trend could be identified and no antibiotic substance group was identified as a risk factor neither in the resistance rate nor in the incidence density, the fact of not estimable counts of the pathogen species needs to be underlined. Missing observations and resulting blank values during data collection led to non-calculable results that are impossible to interpret in a reliable manner. However, compared to VRE. *faecium* a lower prevalence of VRE. *faecalis* has been reported in the literature [27,57,82] and is consistent with the observation in this retrospective study. Consequently, the resulting significant data of beta-lactamase penicillin that showed a protecting effect on the subspecies' resistance rate and incidence density, what also needs to be considered with caution precisely because of those calculation limits.

Lastly, for the differentiation of the analyzed data the defined difference between incidence density and resistance rate needs to be respected to prevent interpretation mistakes. The incidence density analyses individual months with counts of available pathogen isolates per logarithmized patient days and refers to months in which the pathogens were available. By contrast, the resistance rate per 100 pathogens refers to all months and describes a ratio, what results in an aggregated number per month. That in turn, explains the difference in the resulting antibiotics between the VRE resistance rates and resistance density.

6.2 Recommendation for further research

This study provided new insights into the relationship between increasing VRE. *faecium* density and an increased use of carbapenems in German ICUs. There is currently no extensive data or study findings available in other European countries, which points out the possible relevance of atypical antimicrobial agents in case of resistance evolution in this pathogen species. Considering the multifactorial development of resistance mechanism in general and its rapid exchange among observed pathogens, the extensive data collection via surveillance systems, and additional accurate screening and protection strategies will be essential. Generally, the control of AMR seems challenging, due to missing data and inadequate or non-consistent data collection [19]. Thus, further surveillance on a regional, national and global level is needed to deliver standardized data and allows above listed limitations to be reduced in future study designs. For this a rededicated, coordinated and collaborative global effort of all stakeholders, including healthcare institutions, governmental agencies, research groups, as well as pharmaceutical and food industry is indispensable [21]. Further regulations, including a strict monitoring of antibiotic use in hospital settings, as well in life stock farming should be implemented as part of the health policy. Additional data collecting on medical devices and the length of hospitalization would enable new comprehensive data analyses.

To follow up on the relevance of gen typing mentioned previously, another retrospective study that examines captured isolates and allows genotyping of the resistant E. *faecium* strains would eventually reveal further causality of relevant antibiotic application densities. Another aspect that would possibly lead to novel findings includes the above-mentioned, yet incomplete theory of the biofilm forming in colonized or infected patients. Future studies should examine the mechanism by which enterococci can colonize a patient's GI tract more precisely, which would allow a resulting focus on the ways to reduce or prevent colonization in the first place. However, these study approaches include extensive biomolecular and

biotechnical procedures that are expensive and time-consuming. But considering the fact that enterococci have shown the ability to evolve rapidly and develop resistances to every antibiotic substance that is used against them [54,85], further comprehensive research is inevitable, novel approaches for therapy and protection measures are needed.

7. Conclusion

This 15-year retrospective study revealed that significant changes in antimicrobial application densities might have affected antimicrobial resistance of enterococci in German ICUs, with a focus on vancomycin-resistant E. *faecium* strains. While VRE. *faecalis* was less frequent, VRE. *faecium* showed a continuous increasing trend, which correlated positively amongst others with the increasing use of carbapenems. Consequently, E. *faecium* has emerged as the more therapeutically challenging organism in the context of intensive care medicine.

These findings reiterate the importance of antimicrobial resistance, and particularly the importance of VRE in the context of nosocomial infections. Continued surveillance and study of enterococci, including the pathogens' biology and genetics, is therefore essential and will contribute to a better understanding of the development of resistant enterococci. For this, appropriate infection control measures are fundamental in German and European hospitals. Therefore, these research data should serve researcher for further research approaches, and clinicians and decision makers in the future, to improve antibiotic prescription strategies to prevent a further rise in VRE.

Bibliography

1. Antimicrobial resistance: a top ten global health threat. E Clinical Medicine. November 2021;41(2021): 101221. doi: https://doi.org/10.1016/j.eclinm.2021.101221.
2. World Health Organization. Antimicrobial resistance [Internet]. 2023 [cited 2023 Jun 12]. Available from: https://www.who.int/health-topics/antimicrobial-resistance.
3. O'Neill J. Tackling drug-resistant infections globally: The review on antimicrobial resistance [Internet]. 2018 [cited 2023 Jun 12]. Available from: https://amr-review.org/.
4. Dutescu IA, Hillier SA. Encouraging the Development of New Antibiotics: Are Financial Incentives Ritgh Way Forward? A Systematic Review and Case Study. Infect Drug Resist, 2021 February 05; 2021;(14): 415-434. doi: https://doi.org/10.2147%2-FIDR.S287792.
5. Willems RJL, Top J, van Santen M, Robinson DA, Coque TM, Baquero F, Grundmann H, Bonten MJM. Global Spread of Vancomycin-resistant Enterococcus faecium from Distinct Nosocomial Genetic Complex. Emerg Infect Dis. 2005 Jun; 11(6):821-828. doi: 10.3201/eid1106.041204.
6. Werner G, Neumann B, Weber RE, Kresken M, Wendt C, Bender JK. Thirty years of VRE in Germany – "expect the unexpected": The view from the National Reference Center for Staphylococci and Enterococci. Drug Resistance Updates. 2020 Dec;(53):100732. doi: https://doi.org/10.1016/j.drup.2020.100732.
7. Weber RE, Bender JK, Noll I, Abu Sin M, Eckmanns T, Werner G. Eigenschaften, Häufigkeit und Verbreitung von Vancomycin-resistenten Enterokokken in Deutschland – Update 2019/2020. Epid Bull. 2021;(27):32-42. doi: 10.25646/8710.
8. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M, Outterson K, Patel J, Cavaleri M, Cox EM, Houchens CR, Grayson ML, Hansen P, Singh N, Theuretzbacher U, Magrini NDiscovery, research, and development of new antibiotics: The WHO priority list of antibiotic-resistant bacteria and tuberculosis. Lancet Infect Dis. 2018;18(3):318–27. doi: 10.1016/S1473-3099(17)30753-3.
9. Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front Public Health. 2014 Sep 16;(2): 145. doi: 10.3389/fpubh.2014.00145.
10. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MKF, Baloch Z. Antibiotic resistance: a rundown of a global crisis. Infect Drug Resist. 2018 Oct 10;(11):1645-1658. doi: 10.2147/IDR.S173867.

11. Michael CA, Dominey-Howes D, Labbate M. The antimicrobial resistance crisis: causes, consequences, and management. Front. Public Health. Sec. Infectious Agents and Disease 2014 Sep 16;(2). doi: https://doi.org/10.3-389/fp-ubh.2014.00145.
12. World Organization for Animal Health. 2007 List of antimicrobials of veterinary importance [Internet]. 2023 [cited 2023 Jul 17]. Available from: http://www.oie.int/fileadmin/Home/eng/Internationa_Standard_Setting/docs/pdf/OIE_list_antimicrobials.pdf.
13. Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrob Resist Infect Control 2017 May 15;(6):47. doi: https://doi.org/10.1186/s13756-017-0208-x.
14. Spellberg B, Gilbert DN. The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. Clin Infect Dis. 2014;59(2):71–75. doi: 10.10-93/cid/ciu392.
15. Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. Clin Infect Dis. 2013 Feb 12; 56(10):1445–1450. doi: 10.1093/cid/cit070.
16. Kuehn BM. Excessive antibiotic prescribing for sore throat and acute bronchitis remains common. J Am Med Assoc. 2013 Nov 27; 310(20): 2135–6. doi:10.1001/ja-ma.2013.281452.
17. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5- and 7-day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. J Antimicrob Chemother. 2004 Jul 21;(54):515–23. doi:10.1093/jac/dkh356.
18. Agarwal G, Awasthi S, Kabra SK, Kaul A, Singhi S, Walter SD. Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomized controlled trial. BMJ. 2004 Apr 3; 328(7443):791. doi: 10.1136/bmj.38049.490255.de.
19. Samreen, Ahmad I, Malak HA, Abulreesh HH. Environmental antimicrobial resistance and its drivers: a potential threat to public health. Journal of Global Antimicrobial Resistance. 2021 Aug 25;(27):101-111. doi: https://doi.org/10.10-16/j.jgar.2021.08.001
20. Graham DW, Bergeron G, Bourassa MW, Dickson J, Gomes F, Howe A, Kahn LH, Morley PS, Scott HM, Simjee S, Singer RS, Smith TC, Storrs C, Wittum TE. Complexities in understanding antimicrobial resistance across domesticated animal, human, and environmental systems. Annals of the New York Academy of Sciences. 2019 Mar 29;1441(1):17-30. doi: https://doi.org/10.1111/nyas.14036.

21. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015 Oct; 109(7):309-318. doi: https://doi.org/10.1179%2F2047773215Y.0000000030.
22. Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MKF, Baloch Z. Antibiotic resistance: a rundown of a global crisis. Infection and Drug Resistance. 2018; (11):1645-1658.
23. Remschmidt C, Behnke M, Kola A, Pena Diaz LA, Rhode AM, Gastmeier P, Schwab F. The effect of antibiotic use on prevalence of nosocomial vancomycin-resistant enterococci- an ecologic study. Antimicrobial Resistance and Infection Control. 2017 Sep 13; (6):95.
24. World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics [Internet]. 2017 [cited 2023 Sep 06]. Available from: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed.
25. Zhang Y, Du M, Chang Y, Chen L, Zhang Q. Incidence, clinical characteristics, and outcomes of nosocomial Enterococcus spp. bloodstream infections in a tertiary-care hospital in Beijing, China: a four-year retrospective study. Antimicrobial Resistance & Infection Control. 2017 Jul 04;6(1):73.
26. Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. Nat Rev Microbiol. 2012 Mar 16;10(4):266–278. doi: https://doi.org/10.1038/nrmicro2761.
27. European Center for Disease Control. Surveillance atlas of infectious diseases [Internet]. 2023 [cited 2023 Oct 17]. Available from: https://atlas.ecdc.europa.eu/public/index.aspx.
28. European Center for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe 2018 [Internet]. 2019 [cited 2023 Jul 24]. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2018.
29. European Centre for Disease Prevention and Control. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report 2021 [Internet]. 2022 [cited 2023 Sep 06]. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2021.
30. Werner G, Neumann B, Weber RE, Kresken M, Wendt C, Bender JK. Thirty years of VRE in Germany - "expect the unexpected": The view from the National Reference Centre for Staphylococci and Enterococci. Drug Resist Updat. 2020 Dec; (53):100732. doi: 10.1016/j.drup.2020.100732.

31. Remschmidt C, Schroder C, Behnke M, Gastmeier P, Geffers C, Kramer TS. Continuous increase of vancomycin resistance in enterococci causing nosocomial infections in Germany – 10 years of surveillance. Antimicrobial resistance and infection control. 2018 Apr 24;(7):54. doi: 10.1186/s13756-018-0353-x.
32. Weber A, Maechler F, Schwab F, Gastmeier P, Kola A. Increase of vancomycin-resistant Enterococcus faecium strain type ST117 CT71 at Charité – Universitätsmedizin Berlin, 2008 to 2018. Antimicrob Resist Infect Control. 2020 Jul 16;9(1):109. doi: 10.1186/s13756-020-00754-1.
33. Reece JB, Meyers N, Urry LA, Cain ML, Wassermann SA, Minorsky PV, Jackson RB, Cooke BN. Structural and functional adaptions contribute to prokaryotic success. In: Campbell. Biology. Melbourne Australia: Pearson; 2015. p.580-590.
34. Hof H, Schlüter D. Duale Reihe Medizinische Mikrobiologie. 8th Ed. Stuttgart: Thieme; 2022. doi:10.1055/b000000575.
35. Josenhans C, Hahn H. Bakterien: Definition und Aufbau. In Suerbaum S, Burchard GD, Kaufmann SHE, Schulz TF, editors. Medizinische Mikrobiologie und Infektiologie Berlin Heidelberg: Springer Verlag; 2016. p.173-175.
36. Holtmann H, Nitsche J. BASICS. Medizinische Mikrobiologie, Hygiene und Infektiologie. 4th edition. München: Elsevier GmbH; 2017.
37. Kayser F, Böttger E, Deplazes P, Haller O, Roers A. Taschenlehrbuch Medizinische Mikrobiologie. Stuttgart: Thieme; 2022. doi:10.1055/b000000773.
38. Gatermann S. Enterokokken und weitere katalase-negative grampositive Kokken. In: Medizinische Mikrobiologie und Infektiologie. Berlin Heidelberg: Springer Verlag; 2016. doi: 10.1007/978-3-662-48678-8_26.
39. WebMD LLC. What Are Enterococcal Infections? [Internet] 2023 [cited 2023 Sep 06]. Available from: https://www.webmd.com/a-to-z-guides/what-are-enterococcal-infections.
40. Groß U. Streptokokken und Enterokokken. In: Groß U, editor. Kurzlehrbuch Medizinische Mikrobiologie und Infektiologie. 3rd edition. Stuttgart: Thieme; 2013.
41. Kristich CJ, Rice LB, Arias CA. Enterococcal Infection – Treatment and Antibiotic Resistance. In: Gilmore MS, Clewell DB, Ike Y, editors. Enterococci: From Commensals to Leading Causes of Drug Resistant Infection. Massachusetts, Boston: Eye and Ear Infirmary; 2014 Feb 06.
42. Zeising S, Fille M. Resistenz. In: Medizinische Mikrobiologie und Infektiologie. Berlin Heidelberg: Springer Verlag; 2016. doi:10.1007/978-3-662-48678-8_26.
43. Martino PD. Antimicrobial agents and microbial ecology. AIMS Microbiol. 2022 Jan 06;8(1):1-4. doi: https://doi.org/10.3934%2Fmicrobiol.2022001.

44. Britannica Science and Tech. Antibiotic chemical compound [Internet]. 2023 [cited 2023 Aug 14]. Available from: https://www.britannica.com/science/antibiotic.
45. Ortho Bullets. Antibiotic Classification & Mechanism [Internet]. 2023 Apr 06 [cited 2023 Nov 07]. Available from: https://www.orthobullets.com/basic-science-/9059/antibiotic-classification-and-mechanism.
46. Abushaheen MA, Muzaheed, Fatani AJ, Alosaimi M, Mansy W, George M, Acharya S, Rathod S, Divakar DD, Jhugroo C, Vellappally S, Khan AA, Shaik J, Jhugroo P. Antimicrobial resistance, mechanisms and its clinical significance. Disease-a-Month. 2020 Mar 20;66(6):100971. doi: https://doi.org/10.1016/j.disa-month.2020.100971.
47. Wandeler G, Gastmeier P, Mühlemann K. Infektionskrankheiten. In: Egger M, Razum O, editors. Public Health: Sozial- und Präventivmedizin kompakt. Berlin: De Gruyter, 2012. p.296-298.
48. Noll I, Schweickert B, Tenhagen BA, Käsbohrer A. Antibiotikaverbrauch und Antibiotikaresistenz in der Human- und Veterinärmedizin. Überblick über die etablierten nationalen Surveillance-Systeme. Bundesgesundheitsblatt. 2018;(61): 522-532.
49. Pletz MW, EckmannC, Hagel S, Heppner HJ, Huber K, Kämmerer W, Schmitz FJ, Wilke M, Grabein B. Multiresistente Erreger – Infektionsmanagement 2015. Deutsche Medizinische Wochenschrift. 2015;(140):975-981.
50. Robert Koch-Institut. Bekanntmachung: Hygienemaßnahmen bei Infektionen oder Besiedlung mit multiresistenten gramnegativen Stäbchen. Empfehlungen der Kommission für Krankenhaushygiene und Infektionsprävention (KRINKO) beim Robert Koch-Institut (RKI). Bundesgesundheitsblatt. 2012;(55):1311-1354.
51. Hof H. Einführung in die Medizinische Mikrobiologie und Hygiene. In: Hof H, Geginat G, Reischl U, editors. Duale Reihe Medizinische Mikrobiologie. 8th edition. Stuttgart: Thieme; 2022.
52. Raza T, Ullah SR, Mehmood K, Andleeb S. Vancomycin resistant Enterococci: A brief review. J Pak Med Assoc. 2018 May; 68(5):768-772.
53. Oxford Reference, Plasmid definition [Internet]. 2023 [cited 2023 Oct 19]. Available from: https://www.oxfordreference.com/display/10.1093/acref/9780199204625.001.0001/acref-9780199204625-e-3471.
54. Collins, Definition transposon in American English [Internet]. 2023 [cited 2023 Oct 19]. Available from: https://www.collinsdictionary.com/de/worterbuch/englisch/transposon#google_vignette.

55. Stogios PJ, Savchenko A. Molecular mechanisms of vancomycin resistance. Protein Sci. 2020 Jan 23;29(3):654-669. Available from: doi: https://doi.org/10.10-02%2Fpro.3819.
56. Miller WR, Munita JM, Arias CA. Mechanisms of antibiotic resistance in enterococci. Expert Rev Anti Infect Ther. 2014 Oct;12(10):1221-36. doi: 10.1586/1478-7210.2014.956092.
57. Arias CA, Murray BE. The rise of the Enterococcus: beyond vancomycin resistance. Nat Rev Microbiol. 2012 Mar 16;10(4):266-78. doi: 10.1038/nrmicro2761.
58. Klare I, Witte W, Wendt C, Werner G. Vancomycin-resistente Enterokokken (VRE). Aktuelle Daten und Trends zur Resistenzentwicklung. Bundesgesundheitsbltt. 2012 Okt 21;(55):1387-1400. doi: 10.1007/s00103-012-1564-6.
59. Amboss. Nosokomiale Infektionen [Internet]. 2023 [cited 2023 Oct 02]. Available from: https://next.amboss.com/de/article/_f05K2?q=VRE#mmcVT10.
60. O'Driscoll T, Crank CW. Vancomycin-resistant enterococcal infections: epi-demiology, clinical manifestations, and optimal management. 2015 Jul 24; 8: 217-230. doi: https://doi.org/10.2147%2FIDR.S54125.
61. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, Fridkin SK. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. Infect Control Hosp Epidemiol. 2008 Nov 29;29(11):996-1011. doi: https://doi.org/10.1086/591861.
62. Linden PK. Optimizing therapy for vancomycin-resistant enterococci (VRE). Semin Respir Crit Care Med. 2007 Dec;28(6):632–645. doi: https://doi.org/10.1055/s-2007-996410.
63. Nelson KE, Williams CM. Infectious Disease Epidemiology: Theory and Practice. Burlington, MA: Jones & Bartlett Learning; 2014.
64. Straif-Bourgeois S, Ratard R, Kretzschmar M. Infectious Disease Epidemiology. Handbook of Epidemiology. 2014: 2041-2119. doi: https://doi.org/10.1007%2F978-0-387-09834-0_34.
65. World Health Organization. Global Antimicrobial Resistance and Use Surveillance System (GLASS) [Internet]. 2023 [cited 2023 Aug 01]. Available from: https://www.who.int/initiatives/glass.
66. European Centre for Disease Prevention and Control. EARS-Net Reporting protocol 2023 [Internet]. 2023 [cited 2023 Aug 01]. Available from: https://www.ec-dc.europa.eu/en/publications-data/ears-net-reporting-protocol-2023.

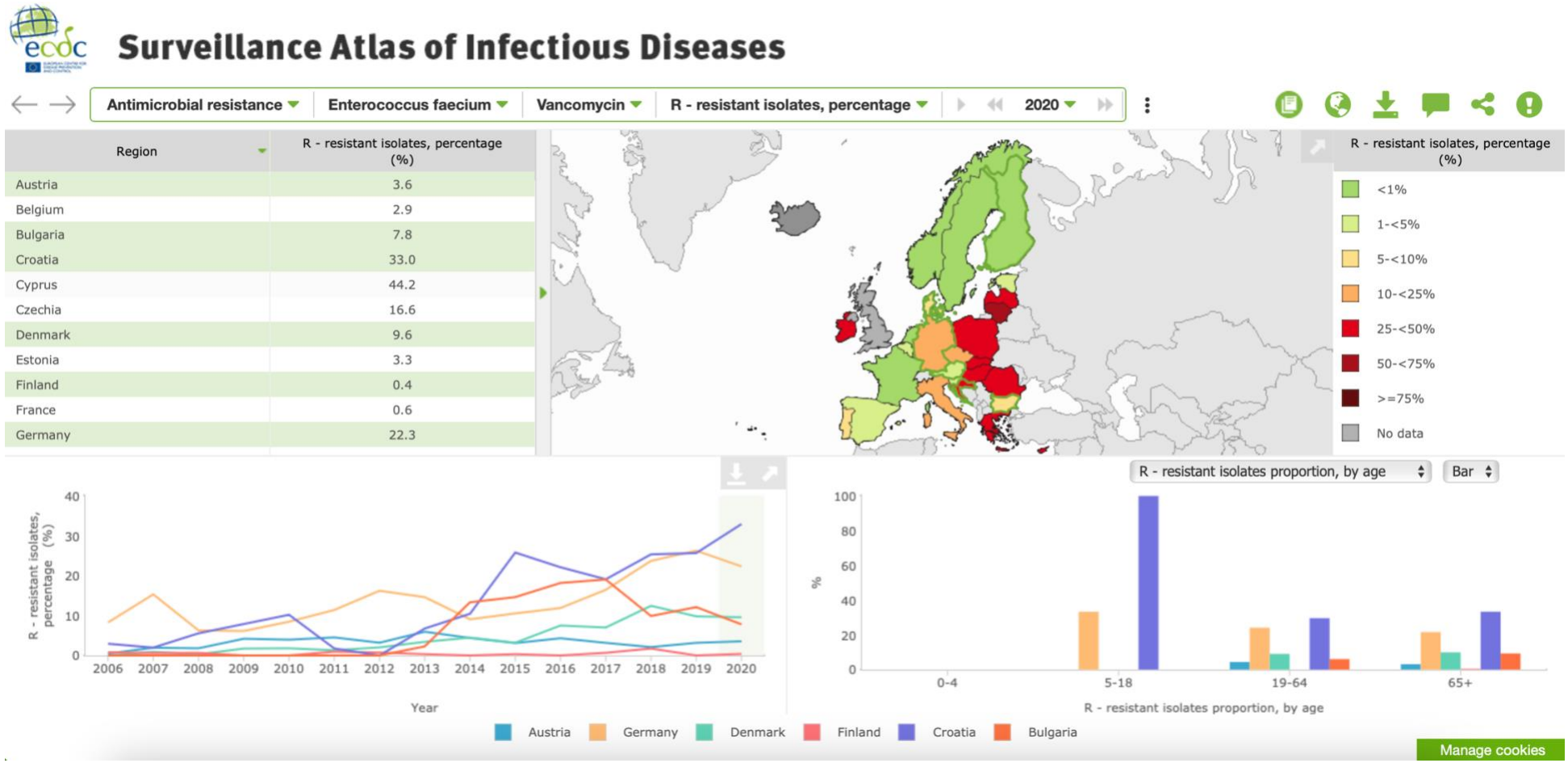
67. Robert Koch-Institute. ARS-Antibiotika-Resistenz-Surveillance [Internet]. 2023 [cited 2023 Aug 18]. Available from: https://www.rki.de/DE/Content/Infekt/Sentinel/ARS/ARS.html.
68. Meyer E, Jonas D, Schwab F, Gastmeier P, Rüden H, Daschner FD. SARI: Surveillance der Antibiotikaanwendung und bakteriellen Resistenzentwicklung auf deutschen Intensivstationen Zu den Zusammenhängen von Antibiotikaverbrauch und Resistenzsituation. Bundesgesundheitsblatt. 2004 Apr 01; 4.
69. Meyer E, Schwab F. Das SARI-Projekt. Krankenhaushygiene up2date. 2008;3(1): 61-72. doi: 10.1055/s-2007-995458.
70. Robert Koch-Institute. AVS-Antibiotika Verbrauch Surveillance. Methodik [Internet]. 2023 [cited 2023 Nov 24]. Available from: https://avs.rki.de/Content/Project/Methodology.aspx.
71. Wang X, Kattan MW. Cohort Studies: Design, Analysis, and Reporting. Chest. 2020 Jul 02;158(1):72-87. doi: https://doi.org/10.1016/j.chest.2020.03.014.
72. Meyer E, Jonas D, Schwab F, Rueden H, Gastmeier P, Daschner FD. Design of a surveillance system of antibiotic use and bacterial resistance in German intensive care units (SARI). Infection 2003 Aug;(31):208-215. doi: https://doi.org/10.1007/s15010-003-3201-7.
73. Meyer E, Schwab F, Jonas D, Rueden H, Gastmeier P, Daschner FD. Surveillance of antimicrobial use and antimicrobial resistance in intensive care units (SARI): 1. antimicrobial use in German intensive care units. Intensive Care Med 2004;(30): 1089–96.
74. Nationales Referenzzentrum für Surveillance von nosokomialen Infektionen. SARI Protokoll [Internet]. 2009 [cited 2023 Aug 26]. Available from: http://www.nrz-hygiene.de.
75. Remschmidt C, Schneider S, Meyer E, Schroeren-Boersch B, Gastmeier P, Schwab F. Surveillance of antibiotic use and resistance in intensive care units (SARI): A 15-year cohort study. Dtsch Arztebl Int. 2017 Sep 18;(114):858-65. doi: 10.3238/arztebl.2017.0858.
76. World Health Organization. Defined Daily Dose (DDD) Definition and general considerations [Internet]. 2023 [cited 2023 Aug 28]. Available from: https://www.who.int/tools/atc-ddd-toolkit/about-ddd.
77. Meyer E, Jonas D, Schwab F, Rueden H, Gastmeier P, Daschner FD. Design of a surveillance system of antibiotic use and bacterial resistance in German intensive care units (SARI). Infection. 2003 Aug;31(4):208-15. doi: 10.1007/s15010-003-3201-7.

78. Backhaus K, Erichson B, Plinke W, Weiber R. Multivariate Analysemethoden. Eine anwendungsorientierte Einführung. 14th edition. Berlin Heidelberg: Springer; 2016.
79. Faraway JJ. Generalized Linear Models. International Encyclopedia od Education (Third edition). Elsevier; 2010. doi: https://doi.org/10.1016/B978-0-08-044894-7.01331-2.
80. Lipi N, Mohammad SA, Syed SH. A Generalized Estimating Equations Approach for Modeling Spatially Clustered Data. Austrian Journal of Statistics. 2021,50 (4):36–52. doi: https://doi.org/10.17713/ajs.v50i4.1097.
81. Cimen C, Berends MS, Bathoorn E, Lokate M, Voss A, Friedrich AW, Glasner C, Hamprecht A. Vancomycin-resistant enterococci (VRE) in hospital settings across European borders: a scoping review comparing the epidemiology in the Netherlands and Germany. Antimicrob Resist Infect Control. 2023;(12). https://doi.org/10.11-86/s13756-023-01278-0.
82. Robert Koch Institut. Aktuelle Daten und Informationen zu Infektionskrankheiten und Public Health. Epid Bull. 2023;(41). https://www.rki.de/DE/Con-tent/Infekt/EpidBull/Archiv/2023/Ausgaben/41_23.pdf?__blob=publicationFile.
83. WHO Regional Office for Europe/European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2022 – 2020 data. Copenhagen: WHO Regional Office for Europe; 2022.
84. Stoodley P, Brooks J, Peters CW, Jiang N, Delury CP, Laycock PA, Aiken SS, Dusane DH. Prevention and Killing Efficacy of Carbapenem Resis-tant Enterobacteriaceae (CRE) and Vancomycin Resistant Enterococci (VRE) Biofilms by Antibiotic-Loaded Calcium Sulfate Beads. Materials (Basel). 2020 Jul 22;13(15):3258. doi: 10.3390/ma13153258.
85. Lee MC, Lu CH, Lee WY, Lee CM. Correlation between Nosocomial Carriage of Vancomycin-Resistant Enterococci and Antimicrobial Use in Taiwan. Am J Trop Med Hyg. 2020 Dec 14;104(3):1131-1136. doi: 10.4269/ajtmh.20-0842.
86. Gouliouris T, Warne B, Cartwright EJP, Bedford L, Weerasuriya CK, Raven KE, Brown NM, Török ME, Limmathurotsakul D, Peacock SJ. Duration of exposure to multiple antibiotics is associated with increased risk of VRE bacteraemia: a nested case-control study. J Antimicrob Chemother 2018;(73):1692–1699.
87. Harbarth S, Cosgrove S, Carmeli Y. Effects of antibiotics on nosocomial epidemiology of vancomycin-resistant entero- cocci. Antimicrob Agents Chemother. 2002;(46):1619–1628.
88. Donskey CJ, Chowdhry TK, Hecker MT, Hoyen CK, Hanrahan JA, Hujer AM, Hutton-Thomas RA, Whalen CC, Bonomo RA, Rice LB. Effect of antibiotic therapy

on the density of vancomycin-resistant enterococci in the stool of colonized patients. N Engl J Med. 2000 Dec 28;(343):1925–1932.

Appendix I

VRE. *faecium* isolates in Europe from 2006 to 2020 (part1/2) [27]



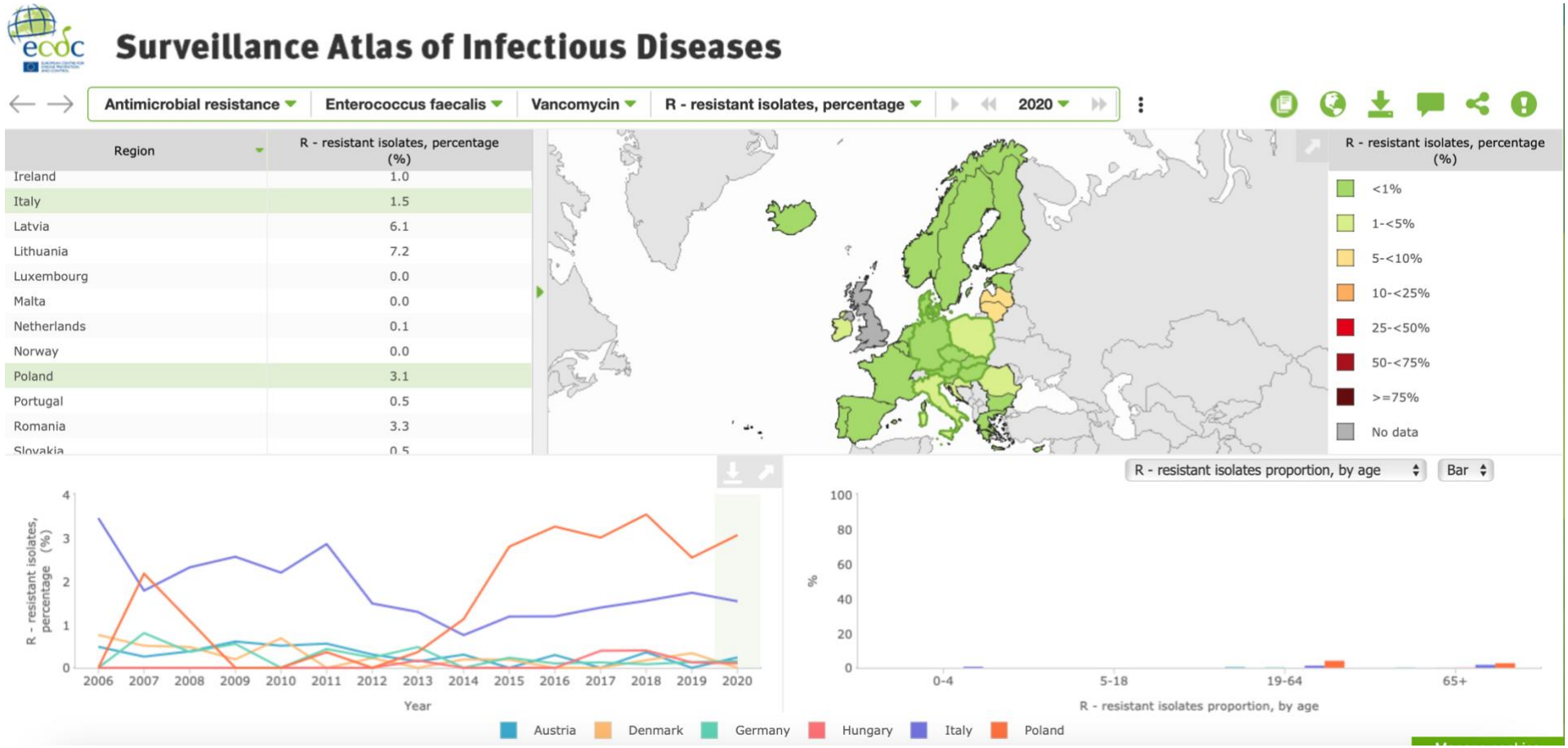
VRE. *faecium* isolates in Europe from 2006 to 2020 (part 2/2) [27]

Surveillance Atlas of Infectious Diseases

Antimicrobial resistance | Enterococcus faecium | Vancomycin | R - resistant isolates | 2020

Region	R - resistant isolates, percentage (%)	Total tested isolates (N)	R - resistant isolates (N)	I - 'susceptible, increased exposure' isolates (N)	S - susceptible isolates (N)
Estonia	3.3	61	2	0	59
Finland	0.4	259	1	0	258
France	0.6	1385	8	3	1374
Germany	22.3	3906	872	0	3034
Greece	41.8	445	186	0	259
Hungary	34.8	471	164	0	307
Iceland	-	19	0	0	19
Ireland	35.7	471	168	0	303
Italy	23.6	4166	983	0	3183
Latvia	29.0	62	18	0	44
Lithuania	56.6	145	82	0	63
Luxembourg	11.9	42	5	0	37
Malta	21.7	23	5	0	18
Netherlands	0.5	1310	6	0	1304
Norway	0.6	180	1	0	179
Poland	38.5	527	203	0	324
Portugal	7.8	399	31	0	368
Romania	39.3	112	44	0	68
Slovakia	40.0	120	48	0	72
Slovenia	1.1	177	2	0	175
Spain	1.2	1079	13	2	1064
Sweden	0.2	600	1	0	599
United Kingdom	.	.	.	.	Manage cookies

VRE. *faecalis* isolates in Europe from 2006 to 2020 (part 1/2) [27]



VRE. *faecalis* isolates in Europe from 2006 to 2020 (part 2/2) [27]

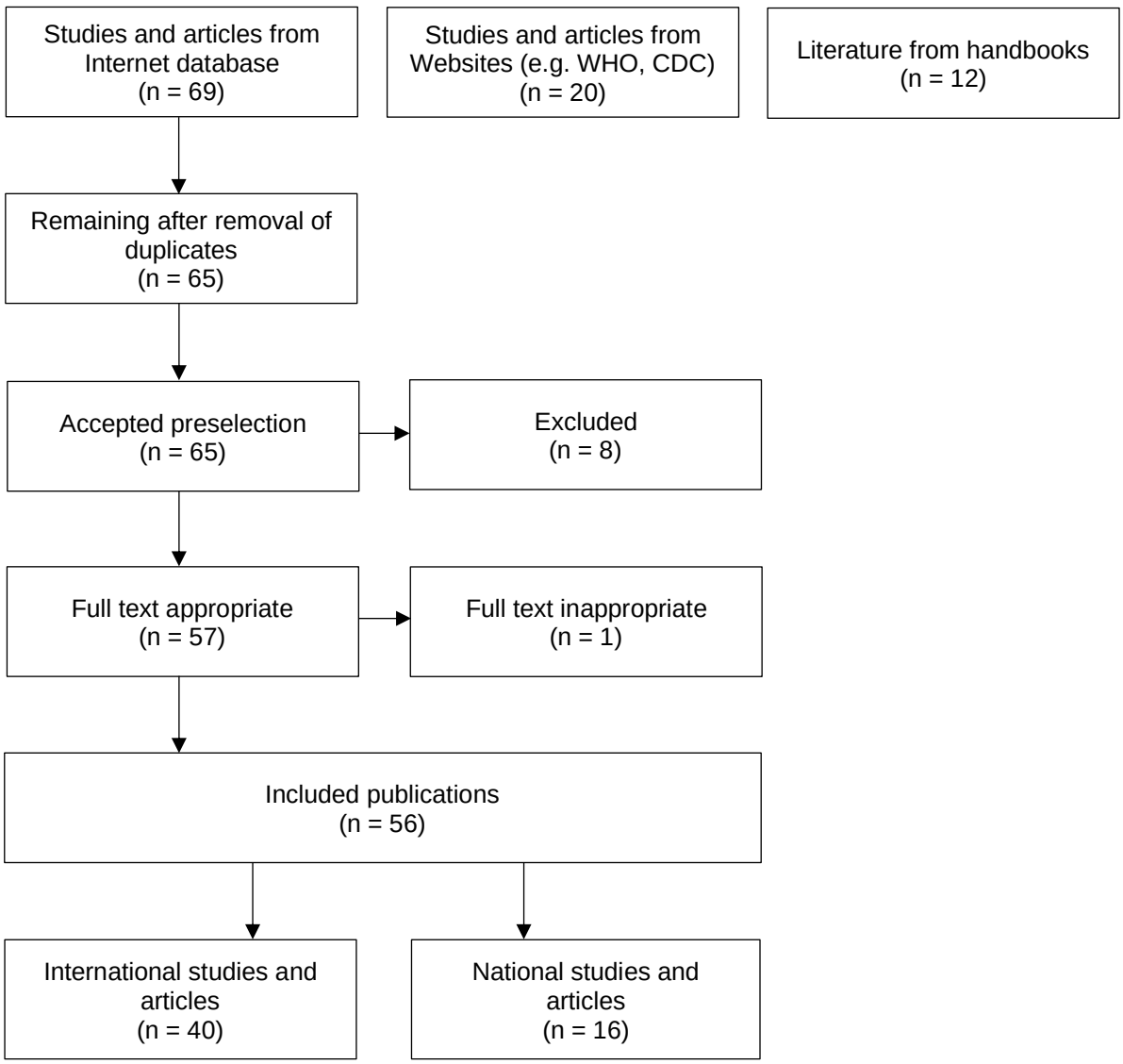
Surveillance Atlas of Infectious Diseases

Antimicrobial resistance | Enterococcus faecalis | Vancomycin | R - resistant isolates, percentage | 2020

Region	R - resistant isolates, percentage (%)	Total tested isolates (N)	R - resistant isolates (N)	I - 'susceptible, increased exposure' isolates (N)	S - susceptible isolates (N)
Estonia	0.0	107	0	0	107
Finland	0.4	566	2	0	564
France	0.1	4303	4	1	4298
Germany	0.2	4627	7	0	4620
Greece	0.0	367	0	0	367
Hungary	0.1	955	1	0	954
Iceland	0.0	30	0	0	30
Ireland	1.0	312	3	0	309
Italy	1.5	6189	95	0	6094
Latvia	6.1	98	6	0	92
Lithuania	7.2	139	10	0	129
Luxembourg	0.0	95	0	0	95
Malta	0.0	28	0	0	28
Netherlands	0.1	1191	1	0	1190
Norway	0.0	520	0	0	520
Poland	3.1	783	24	0	759
Portugal	0.5	966	5	0	961
Romania	3.3	152	5	0	147
Slovakia	0.5	199	1	0	198
Slovenia	0.5	182	1	0	181
Spain	0.1	1502	2	0	1500
Sweden	0.0	1435	0	0	1435

Appendix II

Literature search (own flowchart)



Appendix III

SPSS exemplary syntax

```
* Encoding: UTF-8.

DATASET ACTIVATE DataSet1.
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS CI(95) R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT tR13A4
  /METHOD=ENTER Jahreszahl.

REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS CI(95) R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT RR13A4
  /METHOD=ENTER Jahreszahl.

DATASET ACTIVATE DataSet1.
REGRESSION
  /MISSING LISTWISE
  /STATISTICS COEFF OUTS CI(95) R ANOVA
  /CRITERIA=PIN(.05) POUT(.10)
  /NOORIGIN
  /DEPENDENT g10
  /METHOD=ENTER Jahreszahl.
```

SAS model codes

SAS code: Analysis of incidence densities of VRE. *faecium* and VRE. *faecalis* / 1000 patient days

```
proc genmod data=dataset;
      class Station saison(ref='1') jahr(ref='2006')  monat(ref='1');
      model tR13A4 = time ADuse / dist=NEGBIN offset=lnpattage link=log
      type3 ;
repeated subject= Station /  type=AR;
ods output GEEEmpPEst = koeff;
run;
```

SAS code: Analysis of resistance rates of resistant VRE. *faecium* and VRE. *faecalis* / 100 pathogens

```
proc genmod data= dataset;
   class Station saison(ref='1') jahr(ref='2006')  monat(ref='1');
   model resERR/getERR = time ADuse / dist = bin link = logit lrci type3;
repeated subject=KRHICU /  type=AR;
ods output GEEEmpPEst = koeff;
run;
```

SPSS output of the Linear regression analysis (RR and RD VRE. *faecium* and VRE. *faecalis*)

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: tR13A4

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,903[a]	,815	,800	90,761

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	470680,000	1	470680,000	57,138
	Nicht standardisierte Residuen	107088,400	13	8237,569	
	Gesamt	577768,400	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: tR13A4

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	-78,800	49,316		-1,598	,134
	Jahr_codiert	41,000	5,424	,903	7,559	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	-185,340	27,740
	Jahr_codiert	29,282	52,718

a. Abhängige Variable: tR13A4

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: tR6A4

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,150[a]	,023	-,053	3,385

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	3,432	1	3,432	,300
	Nicht standardisierte Residuen	148,968	13	11,459	
	Gesamt	152,400	14		

ANOVA[a]

Modell		Sig.
1	Regression	,593[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: tR6A4

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	2,314	1,839		1,258	,230
	Jahr_codiert	,111	,202	,150	,547	,593

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	-1,659	6,288
	Jahr_codiert	-,326	,548

a. Abhängige Variable: tR6A4

RR VRE. *faecium* and VRE. *faecalis*

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: RR13A4

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,923[a]	,853	,841	4,6343582937

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	1613,787	1	1613,787	75,139
	Nicht standardisierte Residuen	279,205	13	21,477	
	Gesamt	1892,992	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: RR13A4

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	-3,358	2,518		-1,333	,205
	Jahr_codiert	2,401	,277	,923	8,668	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	-8,798	2,082
	Jahr_codiert	1,802	2,999

a. Abhängige Variable: RR13A4

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: RR6A4

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,153[a]	,023	-,052	,24009513270

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	,018	1	,018	,310
	Nicht standardisierte Residuen	,749	13	,058	
	Gesamt	,767	14		

ANOVA[a]

Modell		Sig.
1	Regression	,587[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: RR6A4

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	,165	,130		1,268	,227
	Jahr_codiert	,008	,014	,153	,557	,587

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	-,116	,447
	Jahr_codiert	-,023	,039

a. Abhängige Variable: RR6A4

RD VRE. *faecium* and VRE. *faecalis*

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: RP13A4

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,904[a]	,818	,804	,42930480138

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	10,755	1	10,755	58,357
	Nicht standardisierte Residuen	2,396	13	,184	
	Gesamt	13,151	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: RP13A4

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	-,387	,233		-1,660	,121
	Jahr_codiert	,196	,026	,904	7,639	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	-,891	,117
	Jahr_codiert	,141	,251

a. Abhängige Variable: RP13A4

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: RP6A4

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,142[a]	,020	-,055	,01519139833

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	,000	1	,000	,267
	Nicht standardisierte Residuen	,003	13	,000	
	Gesamt	,003	14		

ANOVA[a]

Modell		Sig.
1	Regression	,614[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: RP6A4

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	,011	,008		1,355	,198
	Jahr_codiert	,000	,001	,142	,517	,614

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	-,007	,029
	Jahr_codiert	-,001	,002

a. Abhängige Variable: RP6A4

SPSS output of the Linear regression analysis (antibiotic application density g1—g12, g14, g16, g18, g21, g22)

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g1

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,568[a]	,322	,270	2,8751668136

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	51,071	1	51,071	6,178
	Nicht standardisierte Residuen	107,466	13	8,267	
	Gesamt	158,537	14		

ANOVA[a]

Modell		Sig.
1	Regression	,027[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g1

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	17,941	1,562		11,484	<,001
	Jahr_codiert	,427	,172	,568	2,486	,027

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	14,566	21,316
	Jahr_codiert	,056	,798

a. Abhängige Variable: g1

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g2

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,611[a]	,373	,325	18,510336247

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	2654,461	1	2654,461	7,747
	Nicht standardisierte Residuen	4454,223	13	342,633	
	Gesamt	7108,684	14		

ANOVA[a]

Modell		Sig.
1	Regression	,016[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g2

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	87,716	10,058		8,721	<,001
	Jahr_codiert	-3,079	1,106	-,611	-2,783	,016

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	65,988	109,445
	Jahr_codiert	-5,469	-,689

a. Abhängige Variable: g2

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g3

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,844[a]	,713	,691	13,796493455

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	6149,144	1	6149,144	32,306
	Nicht standardisierte Residuen	2474,462	13	190,343	
	Gesamt	8623,606	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g3

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	17,808	7,496		2,375	,034
	Jahr_codiert	4,686	,824	,844	5,684	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	1,612	34,003
	Jahr_codiert	2,905	6,468

a. Abhängige Variable: g3

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g4

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,964[a]	,929	,923	21,083051063

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	75087,581	1	75087,581	168,928
	Nicht standardisierte Residuen	5778,436	13	444,495	
	Gesamt	80866,016	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g4

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	107,720	11,456		9,403	<,001
	Jahr_codiert	16,376	1,260	,964	12,997	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	82,972	132,469
	Jahr_codiert	13,654	19,098

a. Abhängige Variable: g4

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g5

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,438[a]	,192	,129	3,4781161111

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	37,273	1	37,273	3,081
	Nicht standardisierte Residuen	157,265	13	12,097	
	Gesamt	194,538	14		

ANOVA[a]

Modell		Sig.
1	Regression	,103[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g5

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	32,289	1,890		17,085	<,001
	Jahr_codiert	,365	,208	,438	1,755	,103

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	28,206	36,372
	Jahr_codiert	-,084	,814

a. Abhängige Variable: g5

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g6

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,883[a]	,780	,763	10,339309059

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	4913,501	1	4913,501	45,963
	Nicht standardisierte Residuen	1389,717	13	106,901	
	Gesamt	6303,218	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g6

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	111,822	5,618		19,904	<,001
	Jahr_codiert	-4,189	,618	-,883	-6,780	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	99,685	123,959
	Jahr_codiert	-5,524	-2,854

a. Abhängige Variable: g6

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g7

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,921[a]	,848	,836	6,1786099165

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	2768,634	1	2768,634	72,524
	Nicht standardisierte Residuen	496,278	13	38,175	
	Gesamt	3264,911	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g7

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	127,363	3,357		37,937	<,001
	Jahr_codiert	-3,145	,369	-,921	-8,516	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	120,111	134,616
	Jahr_codiert	-3,942	-2,347

a. Abhängige Variable: g7

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g7a

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,688[a]	,473	,433	4,1760457101

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	203,518	1	203,518	11,670
	Nicht standardisierte Residuen	226,712	13	17,439	
	Gesamt	430,229	14		

ANOVA[a]

Modell		Sig.
1	Regression	,005[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g7a

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	4,078	2,269		1,797	,096
	Jahr_codiert	,853	,250	,688	3,416	,005

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	-,824	8,980
	Jahr_codiert	,313	1,392

a. Abhängige Variable: g7a

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g8

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,973[a]	,948	,943	15,133377434

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	53770,693	1	53770,693	234,787
	Nicht standardisierte Residuen	2977,248	13	229,019	
	Gesamt	56747,941	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g8

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	112,597	8,223		13,693	<,001
	Jahr_codiert	13,858	,904	,973	15,323	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	94,833	130,362
	Jahr_codiert	11,904	15,812

a. Abhängige Variable: g8

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g9

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,605[a]	,366	,318	,22527251555

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	,381	1	,381	7,517
	Nicht standardisierte Residuen	,660	13	,051	
	Gesamt	1,041	14		

ANOVA[a]

Modell		Sig.
1	Regression	,017[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g9

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	,688	,122		5,621	<,001
	Jahr_codiert	-,037	,013	-,605	-2,742	,017

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	,424	,952
	Jahr_codiert	-,066	-,008

a. Abhängige Variable: g9

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g10

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,892[a]	,795	,779	6,6757425377

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	2247,539	1	2247,539	50,432
	Nicht standardisierte Residuen	579,352	13	44,566	
	Gesamt	2826,891	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g10

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	35,080	3,627		9,671	<,001
	Jahr_codiert	2,833	,399	,892	7,102	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	27,244	42,917
	Jahr_codiert	1,971	3,695

a. Abhängige Variable: g10

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g11

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,723[a]	,523	,487	21,424888031

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	6552,881	1	6552,881	14,276
	Nicht standardisierte Residuen	5967,336	13	459,026	
	Gesamt	12520,217	14		

ANOVA[a]

Modell		Sig.
1	Regression	,002[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g11

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	194,261	11,641		16,687	<,001
	Jahr_codiert	-4,838	1,280	-,723	-3,778	,002

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	169,112	219,411
	Jahr_codiert	-7,604	-2,072

a. Abhängige Variable: g11

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g12

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,698[a]	,488	,448	6,5502189950

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	530,901	1	530,901	12,374
	Nicht standardisierte Residuen	557,770	13	42,905	
	Gesamt	1088,671	14		

ANOVA[a]

Modell		Sig.
1	Regression	,004[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g12

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	19,856	3,559		5,579	<,001
	Jahr_codiert	1,377	,391	,698	3,518	,004

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	12,167	27,545
	Jahr_codiert	,531	2,223

a. Abhängige Variable: g12

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g14

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,161[a]	,026	-,049	5,4240705933

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	10,179	1	10,179	,346
	Nicht standardisierte Residuen	382,467	13	29,421	
	Gesamt	392,646	14		

ANOVA[a]

Modell		Sig.
1	Regression	,566[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g14

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	24,092	2,947		8,174	<,001
	Jahr_codiert	,191	,324	,161	,588	,566

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	17,725	30,459
	Jahr_codiert	-,510	,891

a. Abhängige Variable: g14

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g16

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,012[a]	,000	-,077	12,575267583

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	,276	1	,276	,002
	Nicht standardisierte Residuen	2055,786	13	158,137	
	Gesamt	2056,062	14		

ANOVA[a]

Modell		Sig.
1	Regression	,967[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g16

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	96,285	6,833		14,091	<,001
	Jahr_codiert	,031	,752	,012	,042	,967

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	81,523	111,046
	Jahr_codiert	-1,592	1,655

a. Abhängige Variable: g16

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g18

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,652[a]	,426	,382	3,3394909007

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	107,458	1	107,458	9,636
	Nicht standardisierte Residuen	144,979	13	11,152	
	Gesamt	252,436	14		

ANOVA[a]

Modell		Sig.
1	Regression	,008[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g18

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	25,367	1,815		13,980	<,001
	Jahr_codiert	,619	,200	,652	3,104	,008

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	21,447	29,287
	Jahr_codiert	,188	1,051

a. Abhängige Variable: g18

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g21

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,936[a]	,876	,866	4,0136438073

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	1476,206	1	1476,206	91,637
	Nicht standardisierte Residuen	209,421	13	16,109	
	Gesamt	1685,627	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g21

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	62,699	2,181		28,750	<,001
	Jahr_codiert	-2,296	,240	-,936	-9,573	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	57,987	67,410
	Jahr_codiert	-2,814	-1,778

a. Abhängige Variable: g21

Aufgenommene/Entfernte Variablen[a]

Modell	Aufgenommene Variablen	Entfernte Variablen	Methode
1	Jahr_codiert[b]	.	Einschluß

a. Abhängige Variable: g22

b. Alle gewünschten Variablen wurden eingegeben.

Modellzusammenfassung

Modell	R	R-Quadrat	Korrigiertes R-Quadrat	Standardfehler des Schätzers
1	,933[a]	,871	,862	7,0033553159

a. Einflußvariablen : (Konstante), Jahr_codiert

ANOVA[a]

Modell		Quadratsumme	df	Mittel der Quadrate	F
1	Regression	4321,160	1	4321,160	88,102
	Nicht standardisierte Residuen	637,611	13	49,047	
	Gesamt	4958,771	14		

ANOVA[a]

Modell		Sig.
1	Regression	<,001[b]
	Nicht standardisierte Residuen	
	Gesamt	

a. Abhängige Variable: g22

b. Einflußvariablen : (Konstante), Jahr_codiert

Koeffizienten[a]

Modell		Nicht standardisierte Koeffizienten		Standardisierte Koeffizienten		
		Regressionskoeffizient B	Std.-Fehler	Beta	T	Sig.
1	(Konstante)	34,930	3,805		9,179	<,001
	Jahr_codiert	3,928	,419	,933	9,386	<,001

Koeffizienten[a]

Modell		95,0% Konfidenzintervalle für B	
		Untergrenze	Obergrenze
1	(Konstante)	26,709	43,151
	Jahr_codiert	3,024	4,833

a. Abhängige Variable: g22

Appendix IV

Pooled antibiotic application density (including individual substances per group and application form)

Variable name	Label (ATC code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
g1	**Beta-lactamase sensitive penicillin (J01CE)**	**23.0**	**20.0**	**17.2**	**19.4**	**20.2**	**18.7**	**18.3**	**15.1**	**23.0**	**26.4**	**22.9**	**20.7**	**23.8**	**26.1**	**25.5**
AD82	Benzylpenicillin (p) (J01CE01)	19.8	19.0	16.6	19.1	19.6	18.3	17.4	14.6	21.2	25.2	20.8	20.1	23.2	25.1	24.8
AD102	Phenoxymethylpenicillin (o) (J01CE02)	3.3	0.9	0.6	0.3	0.6	0.4	0.9	0.5	1.8	1.2	2.0	0.6	0.6	1.0	0.7
AD130	Propicillin (o) (J01CE03)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD150	Benzathine benzylpenicillin (J01CE08)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
g2	**Broadspectrum penicillin (J01CA)**	**100.9**	**103.4**	**81.6**	**89.2**	**66.6**	**60.7**	**47.5**	**33.6**	**36.5**	**38.9**	**39.6**	**64.4**	**57.7**	**60.0**	**65.6**
AD30	Ampicillin (p) (J01CA01)	19.8	24.6	18.2	21.6	18.4	22.6	26.1	20.5	24.6	27.6	26.6	52.4	43.6	48.3	55.9
AD29	Ampicillin (o) (J01CA01)	0.8	-0.1	0.0	0.2	0.0	0.0	-0.1	0.0	0.0	0.8	0.8	0.1	0.0	0.0	0.0
AD32	Amoxicillin (p) (J01CA04)	0.7	1.1	0.4	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0
AD31	Amoxicillin (o) (J01CA04)	9.9	14.7	14.2	13.8	6.7	10.8	8.1	11.1	10.9	9.7	11.9	11.4	13.2	11.0	8.9
AD219	Pivmecillinam (o) (J01CA08)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.2	0.3	0.5	0.5
AD34	Azlocillin (p) (J01CA09)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD66	Mezlocillin (p) (J01CA10)	16.4	14.8	11.7	7.2	7.3	4.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD72	Piperacillin (p) (J01CA12)	53.2	48.4	37.2	46.4	34.1	23.2	13.3	1.7	1.0	0.8	0.3	0.3	0.1	0.2	0.2
AD145	Temocillin (p) (J01CA17)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Variable name	Label (ATC code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
g3	**Beta-lactamase resistant penicillin (J01CF)**	**37.3**	**45.2**	**40.7**	**41.7**	**25.0**	**32.5**	**34.3**	**33.4**	**49.7**	**53.1**	**75.5**	**86.2**	**85.7**	**90.6**	**98.5**
AD2	Oxacillin (p) (J01CF04)	0.1	0.5	1.1	0.9	0.1	0.3	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0
AD1	Oxacillin (o) (J01CF04)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD56	Flucloxacillin (p) (J01CF05)	36.6	43.1	39.4	40.4	24.5	31.9	34.1	33.3	49.4	52.3	75.4	85.7	85.6	90.6	97.9
AD55	Flucloxacillin (o) (J01CF05)	0.6	1.6	0.2	0.4	0.1	0.3	0.2	0.1	0.3	0.8	0.0	0.5	0.1	0.1	0.6
AD64	Methicillin (p) (J01CF03)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD128	Dicloxacillin (p) (J01CF01)	0.0	0.0	0.1	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD129	Dicloxacillin (o) (J01CF01)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
g4	**Penicillin + lactamase inhibitors (J01CR) (pseudomonas efficacy excluded)**	**157.6**	**160.2**	**145.2**	**135.9**	**160.9**	**193.8**	**227.1**	**262.8**	**267.8**	**276.4**	**273.0**	**284.4**	**328.6**	**354.3**	**353.0**
AD25	Ampicillin-Sulbactam (p) (J01CR01)	76.5	91.2	81.2	59.2	69.0	83.7	107.6	136.9	128.8	123.8	121.8	134.5	162.7	171.1	173.7
AD105	Sultamicillin (o) (J01CR04)	2.0	3.5	2.3	2.3	1.9	2.2	0.6	2.5	2.3	8.9	2.0	2.0	1.4	1.4	1.4
AD87	Amoxicillin-Clavulanacid (p) (J01CR02)	25.1	15.8	10.9	18.1	15.3	17.2	11.5	0.4	0.3	0.8	0.2	0.1	0.4	1.6	1.0
AD26	Amoxicillin-Clavulanacid (o) (J01CR02)	13.0	7.4	6.2	6.3	3.8	3.4	2.8	1.3	1.0	1.7	1.6	3.0	2.5	4.4	4.0
AD24	Piperacillin-Tazobactam (p) (J01CR05)	41.0	42.3	44.6	50.0	71.0	87.3	104.6	121.7	135.3	141.2	147.4	144.8	161.6	175.8	173.0
g5	**Cephalosporines (1st generation) (J01DB)**	**39.2**	**32.8**	**28.5**	**34.1**	**28.6**	**35.5**	**38.1**	**35.3**	**36.7**	**33.5**	**32.2**	**35.4**	**40.2**	**40.9**	**37.0**
AD37	Cefazolin (p) (J01DB04)	39.2	32.7	28.5	33.8	28.4	35.4	38.1	35.3	36.5	33.1	32.1	35.3	40.0	40.5	36.8
AD106	Cefalexin (o) (J01DB01)	0.0	0.1	0.0	0.3	0.3	0.1	0.0	0.0	0.2	0.3	0.1	0.1	0.2	0.4	0.2
AD131	Cefadroxil (o) (J01DB05)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
g6	**Cephalosporines (2nd generation) (J01DC)**	**93.6**	**97.9**	**95.3**	**95.3**	**92.9**	**92.7**	**88.4**	**89.7**	**74.0**	**93.5**	**71.8**	**62.3**	**46.7**	**44.0**	**36.6**

Variable name	Label (ATC code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
AD36	Cefmandol (J01DC03)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD46	Cefuroxim (p) (J01DC02)	84.1	85.5	84.0	80.7	80.5	77.1	75.9	78.7	66.0	72.5	63.6	53.3	42.2	40.2	32.3
AD45	Cefuroxim-Axetil (o) (J01DC02)	5.4	10.5	7.6	11.7	11.4	15.3	12.1	10.9	7.8	20.7	7.7	7.4	4.2	3.5	3.9
AD41	Cefotiam (J01DC07)	3.8	1.8	3.7	2.8	0.9	0.4	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD42	Cefoxitin (J01DC01)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.9	0.0	0.0	0.0
AD108	Cefaclor (o) (J01DC04)	0.4	0.0	0.0	0.0	0.2	0.0	0.1	0.2	0.2	0.3	0.5	0.7	0.3	0.3	0.4
g7	**Cephalosporines (3rd generation) (J01DD)**	**124.0**	**111.8**	**111.6**	**122.6**	**117.7**	**115.1**	**109.2**	**98.8**	**91.2**	**99.3**	**92.1**	**99.3**	**83.3**	**81.6**	**75.6**
AD18	Cefotaxim (p) (J01DD01)	18.9	16.2	18.1	17.0	14.6	10.1	14.1	13.5	7.7	7.7	7.0	8.5	8.2	9.0	11.3
AD21	Ceftazidim (p) (J01DD02)	34.9	36.0	37.6	43.6	40.5	39.8	36.5	29.0	26.5	24.8	30.5	35.2	25.7	24.1	19.7
AD43	Ceftizoxime (p) (J01DD22)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD44	Ceftriaxon (p) (J01DD04)	69.7	59.3	55.5	61.8	62.3	64.8	58.4	56.0	56.7	65.8	54.3	53.9	47.0	45.2	41.5
AD140	Ceftibuten (J01DD14)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD40	Cefoperazon (J01DD32)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD39	Cefodizim (J01DD25)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD107	Cefixim (o) (J01DD08)	0.3	0.1	0.2	0.0	0.1	0.2	0.2	0.1	0.0	0.2	0.0	0.4	0.1	0.0	0.0
AD109	Cefpodoxin (o) (J01DD13)	0.1	0.2	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.8	0.2	0.7	0.4	0.7	0.5
AD146	Ceftazidim + beta-lactamase inhibitor (p) (J01DD52)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6	1.9	2.6	2.7
g7a	**Cephalosporines (4th generation) (J01DE)**	**10.8**	**10.2**	**4.1**	**4.0**	**4.3**	**4.8**	**14.8**	**14.6**	**6.3**	**8.6**	**10.7**	**16.4**	**16.3**	**16.1**	**21.5**
AD38	Cefepim (p) (J01DE24)	10.8	10.2	4.1	4.0	4.3	4.8	14.8	14.6	6.3	8.6	10.7	16.4	16.3	16.1	21.5

Variable name	Label (ATC code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
g8	**Carbapenems (J01DH)**	**120.2**	**132.8**	**142.9**	**167.7**	**184.1**	**213.5**	**230.7**	**233.1**	**248.3**	**244.7**	**266.4**	**245.2**	**278.1**	**304.3**	**339.9**
AD22	Imipenem (p) (J01DH51)	53.1	63.1	62.1	74.3	73.2	62.1	65.4	55.3	43.5	43.5	38.0	30.2	28.2	22.8	17.7
AD63	Meropenem (p) (J01DH02)	60.1	62.3	71.6	84.6	104.6	146.6	162.0	173.0	201.4	198.2	225.5	212.9	248.5	278.9	320.1
AD123	Ertapenem (p) (J01DH03)	6.9	7.3	9.3	7.0	4.9	4.2	3.3	4.8	3.4	2.9	3.0	2.1	1.3	2.6	2.0
AD135	Doripenem (p) (J01DH04)	0.0	0.0	0.0	1.8	1.3	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
g9	**Monobactams (J01DF)**	**1.2**	**0.6**	**0.4**	**0.4**	**0.6**	**0.2**	**0.4**	**0.5**	**0.1**	**0.3**	**0.2**	**0.2**	**0.5**	**0.3**	**0.2**
AD35	Aztreonam (p) (J01DF01)	1.2	0.6	0.4	0.4	0.6	0.2	0.4	0.5	0.1	0.1	0.2	0.0	0.1	0.3	0.2
AD143	Aztreonam (o) (J01DF01)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.4	0.0	0.0
g10	**Glycopeptides (J01XA)**	**40.3**	**37.9**	**36.2**	**45.6**	**61.5**	**54.3**	**56.6**	**59.2**	**62.4**	**58.2**	**64.7**	**58.6**	**64.1**	**77.2**	**89.3**
AD4	Vancomycin (p) (J01XA01)	37.6	34.8	34.1	44.6	59.7	53.1	53.5	54.2	59.6	55.0	59.3	57.0	55.8	54.7	70.2
AD3	Vancomycin (o) (J01XA01)	0.4	0.3	0.0	0.2	0.1	0.1	0.3	0.2	0.2	0.1	0.3	0.0	0.1	0.1	0.3
AD5	Teicoplanin (p) (J0XA02)	2.3	2.9	2.1	0.8	1.8	1.2	2.8	4.8	2.7	3.1	5.1	1.6	8.2	22.5	18.8
g11	**Fluorochinolones (J01MA)**	**172.3**	**168.7**	**164.6**	**170.7**	**171.6**	**184.5**	**183.6**	**160.5**	**152.2**	**172.1**	**167.3**	**157.2**	**128.9**	**88.9**	**90.2**
AD8	Ciprofloxacin (p) (J01MA02)	83.5	86.6	84.6	96.2	106.5	118.5	110.1	96.8	100.4	110.2	108.4	87.1	75.6	50.1	48.1
AD7	Ciprofloxacin (o) (J01MA02)	27.8	29.3	24.7	25.6	17.9	16.7	18.3	14.5	14.4	18.4	13.9	12.9	14.4	8.4	5.2
AD10	Ofloxacin (p) (J01MA01)	3.8	0.0	0.0	0.0	0.6	0.0	0.8	0.3	0.0	0.3	0.0	0.0	0.0	0.0	0.0
AD9	Ofloxacin (o) (J01MA01)	0.0	0.2	0.0	0.0	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD12	Levofloxacin (p) (J01MA12)	17.7	10.2	14.0	16.0	18.5	23.8	28.9	25.0	21.1	22.6	30.0	43.9	25.4	21.7	28.2
AD88	Levofloxacin (o) (J01MA12)	5.4	5.3	4.5	3.6	4.1	5.6	5.5	4.7	3.5	4.2	3.6	2.3	3.4	2.4	2.9

Variable name	Label (ATC code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
AD13	Grepafloxacin (J01MA11)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD14	Sparfloxacin (p) (J01MA09)	0.0	0.0	0.2	0.0	0.0	0.0	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD15	Moxifloxacin (p) (J01MA14)	15.6	20.3	21.0	18.8	15.7	14.2	14.4	14.0	8.8	10.7	7.1	8.2	7.9	4.6	4.0
AD116	Moxifloxacin (o) (J01MA14)	18.2	16.8	15.6	10.4	8.2	5.6	5.1	5.0	3.9	5.8	4.1	2.9	2.3	1.6	1.7
AD16	Norfloxacin (o) (J01MA06)	0.2	0.0	0.1	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1
AD89	Gatifloxacin (J01MA06)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
g12	**Sulfonamides and trimethoprim (J01E)**	**17.1**	**19.8**	**26.0**	**24.5**	**22.5**	**20.3**	**34.4**	**33.5**	**42.6**	**44.6**	**42.3**	**37.6**	**33.2**	**32.7**	**31.9**
AD133	Trimetoprim (p) (J01EA01)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD134	Trimetoprim(o) (J01EA01)	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD27_28	Trimethoprim/Sulfamethoxazol 40:8 (p) (J01EE01)	7.0	8.6	11.4	11.2	12.2	12.0	16.1	17.1	21.0	17.2	20.7	21.2	19.5	22.9	18.6
AD85_86	Trimethoprim/Sulfamethoxazol 40:8/80:16 (o) (J01EE01)	10.0	11.1	13.9	11.9	9.7	8.4	17.1	14.4	19.1	20.1	18.1	15.8	13.7	9.8	12.4
AD118	Tetroxoprim 100mg (o)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD119	Sulfadiazim 250mg (o) (J01EC02)	0.0	0.1	0.7	1.4	0.5	0.0	1.3	2.1	2.4	7.3	3.6	0.6	0.0	0.0	0.8
g14	**Tetracyclines (J01AA)**	**13.6**	**24.2**	**21.8**	**28.0**	**35.8**	**25.5**	**26.7**	**25.6**	**24.0**	**31.9**	**33.2**	**24.2**	**24.8**	**22.3**	**22.7**
AD54	Doxycyclin (p) (J01AA02)	3.5	5.1	2.5	3.5	10.7	3.3	3.1	2.8	2.5	4.2	4.4	2.1	3.5	1.8	2.4
AD53	Doxycyclin (o) (J01AA02)	6.4	5.6	5.7	8.0	3.3	4.4	6.7	5.1	7.5	7.4	8.1	6.5	6.6	5.0	4.7
AD78	Tetracyclin (p) (J01AA07)	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD77	Tetracyclin (o) (J01AA07)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD68	Minocyclin (p) (J01AA08)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Variable name	Label (ATC code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
AD67	Minocyclin (o) (J01AA08)	0.0	0.0	0.0	0.2	0.1	0.0	0.0	0.0	0.1	0.3	0.1	0.2	0.1	0.4	0.1
AD125	Tigecyclin (p) (J01AA12)	3.8	13.6	13.5	16.2	21.6	17.9	17.0	17.7	13.9	20.0	20.6	15.4	14.6	15.0	15.5
g16	**Macrolides (J01FA)**	**74.7**	**83.1**	**89.1**	**106.4**	**107.9**	**111.4**	**105.8**	**109.9**	**99.8**	**113.8**	**91.6**	**90.3**	**89.0**	**82.9**	**92.5**
AD20	Erythromycin (p) (J01FA01)	40.2	45.3	44.3	53.1	52.5	55.7	49.7	49.2	43.7	46.8	34.2	34.4	32.8	26.8	35.7
AD19	Erythromycin (o) (J01FA01)	1.5	2.3	1.5	1.7	0.8	0.9	3.8	3.2	2.3	2.1	1.3	0.6	0.6	0.4	0.7
AD114	Erythromycin-ethylsuccinat (o) (J01FA01)	0.1	0.1	0.2	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD75	Roxithromycin (o) (J01FA06)	3.2	5.1	6.2	6.9	3.4	3.7	3.4	2.4	4.7	10.5	2.6	2.6	2.8	1.5	2.1
AD115	Clarithromycin (p) (J01FA09)	10.9	11.7	14.4	18.9	27.5	32.4	28.5	34.7	31.3	29.6	30.8	30.7	30.3	32.3	34.7
AD49	Clarithromycin (o) (J01FA09)	18.3	17.9	20.8	25.0	22.1	17.5	18.9	18.8	16.2	21.2	20.5	19.0	18.0	17.1	13.1
AD33	Azithromycin (o) (J01FA10)	0.6	0.7	1.6	0.4	1.4	1.1	1.1	1.5	1.6	3.4	2.1	2.7	4.1	4.1	4.4
AD132	Azithromycin (p) (J01FA10)	0.0	0.0	0.0	0.2	0.1	0.1	0.3	0.2	0.1	0.2	0.1	0.3	0.4	0.6	1.7
g18	**Aminogklycosides (J01G)**	**29.8**	**28.1**	**25.2**	**27.6**	**32.6**	**29.2**	**28.8**	**24.4**	**26.1**	**29.0**	**33.7**	**29.8**	**35.6**	**35.7**	**39.3**
AD76	Streptomycin (p) (J01GA01)	0.0	0.2	0.0	0.1	0.1	0.5	0.5	0.1	0.3	0.2	0.1	0.0	0.0	0.0	0.0
AD81	Tobramycin (p) (J01GB01)	10.4	8.3	8.3	13.8	14.1	13.3	15.1	11.8	10.3	10.0	9.6	11.8	15.5	16.7	23.4
AD110	Tobramycin (kap) (J01GB01)	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD136	Tobramycin (inh) (J01GB01)	0.0	0.0	0.0	0.5	4.5	2.3	2.4	0.9	3.0	5.5	8.2	6.4	6.9	6.2	3.3
AD6	Gentamicin (p) (J01GB03)	16.9	16.7	15.9	12.4	13.2	12.1	9.9	10.4	11.4	13.0	15.1	11.5	13.0	12.6	12.4
AD60	Kanamycin (J01GB04)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD69	Neomycin (o) (J01GB05)	0.0	2.2	0.0	0.0	0.0	0.4	0.4	0.5	0.1	0.0	0.0	0.0	0.0	0.0	0.0

Variable name	Label (ATC code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
AD23	Amikacin (p) (J01GB06)	2.4	0.8	1.0	0.8	0.7	0.5	0.4	0.6	0.9	0.3	0.6	0.1	0.2	0.2	0.2
AD71	Netilmicin (p) (J01GB07)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
g21	**Imidazolderivates (J01XD)**	**66.6**	**59.6**	**51.4**	**48.3**	**46.4**	**47.3**	**48.0**	**45.2**	**41.2**	**48.2**	**39.8**	**36.5**	**32.7**	**29.1**	**24.6**
AD65	Metronidazol (p) (J01XD01)	61.7	53.9	46.6	45.0	43.3	44.5	44.4	42.1	38.7	44.9	38.5	35.0	31.6	28.1	23.8
AD91	Metronidazol (o) (J01XD01)	4.9	5.7	4.9	3.3	3.1	2.8	3.5	3.1	2.5	3.3	1.3	1.4	1.2	1.0	0.8
AD127	Tinidazol (o) (J01XD02)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
g22	**Other antibiotics (J01XX)**	**39.8**	**38.2**	**45.3**	**50.5**	**60.8**	**60.8**	**73.0**	**72.0**	**58.8**	**67.7**	**77.1**	**71.7**	**82.9**	**91.4**	**105.4**
AD57	Fosfomycin (p) (J01XX01)	6.2	4.7	8.1	9.4	13.4	4.4	9.6	11.1	9.4	11.6	8.9	12.4	11.4	16.5	19.3
AD141	Fosfomycin (o) (J01XX01)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.2	0.4	0.5	0.8	1.0
AD142	Nitroxolin (o) (J01XX07)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD111	Linezolid (p) (J01XX08)	27.2	23.8	28.0	33.0	33.3	43.7	40.8	39.1	30.8	37.1	44.3	40.0	45.3	48.9	51.9
AD112	Linezolid (o) (J01XX08)	4.5	2.9	3.6	2.2	2.2	1.4	1.5	2.6	2.4	1.6	2.0	1.7	2.0	1.4	2.2
AD126	Daptomycin (p) (J01XX09)	0.1	4.5	3.4	4.3	9.8	8.9	18.7	16.3	15.1	14.9	20.6	14.5	21.9	22.7	28.4
AD90	Paromomycin (o) (A07AA06))	2.0	2.3	2.1	1.7	1.9	2.1	1.8	2.4	1.3	1.2	0.4	0.4	0.5	0.5	0.1
AD120	Taurolidin (o) (B05CA05)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD121	Atovaquon (o) (P01AX06)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AD122	Nitrofurantoin (o) (J01XE01)	0.0	0.0	0.0	0.0	0.1	0.2	0.5	0.5	-0.1	0.8	0.7	2.3	1.3	0.6	2.5

Application forms: p = parenteral, o = oral, kap = capsule, inh = inhalative.

Appendix V

Pathogen rates of VRE. *faecium* and VRE. *faecalis*

Label	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Total E. *faecium*	1320	1406	1168	1223	1310	1509	1385	1624	1395	1534	1771	1819	1832	1780	1325
Total resistant VRE. *faecium*	38	47	92	84	95	175	134	215	133	231	361	399	563	693	478
Total tested E. f*aecium*	1306	1384	1149	1211	1300	1495	1376	1613	1364	1503	1756	1804	1818	1773	1308
Total E. *faecalis*	1707	1602	1360	1388	1313	1381	1620	1542	1245	1456	1559	1781	1510	1425	1064
Total resistant VRE. *faecalis*	0	1	3	0	4	3	5	11	8	0	1	1	7	3	1
Total tested E. *faecalis*	1682	1579	1337	1375	1291	1362	1539	1516	1209	1405	1542	1751	1480	1405	997

Resistance rates and resistance density of VRE. *faecium* and VRE. *faecalis*

Label	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	trend	95% CI	p*
VRE. *faecium* per 100 E. *faecalis* (RR)	2.9	3.4	8.0	6.9	7.3	11.7	9.7	13.3	9.8	15.4	20.6	22.1	31.0	39.1	36.5	**1.0174**	1.015-1.019	**<.0001**
VRE. *faecalis* per 100 E. *faecium* (RR)	0.0	0.1	0.2	0.0	0.3	0.2	0.3	0.7	0.7	0.0	0.1	0.1	0.5	0.2	0.1	1.0032	0.997-1.008	0.2236
VRE. *faecium* /1000 patient days (RD)	0.18	0.23	0.49	0.43	0.49	0.86	0.56	0.91	0.66	1.07	1.58	1.79	2.55	3.29	2.61	**1.0159**	1.013-1.015	**<.0001**
VRE. *faecalis* /1000 patient days (RD)	0.00	0.00	0.02	0.00	0.02	0.01	0.02	0.05	0.04	0.00	0.00	0.00	0.03	0.01	0.01	0.9979	0.997-1.007	0.2748

*Significance level of 5%; p=0.05

Appendix VI

Univariable analysis of antibiotic application density (AD = DDDs / 1.000 patient days) AND RR of VRE. *faecium*

Variable (incl. ATC-Code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	trend	95%CI	p*
Beta-lactamase sensitive penicillin (J01CE)	23.0	20.0	17.2	19.4	20.2	18.7	18.3	15.1	23.0	26.4	22.9	20.7	23.8	26.1	25.5	1.002	0.99-1.00	0.46
Broad-spectrum penicillin (J01CA)	100.9	103.4	81.6	89.2	66.6	60.7	47.5	33.6	36.5	38.9	39.6	64.4	57.7	60.0	65.6	0.998	0.99-1.00	0.601
Beta-lactamase resistant penicillin (J01CF)	37.3	45.2	40.7	41.7	25.0	32.5	34.3	33.4	49.7	53.1	75.5	86.2	85.7	90.6	98.5	**1.008**	1.00-1.01	**0.049**
Penicillin + lactamase inhibitors (J01CR)	157.6	160.2	145.2	135.9	160.9	193.8	227.1	262.8	267.8	276.4	273.0	284.4	328.6	354.3	353.0	**1.005**	1.00-1.01	**0.036**
Cephalosporines (1st Generation) (J01DB)	39.2	32.8	28.5	34.1	28.6	35.5	38.1	35.3	36.7	33.5	32.2	35.4	40.2	40.9	37.0	0.991	0.97-1.00	0.186
Cephalosporines (2nd generation) (J01DC)	93.6	97.9	95.3	95.3	92.9	92.7	88.4	89.7	74.0	93.5	71.8	62.3	46.7	44.0	36.6	**0.986**	0.97-0.99	**0.007**
Cephalosporines (3rd generation) (J01DD)	124.0	111.8	111.6	122.6	117.7	115.1	109.2	98.8	91.2	99.3	92.1	99.3	83.3	81.6	75.6	0.996	0.99-1.00	0.295
Cephalosporines (4th generation) (J01DE)	10.8	10.2	4.1	4.0	4.3	4.8	14.8	14.6	6.3	8.6	10.7	16.4	16.3	16.1	21.5	1.013	0.99-1.03	0.103
Carbapenems (J01DH)	120.2	132.8	142.9	167.7	184.1	213.5	230.7	233.1	248.3	244.7	266.4	245.2	278.1	304.3	339.9	**1.01**	1.00-1.01	**<.0001**
Monobactams (J01DF)	1.2	0.6	0.4	0.4	0.6	0.2	0.4	0.5	0.1	0.3	0.2	0.2	0.5	0.3	0.2	0.969	0.88-1.06	0.517
Glycopeptides (J01XA)	40.3	37.9	36.2	45.6	61.5	54.3	56.6	59.2	62.4	58.2	64.7	58.6	64.1	77.2	89.3	**1.019**	1.00-1.03	**0.005**
Fluoroquinolones (J01MA)	172.3	168.7	164.6	170.7	171.6	184.5	183.6	160.5	152.2	172.1	167.3	157.2	128.9	88.9	90.2	0.994	0.98-1.00	0.056
Sulfonamides and trimethoprim (J01E)	17.1	19.8	26.0	24.5	22.5	20.3	34.4	33.5	42.6	44.6	42.3	37.6	33.2	32.7	31.9	1.006	0.99-1.01	0.075
Tetracyclines (J01AA)	13.6	24.2	21.8	28.0	35.8	25.5	26.7	25.6	24.0	31.9	33.2	24.2	24.8	22.3	22.7	1.002	0.99-1.00	0.274
Macrolides (J01FA)	74.7	83.1	89.1	106.4	107.9	111.4	105.8	109.9	99.8	113.8	91.6	90.3	89.0	82.9	92.5	1.00	0.99-1.00	0.862
Aminoglycosides (J01G)	29.8	28.1	25.2	27.6	32.6	29.2	28.8	24.4	26.1	29.0	33.7	29.8	35.6	35.7	39.3	**1.014**	1.00-1.02	**0.007**
Imidazolderivates (J01XD)	66.6	59.6	51.4	48.3	46.4	47.3	48.0	45.2	41.2	48.2	39.8	36.5	32.7	29.1	24.6	0.983	0.96-1.00	0.098
Other antibiotics (J01XX)	39.8	38.2	45.3	50.5	60.8	60.8	73.0	72.0	58.8	67.7	77.1	71.7	82.9	91.4	105.4	**1.013**	1.00-1.02	**0.0005**

*Significance level of 5%; p=0.05

Univariable analysis of antibiotic application density (AD = DDDs / 1.000 patient days) AND RD of VRE. *faecium*

Variable (incl. ATC-Code)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	trend	95%CI	p*
Beta-lactamase sensitive penicillin (J01CE)	23.0	20.0	17.2	19.4	20.2	18.7	18.3	15.1	23.0	26.4	22.9	20.7	23.8	26.1	25.5	1.004	0.99-1.01	0.288
Broad-spectrum penicillin (J01CA)	100.9	103.4	81.6	89.2	66.6	60.7	47.5	33.6	36.5	38.9	39.6	64.4	57.7	60.0	65.6	0.999	0.99-1.00	0.77
Beta-lactamase resistant penicillin (J01CF)	37.3	45.2	40.7	41.7	25.0	32.5	34.3	33.4	49.7	53.1	75.5	86.2	85.7	90.6	98.5	1.004	0.99-1.01	0.083
Penicillin + lactamase inhibitors (J01CR)	157.6	160.2	145.2	135.9	160.9	193.8	227.1	262.8	267.8	276.4	273.0	284.4	328.6	354.3	353.0	**1.005**	1.00-1.00	**0.0029**
Cephalosporines (1st Generation) (J01DB)	39.2	32.8	28.5	34.1	28.6	35.5	38.1	35.3	36.7	33.5	32.2	35.4	40.2	40.9	37.0	0.998	0.98-1.01	0.784
Cephalosporines (2nd generation) (J01DC)	93.6	97.9	95.3	95.3	92.9	92.7	88.4	89.7	74.0	93.5	71.8	62.3	46.7	44.0	36.6	**0.989**	0.98-0.99	**0.016**
Cephalosporines (3rd generation) (J01DD)	124.0	111.8	111.6	122.6	117.7	115.1	109.2	98.8	91.2	99.3	92.1	99.3	83.3	81.6	75.6	0.997	0.99-1.00	0.332
Cephalosporines (4th generation) (J01DE)	10.8	10.2	4.1	4.0	4.3	4.8	14.8	14.6	6.3	8.6	10.7	16.4	16.3	16.1	21.5	1.01	0.99-1.02	0.142
Carbapenems (J01DH)	120.2	132.8	142.9	167.7	184.1	213.5	230.7	233.1	248.3	244.7	266.4	245.2	278.1	304.3	339.9	**1.013**	1.00-1.01	**<.0001**
Monobactams (J01DF)	1.2	0.6	0.4	0.4	0.6	0.2	0.4	0.5	0.1	0.3	0.2	0.2	0.5	0.3	0.2	0.94	0.85-1.03	0.20
Glycopeptides (J01XA)	40.3	37.9	36.2	45.6	61.5	54.3	56.6	59.2	62.4	58.2	64.7	58.6	64.1	77.2	89.3	**1.02**	1.01-1.02	**<.0001**
Fluoroquinolones (J01MA)	172.3	168.7	164.6	170.7	171.6	184.5	183.6	160.5	152.2	172.1	167.3	157.2	128.9	88.9	90.2	0.996	0.99-1.00	0.08
Sulfonamides and trimethoprim (J01E)	17.1	19.8	26.0	24.5	22.5	20.3	34.4	33.5	42.6	44.6	42.3	37.6	33.2	32.7	31.9	1.003	0.99-1.01	0.264
Tetracyclines (J01AA)	13.6	24.2	21.8	28.0	35.8	25.5	26.7	25.6	24.0	31.9	33.2	24.2	24.8	22.3	22.7	**1.01**	1.00-1.01	**<.0001**
Macrolides (J01FA)	74.7	83.1	89.1	106.4	107.9	111.4	105.8	109.9	99.8	113.8	91.6	90.3	89.0	82.9	92.5	1.002	0.99-1.00	0.302
Aminoglycosides (J01G)	29.8	28.1	25.2	27.6	32.6	29.2	28.8	24.4	26.1	29.0	33.7	29.8	35.6	35.7	39.3	**1.014**	1.00-1.02	**<.0001**
Imidazolderivates (J01XD)	66.6	59.6	51.4	48.3	46.4	47.3	48.0	45.2	41.2	48.2	39.8	36.5	32.7	29.1	24.6	1.01	0.99-1.02	0.109
Other antibiotics (J01XX)	39.8	38.2	45.3	50.5	60.8	60.8	73.0	72.0	58.8	67.7	77.1	71.7	82.9	91.4	105.4	**1.021**	1.01-1.02	**<.0001**

*Significance level of 5%; p=0.05

Appendix VII

Extensive Output of multivariate GLM of RR, RD of VRE and VSE in correlation to AD (incl. confounders)

Tabelle: Multivariable Analyse der Inzidenzdichten für VREKM, und VREKS.

Endpunkt	Parameter	Parameter	Category	IRR	95%CI	p-value
		Parsimonious model				
ID_VREKM	t	Time trend (linear)	per month	1.015	1.012-1.017	<.0001
ID_VREKM	g8	Carbapeneme (J01DH)	per 1 DDD/100 pd	1.009	1.006-1.013	<.0001
ID_VREKM	g10	Glykopeptide (J01XA)	per 1 DDD/100 pd	1.009	1.002-1.015	0.0090
		Model adjusted by confounders				
ID_VREKM	t	Time trend (linear)	per month	1.015	1.012-1.017	<.0001
ID_VREKM	FB3	Type of ICU	medical	0.949	0.655-1.376	0.7840
ID_VREKM	FB3		surgical	1.061	0.694-1.62	0.7858
ID_VREKM	FB3		interdisciplinary	1=reference		
ID_VREKM	KRHType	Type of hospital	*maximum care*	1.460	0.856-2.49	0.1646
ID_VREKM	KRHType		Other	1=reference		
ID_VREKM	g8	Carbapeneme (J01DH)	per 1 DDD/100 pd	1.009	1.005-1.012	<.0001
ID_VREKM	g10	Glykopeptide (J01XA)	per 1 DDD/100 pd	1.007	1-1.013	0.0420
		Model with time as categorical parameter				
ID_VREKM	jahr	Year	2007	1.448	0.664-3.158	0.3524
ID_VREKM	jahr		2008	2.509	1.173-5.362	0.0177
ID_VREKM	jahr		2009	2.705	1.372-5.334	0.0041
ID_VREKM	jahr		2010	2.602	1.295-5.231	0.0073
ID_VREKM	jahr		2011	4.415	2.342-8.322	<.0001
ID_VREKM	jahr		2012	3.050	1.541-6.038	0.0014
ID_VREKM	jahr		2013	4.736	2.395-9.367	<.0001
ID_VREKM	jahr		2014	3.526	1.887-6.592	<.0001
ID_VREKM	jahr		2015	5.679	2.981-10.818	<.0001
ID_VREKM	jahr		2016	8.025	4.385-14.684	<.0001
ID_VREKM	jahr		2017	9.867	5.211-18.684	<.0001
ID_VREKM	jahr		2018	12.329	6.43-23.637	<.0001
ID_VREKM	jahr		2019	16.739	8.457-33.131	<.0001
ID_VREKM	jahr		2020	12.136	6.183-23.82	<.0001
ID_VREKM	jahr		2006	1.000	1-1	0.0000
ID_VREKM	FB3	Type of ICU	medical	0.956	0.667-1.373	0.8091
ID_VREKM	FB3		surgical	1.080	0.713-1.637	0.7151
ID_VREKM	FB3		interdisciplinary	1=reference		
ID_VREKM	KRHType	Type of hospital	Maximal	1.428	0.84-2.428	0.1884
ID_VREKM	KRHType		Other	1=reference		
ID_VREKM	g8	Carbapeneme (J01DH)	per 1 DDD/100 pd	1.009	1.006-1.012	<.0001
ID_VREKM	g10	Glykopeptide (J01XA)	per 1 DDD/100 pd	1.007	1.001-1.014	0.0225
		Model with lag of AB use				
ID_VREKM	t	Time trend (linear)	per month	1.014	1.012-1.016	<.0001
ID_VREKM	g8	Carbapeneme (J01DH) in the current month	per 1 DDD/100 pd	1.008	1.005-1.012	<.0001
ID_VREKM	g10	Glykopeptide (J01XA) in the current month	per 1 DDD/100 pd	1.007	1.001-1.013	0.0211
ID_VREKM	g8lag1	Carbapeneme (J01DH) in the month before the current month	per 1 DDD/100 pd	1.006	1.002-1.009	0.0011
		Parsimonious model				
ID_VREKS	t	Time trend (linear)	per month	1.003	0.998-1.008	0.2160
ID_VREKS	g1	Beta-Lactamase sensitive Penicilline (J01CE)	per 1 DDD/100 pd	0.880	0.81-0.956	0.0025
		Model adjusted by confounders				
ID_VREKS	t	Time trend (linear)	per month	1.003	0.997-1.008	0.3308
ID_VREKS	FB3	Type of ICU	medical	0.831	0.297-2.329	0.7250
ID_VREKS	FB3		surgical	1.215	0.479-3.08	0.6816
ID_VREKS	FB3		interdisciplinary	1=reference		
ID_VREKS	KRHType	Type of hospital	Maximal	0.508	0.128-2.018	0.3358
ID_VREKS	KRHType		Other	1=reference		
ID_VREKS	g1	Beta-Lactamase sensitive Penicilline (J01CE)	per 1 DDD/100 pd	0.888	0.822-0.96	0.0028

Effekt der AB-Anwendungsdichten im Modell ist per 1DDD/100Patiententage;

Tabelle: Multivariable Analyse der Resistenzraten für VREKM und VREKS.

Endpunkt	Parameter	Parameter	Category	IRR	95%CI	p-value
		Parsimonious model				
RR_VREKM	t	Time trend (linear)	per month	1.017	1.015-1.019	<.0001
RR_VREKM	g10	Glykopeptide (J01XA)	per 1 DDD/100 pd	1.015	1.004-1.028	0.0112
RR_VREKM	g18	Aminoglykoside (J01G)	per 1 DDD/100 pd	1.014	1.004-1.024	0.0045
		Model adjusted by confounders				
RR_VREKM	t	Time trend (linear)	per month	1.017	1.015-1.019	<.0001
RR_VREKM	FB3	Type of ICU	medical	1.295	0.73-2.299	0.3766
RR_VREKM	FB3		surgical	1.079	0.602-1.936	0.7980
RR_VREKM	FB3		interdisciplinary	1=reference		
RR_VREKM	KRHType	Type of hospital	Maximum care	1.178	0.588-2.358	0.6437
RR_VREKM	KRHType		Other	1=reference		
RR_VREKM	g10	Glykopeptide (J01XA)	per 1 DDD/100 pd	1.014	1.003-1.026	0.0156
RR_VREKM	g18	Aminoglykoside (J01G)	per 1 DDD/100 pd	1.014	1.004-1.023	0.0045
		Model with time as categorical parameter				
RR_VREKM	jahr	Year	2007	1.131	0.496-2.58	0.7695
RR_VREKM	jahr		2008	2.294	1.029-5.115	0.0423
RR_VREKM	jahr		2009	2.571	1.247-5.299	0.0105
RR_VREKM	jahr		2010	2.068	1.012-4.226	0.0464
RR_VREKM	jahr		2011	3.857	1.966-7.566	<.0001
RR_VREKM	jahr		2012	3.405	1.703-6.81	0.0005
RR_VREKM	jahr		2013	4.977	2.48-9.986	<.0001
RR_VREKM	jahr		2014	3.605	1.888-6.882	0.0001
RR_VREKM	jahr		2015	5.718	2.866-11.409	<.0001
RR_VREKM	jahr		2016	7.807	4.174-14.6	<.0001
RR_VREKM	jahr		2017	9.105	4.805-17.251	<.0001
RR_VREKM	jahr		2018	12.824	6.8-24.182	<.0001
RR_VREKM	jahr		2019	19.557	10.021-38.169	<.0001
RR_VREKM	jahr		2020	15.721	7.724-31.996	<.0001
RR_VREKM	jahr		2006	1.000	1-1	0.0000
RR_VREKM	FB3	Type of ICU	medical	1.304	0.74-2.298	0.3582
RR_VREKM	FB3		surgical	1.088	0.611-1.937	0.7754
RR_VREKM	FB3		interdisciplinary	1=reference		
RR_VREKM	KRHType	Type of hospital	Maximum care	1.153	0.577-2.305	0.6867
RR_VREKM	KRHType		Other	1=reference		
RR_VREKM	g10	Glykopeptide (J01XA)	per 1 DDD/100 pd	1.016	1.003-1.028	0.0127
RR_VREKM	g18	Aminoglykoside (J01G)	per 1 DDD/100 pd	1.014	1.004-1.024	0.0047
		Model with lag of AB use				
RR_VREKM	t	Time trend (linear)	per month	1.017	1.014-1.019	<.0001
RR_VREKM	g10	Glykopeptide (J01XA) in the current month	per 1 DDD/100 pd	1.013	1.004-1.022	0.0045
RR_VREKM	g18	Aminoglykoside (J01G) in the current month	per 1 DDD/100 pd	1.012	1.003-1.021	0.0106
RR_VREKM	g10lag1	Glykopeptide (J01XA) in the month before the current month	per 1 DDD/100 pd	1.015	1.008-1.023	<.0001
RR_VREKM	g2lag1	Penicilline mit erweitertem Spektrum (J01CA) in the month before the current month	per 1 DDD/100 pd	1.005	1-1.01	0.0330
		Parsimonious model				
RR_VREKS	t	Time trend (linear)	per month	1.003	0.998-1.009	0.2182
RR_VREKS	g1	Beta-Lactamase sensitive Penicilline (J01CE)	per 1 DDD/100 pd	0.916	0.869-0.964	0.0008
		Model adjusted by confounders				
RR_VREKS	t	Time trend (linear)	per month	1.003	0.998-1.009	0.2670
RR_VREKS	FB3	Type of ICU	medical	1.107	0.417-2.939	0.8381
RR_VREKS	FB3		surgical	1.267	0.513-3.132	0.6077
RR_VREKS	FB3		interdisciplinary	1=reference		
RR_VREKS	KRHType	Type of hospital	Maximum care	0.449	0.143-1.414	0.1713
RR_VREKS	KRHType		Other	1=reference		
RR_VREKS	g1	Beta-Lactamase sensitive Penicilline (J01CE)	per 1 DDD/100 pd	0.917	0.874-0.961	0.0004

Effekt der AB-Anwendungsdichten im Modell ist per 1DDD/100Patiententage;

Extensive Output of univariate GLM of RR, RD of VRE and VSE in correlation to AD

Tabelle: Univariable Analyse der Inzidenzdichten für VREKM, VSEKM und VREKS und VSEKS.

		ID	ID	ID	ID	ID	ID	ID	ID	ID	ID	ID	ID	ID	ID	ID	ID
		VREKM	VREKM	VREKM	VREKM	VSEKM	VSEKM	VSEKM	VSEKM	VREKS	VREKS	VREKS	VREKS	VSEKS	VSEKS	VSEKS	VSEKS
Parameter m	category	IRR	95%CI_L	95%CI_U	p	IRR	95%CI_L	95%CI_U	p	IRR	95%CI_L	95%CI_U	p	IRR	95%CI_L	95%CI_U	p
ICU type	medical	1.1995	0.7982	1.8026	0.3813	0.8672	0.5630	1.3357	0.5179	0.5576	0.1593	1.9523	0.3610	0.7991	0.5726	1.1152	0.1872
	surgical	1.2940	0.7969	2.1013	0.2973	1.1268	0.7401	1.7154	0.5777	0.8217	0.2530	2.6693	0.7439	0.9545	0.6985	1.3043	0.7700
	interdisciplinary	1=ref				1=ref				1=ref				1=ref			
KRHType	Maximum care	1.6735	0.9254	3.0262	0.0885	1.1857	0.7965	1.7651	0.4015	0.4848	0.1169	2.0107	0.3185	0.9704	0.6569	1.4335	0.8799
	other	1=ref				1=ref				1=ref				1=ref			
Hospital size	>=600 beds	1.4112	0.8677	2.2952	0.1651	1.1813	0.8254	1.6907	0.3623	1.4509	0.4610	4.5665	0.5247	0.8811	0.6617	1.1733	0.3863
	<600 beds	1=ref				1=ref				1=ref				1=ref			
ICU size	>=12 beds	0.9097	0.6162	1.3432	0.6342	1.1862	0.8605	1.6351	0.2971	0.6907	0.2543	1.8755	0.4678	1.3090	1.0257	1.6705	**0.0305**
	<12 beds	1=ref				1=ref				1=ref				1=ref			
Time trend linear	(per month)	**1.0159**	**1.0135**	**1.0183**	**<.0001**	0.9990	0.9974	1.0006	0.2002	1.0027	0.9979	1.0075	0.2748	0.9992	0.9975	1.0008	0.3338
Time categorical	2007	**1.4271**	**0.6485**	**3.1403**	**0.3768**	1.0944	0.8597	1.3931	0.464	1.09E+10				0.9295	0.8311	1.0395	0.2003
jahr	2008	**2.4830**	**1.1386**	**5.4146**	**0.0222**	1.0345	0.8683	1.2327	0.704	3.07E+10				0.9117	0.7869	1.0563	0.2184
jahr	2009	**2.8460**	**1.4063**	**5.7597**	**0.0036**	0.9800	0.7859	1.2220	0.8575	5.29E-01				0.8997	0.7564	1.0702	0.2327
jahr	2010	**2.8092**	**1.3598**	**5.8035**	**0.0053**	1.0358	0.8310	1.2910	0.7543	4.75E+10				0.7834	0.6383	0.9615	**0.0195**
jahr	2011	**4.8035**	**2.4747**	**9.3239**	**<.0001**	1.1294	0.8776	1.4536	0.3445	3.51E+10				0.8133	0.6606	1.0011	0.0513
jahr	2012	**3.3977**	**1.6802**	**6.8709**	**0.0007**	0.9198	0.6874	1.2307	0.5735	5.23E+10				0.7959	0.6198	1.0221	0.0737
jahr	2013	**5.3815**	**2.6404**	**10.9683**	**<.0001**	1.0191	0.7697	1.3495	0.8947	1.07E+11				0.7691	0.5977	0.9895	**0.0412**
jahr	2014	**4.0664**	**2.0991**	**7.8778**	**<.0001**	1.0147	0.7729	1.3322	0.9164	8.08E+10				0.7595	0.6017	0.9587	**0.0206**
jahr	2015	**6.3718**	**3.2163**	**12.6235**	**<.0001**	1.0139	0.7644	1.3448	0.9236	4.85E-01				0.8281	0.6454	1.0626	0.1382
jahr	2016	**9.5551**	**5.0847**	**17.9561**	**<.0001**	1.0085	0.7914	1.2851	0.9457	8.86E+09				0.8359	0.6591	1.0600	0.1391
jahr	2017	**11.1376**	**5.7113**	**21.7196**	**<.0001**	1.0161	0.7779	1.3272	0.907	9.42E+09				0.9706	0.7679	1.2268	0.8030
jahr	2018	**14.3047**	**7.3229**	**27.9433**	**<.0001**	0.9531	0.7390	1.2293	0.7116	6.31E+10				0.8129	0.6398	1.0329	0.0901
jahr	2019	**19.8269**	**9.7313**	**40.3958**	**<.0001**	0.8701	0.6701	1.1297	0.2962	2.93E+10				0.8568	0.6654	1.1034	0.2312
jahr	2020	**15.3567**	**7.5853**	**31.0904**	**<.0001**	0.8372	0.6240	1.1232	0.2359	1.19E+10				0.7114	0.5319	0.9516	**0.0218**
jahr	2006	1=ref				1=ref				1=ref				1=ref			
alleos	Gesamt ohne Sulbactam (J01)	**1.0034**	**1.0024**	**1.0043**	**<.0001**	1.0008	1.0003	1.0013	**0.0016**	1.0039	1.0006	1.0072	**0.0201**	1.0003	0.9997	1.0010	0.2965
g1	Beta-Lactamase sensitive Penicilline (J01CE)	1.0043	0.9964	1.0122	0.2885	0.9995	0.9956	1.0034	0.7954	0.8825	0.8124	0.9588	**0.0031**	0.9973	0.9944	1.0002	0.0638
g2	Penicilline mit erweitertem Spektrum (J01CA)	0.9990	0.9926	1.0055	0.77	1.0012	0.9987	1.0037	0.3441	0.9889	0.9263	1.0556	0.7367	1.0038	1.0016	1.0059	**0.0006**
g3	Beta-Lactamase resistente Penicilline (J01CF)	1.0047	0.9994	1.0101	0.0839	0.9970	0.9931	1.0008	0.1237	0.9965	0.9540	1.0410	0.8755	0.9978	0.9948	1.0007	0.1374
g4a	beta-Lactamaseinhibitor (J01CG)	**0.9887**	**0.9814**	**0.9961**	**0.0028**	1.0029	1.0004	1.0055	**0.0251**	0.9646	0.9139	1.0182	0.1913	1.0036	0.9998	1.0073	0.0629
g4	Kombination von Penicillinen mit Beta-Lactamase-Inhibitor ohne Pseudomonaswirksamkeit (J01CR)	**1.0052**	**1.0018**	**1.0087**	**0.0029**	1.0001	0.9980	1.0023	0.9084	1.0199	1.0110	1.0289	**<.0001**	1.0009	0.9980	1.0038	0.5628
g5	1. Generation Cephalosporin (J01DB)	0.9983	0.9862	1.0105	0.7843	1.0025	0.9951	1.0101	0.506	1.0006	0.9411	1.0639	0.9835	1.0057	0.9995	1.0118	0.0697
g6	2. Generation Cephalosporin (J01DC)	**0.9893**	**0.9807**	**0.9980**	**0.0161**	0.9978	0.9935	1.0021	0.3066	1.0140	1.0003	1.0280	**0.0459**	1.0041	1.0003	1.0078	**0.0324**

jahr	2015	**6.3718**	**3.2163**	**12.6235**	**<.0001**	1.0139	0.7644	1.3448	0.9236	4.85E-01				0.8281	0.6454	1.0626	0.1382
jahr	2016	**9.5551**	**5.0847**	**17.9561**	**<.0001**	1.0085	0.7914	1.2851	0.9457	8.86E+09				0.8359	0.6591	1.0600	0.1391
jahr	2017	**11.1376**	**5.7113**	**21.7196**	**<.0001**	1.0161	0.7779	1.3272	0.907	9.42E+09				0.9706	0.7679	1.2268	0.8030
jahr	2018	**14.3047**	**7.3229**	**27.9433**	**<.0001**	0.9531	0.7390	1.2293	0.7116	6.31E+10				0.8129	0.6398	1.0329	0.0901
jahr	2019	**19.8269**	**9.7313**	**40.3958**	**<.0001**	0.8701	0.6701	1.1297	0.2962	2.93E+10				0.8568	0.6654	1.1034	0.2312
jahr	2020	**15.3567**	**7.5853**	**31.0904**	**<.0001**	0.8372	0.6240	1.1232	0.2359	1.19E+10				0.7114	0.5319	0.9516	**0.0218**
jahr	2006	1=ref				1=ref				1=ref				1=ref			
alleos	Gesamt ohne Sulbactam (J01)	**1.0034**	**1.0024**	**1.0043**	**<.0001**	1.0008	1.0003	1.0013	**0.0016**	1.0039	1.0006	1.0072	**0.0201**	1.0003	0.9997	1.0010	0.2965
g1	Beta-Lactamase sensitive Penicilline (J01CE)	1.0043	0.9964	1.0122	0.2885	0.9995	0.9956	1.0034	0.7954	0.8825	0.8124	0.9588	**0.0031**	0.9973	0.9944	1.0002	0.0638
g2	Penicilline mit erweitertem Spektrum (J01CA)	0.9990	0.9926	1.0055	0.77	1.0012	0.9987	1.0037	0.3441	0.9889	0.9263	1.0556	0.7367	1.0038	1.0016	1.0059	**0.0006**
g3	Beta-Lactamase resistente Penicilline (J01CF)	1.0047	0.9994	1.0101	0.0839	0.9970	0.9931	1.0008	0.1237	0.9965	0.9540	1.0410	0.8755	0.9978	0.9948	1.0007	0.1374
g4a	beta-Lactamaseinhibitor (J01CG)	**0.9887**	**0.9814**	**0.9961**	**0.0028**	1.0029	1.0004	1.0055	**0.0251**	0.9646	0.9139	1.0182	0.1913	1.0036	0.9998	1.0073	0.0629
g4	Kombination von Penicillinen mit Beta-Lactamase-Inhibitor ohne Pseudomonaswirksamkeit (J01CR)	**1.0052**	**1.0018**	**1.0087**	**0.0029**	1.0001	0.9980	1.0023	0.9084	1.0199	1.0110	1.0289	**<.0001**	1.0009	0.9980	1.0038	0.5628
g5	1. Generation Cephalosporin (J01DB)	0.9983	0.9862	1.0105	0.7843	1.0025	0.9951	1.0101	0.506	1.0006	0.9411	1.0639	0.9835	1.0057	0.9995	1.0118	0.0697
g6	2. Generation Cephalosporin (J01DC)	**0.9893**	**0.9807**	**0.9980**	**0.0161**	0.9978	0.9935	1.0021	0.3066	1.0140	1.0003	1.0280	**0.0459**	1.0041	1.0003	1.0078	**0.0324**
g20	Steroid (J01XC)	0.0000				1.2563	1.0713	1.4733	**0.005**	0.0000				1046560.6714	754263.1701	1452131.4078	<.0001
g21	Imidazolderivate (J01XD)	1.0107	0.9976	1.0240	0.1092	1.0146	1.0072	1.0220	**0.0001**	1.0426	0.9799	1.1093	0.1871	1.0174	1.0105	1.0243	<.0001
g23	Tuberkulostatika (J01A)	**1.0069**	**1.0020**	**1.0118**	**0.0059**	0.9956	0.9918	0.9994	**0.0249**	0.9607	0.9110	1.0132	0.1395	0.9968	0.9935	1.0002	0.0618
g22	Andere Antibiotika (J01XX)	**1.0210**	**1.0131**	**1.0290**	**<.0001**	1.0104	1.0056	1.0153	<.0001	1.0060	0.9630	1.0510	0.7878	1.0025	0.9986	1.0064	0.2043

Effekt der AB-Anwendungsdichten im Modell ist per 1DDD/100Patiententage;

Extensive Output of univariate GLM of RR, RD of VRE and VSE in correlation to AD

Tabelle: Univariable Analyse der Resistenzraten für VREKM und VREKS.

		RR_VREKM	RR_VREKM	RR_VREKM	RR_VREKM	RR_VREKS	RR_VREKS	RR_VREKS	RR_VREKS
Parameterm	category	IRR	95%CI_L	95%CI_U	p	IRR	95%CI_L	95%CI_U	p
ICU type	medical	1.3394	0.7258	2.4715	0.3499	0.7900	0.2533	2.4646	0.6847
	surgical	1.1078	0.6074	2.0205	0.7385	0.8669	0.2850	2.6363	0.8012
	interdisciplinary	1=ref.				1=ref.			
KRHType	Maximum care	1.4140	0.7407	2.6991	0.2936	0.4879	0.1424	1.6711	0.2532
	sonst	1=ref.				1=ref.			
Hospital size	>=600 beds	1.3271	0.7942	2.2175	0.2800	1.5859	0.5301	4.7452	0.4095
	<600 beds	1=ref.				1=ref.			
ICU size	>=12 beds	0.7549	0.4794	1.1887	0.2248	0.5017	0.2028	1.2412	0.1356
	<12 beds	1=ref.				1=ref.			
Time trend linear	(per month)	1.0174	1.0150	1.0198	**<.0001**	1.0032	0.9979	1.0086	0.2336
Time categorical	2007	1.1068	0.4790	2.5574	0.8124	1.13E+10			
jahr	2008	2.1195	0.9437	4.7605	0.0688	3.91E+10			
jahr	2009	2.5114	1.2120	5.2039	**0.0132**	1.08E+00			
jahr	2010	2.2688	1.0889	4.7274	**0.0287**	5.49E+10			
jahr	2011	3.7723	1.8876	7.5390	**0.0002**	3.83E+10			
jahr	2012	3.3130	1.6363	6.7077	**0.0009**	5.54E+10			
jahr	2013	4.8446	2.4090	9.7426	**<.0001**	1.22E+11			
jahr	2014	3.6306	1.8841	6.9961	**0.0001**	1.11E+11			
jahr	2015	5.4630	2.7137	10.9977	**<.0001**	1.19E+00			
jahr	2016	7.7691	4.1211	14.6462	**<.0001**	1.08E+10			
jahr	2017	8.9630	4.7246	17.0037	**<.0001**	9.54E+09			
jahr	2018	12.8513	6.8617	24.0692	**<.0001**	7.93E+10			
jahr	2019	20.0116	10.2478	39.0778	**<.0001**	3.57E+10			
jahr	2020	16.8345	8.2691	34.2725	**<.0001**	1.68E+10			
jahr	2006	1=ref.				1=ref.			
alleos	Gesamt ohne Sulbactam (J01)	1.0027	1.0016	1.0039	**<.0001**	1.0021	0.9996	1.0047	0.1016
g1	Beta-Lactamase sensitive Penicilline (J01CE)	1.0026	0.9956	1.0097	0.4607	0.9169	0.8709	0.9653	**0.0010**
g2	Penicilline mit erweitertem Spektrum (J01CA)	0.9983	0.9919	1.0047	0.6016	0.9855	0.9316	1.0425	0.6105
g3	Beta-Lactamase resistente Penicilline (J01CF)	1.0081	1.0000	1.0163	**0.0496**	1.0048	0.9658	1.0453	0.8132
g4a	beta-Lactamaseinhibitor (J01CG)	0.9829	0.9760	0.9899	**<.0001**	0.9577	0.9056	1.0129	0.1304
g4	Kombination von Penicillinen mit BLI ohne Pseudomonaswirksamkeit (J01CR)	1.0055	1.0004	1.0107	**0.0360**	1.0081	1.0009	1.0153	**0.0281**
g5	1. Generation Cephalosporin (J01DB)	0.9913	0.9785	1.0042	0.1862	0.9902	0.9266	1.0582	0.7714
g6	2. Generation Cephalosporin (J01DC)	0.9865	0.9766	0.9964	**0.0079**	1.0018	0.9874	1.0165	0.8039
g7	3. Generation Cephalosporin (J01DD)	0.9968	0.9907	1.0028	0.2959	0.9764	0.9445	1.0093	0.1581
g7a	4. Generation Cephalosporin (J01DE)	1.0137	0.9972	1.0305	0.1037	1.0185	0.9652	1.0747	0.5040
g8	Carbapeneme (J01DH)	**1.0102**	**1.0057**	**1.0147**	**<.0001**	1.0154	0.9993	1.0319	0.0613
g9	Monobactame (J01DF)	0.9696	0.8831	1.0646	0.5176	0.9928	0.6582	1.4973	0.9723
g9a	Andere Cephalosporine und Peneme (J01DI)	1.0950	0.9753	1.2294	0.1242	0.6955	0.4992	0.9691	**0.0319**
g10	Glykopeptide (J01XA)	1.0195	1.0057	1.0334	**0.0054**	1.0155	0.9989	1.0324	0.0674
AD4	Vancomycin (p) (J01XA01)	1.0214	1.0055	1.0376	**0.0082**	1.0110	0.9889	1.0335	0.3332
AD3	Vancomycin (o) (J01XA01)	0.9519	0.7722	1.1733	0.6439	0.0401	0.0169	0.0952	**<.0001**
AD5	Teicoplanin (p) (J01XA02)	1.0115	1.0011	1.0221	**0.0308**	1.0421	1.0000	1.0860	0.0501
g11	Fluorochinolone (J01MA)	0.9949	0.9897	1.0001	0.0567	1.0049	0.9885	1.0215	0.5624
g12	Sulfonamide und Trimethoprim (J01E)	1.0066	0.9993	1.0139	0.0752	0.9512	0.8616	1.0501	0.3211
g13	Streptogramine (J01FG)	0.9165	0.7066	1.1890	0.5116	8.93E+70			
g14	Tetracycline (J01AA)	1.0022	0.9983	1.0062	0.2748	0.9967	0.9549	1.0405	0.8813
g15	Amphenicole (J01B)	0.0000				0.0000			
g16	Makrolide (J01FA)	1.0005	0.9947	1.0063	0.8629	1.0059	0.9606	1.0532	0.8032
g17	Lincosamine (J01FF)	0.9981	0.9803	1.0163	0.8384	1.0439	0.9924	1.0982	0.0963
g18	Aminoglykoside (J01G)	1.0140	1.0038	1.0243	**0.0073**	1.0078	0.9822	1.0341	0.5537
g19	Polymyxine (J01XB)	1.0012	0.9804	1.0225	0.9101	1.0110	0.9778	1.0454	0.5209
g20	Steroid (J01XC)	0.0000				1.0000	1.0000	1.0000	
g21	Imidazolderivate (J01XD)	0.9837	0.9648	1.0031	0.0989	1.0215	0.9521	1.0960	0.5530
g23	Tuberkulostatika (J01A)	1.0132	1.0062	1.0202	**0.0002**	0.9815	0.9332	1.0323	0.4687
g22	Andere Antibiotika (J01XX)	1.0136	1.0060	1.0213	**0.0005**	1.0043	0.9505	1.0611	0.8785

Effekt der AB-Anwendungsdichten im Modell ist per 1DDD/100Patiententage;

Declaration of Academic Honesty

I hereby declare that I wrote this thesis without any assistance and used only the aids listed. Any material taken from other works, either as a quote or idea have been indicated under ‘Sources’.

Hamburg, 08.12.2023