Burden of disease associated with antimicrobial resistance
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2012

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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General introduction
One of the turning points in the history of medicine has been the introduction of antimicrobial drugs. Few people living today have experienced life in the pre-antibiotic era, but it has dramatically changed our expectations regarding children surviving into adolescence, the level of physical health during adulthood and the ability to live to an old age. Antibiotics have improved the clinical outcome of a wide scale of infectious diseases, ranging from upper respiratory infections to wound infections, and can be life saving in severe infections like meningitis and endocarditis. Prescription and administration of antibiotics has become second nature in hospitals as well as in community care. Patients visiting their family doctor regard antibiotics as an indispensable part of medical care. In the hospital advanced interventions, like hip replacements, cancer treatment or transplant surgery, can be performed successfully because antibacterial drugs are available to prevent and/or treat secondary infections. Unfortunately, the excessive use of antibiotics also has had its downside. Development of antimicrobial resistance has become a growing problem among many of the disease causing bacteria. Until now most infections caused by antimicrobial resistant pathogens are still treatable. However, antimicrobial resistance can result in excess morbidity and mortality through delayed administration or reduced effectiveness of the few remaining appropriate drugs. So while the introduction of antibiotic treatment dramatically advanced medicine, development of antimicrobial resistance now threatens a return to the pre-antibiotic era.

**Historical context**

**Cause of disease: From miasmas to pathogens**

It was not before the end of the nineteenth century that it became evident that many epidemic diseases were caused by microbes. Before that time different theories prevailed. The popular miasma theory attributed disease to toxic vapours emanating from decaying matter, animals or plants. At the same time, the theory of spontaneous generation suggested that similar decay could yield living organisms. In 1683 the first observation of bacteria in humans was accomplished by the Dutch tradesman Antoni van Leeuwenhoek. However, he did not associate these ‘animalcules,’ as he called them, with disease.

It took almost two centuries before the germ theory became accepted. According to this theory disease would spread by transmission of living micro-organisms. The first person to become widely known for providing evidence for this hypothesis was Louis Pasteur, a French
chemist and microbiologist. Through his work on silkworms, between 1865 and 1870, he discovered that the economically devastating silkworm diseases, pébrine and flacherie, were caused by micro-organisms. The germ theory gained most of its explanatory power by seminal work carried out by Robert Koch, a German physician. Through improvement of purification techniques and bacterial growth media, he was able to discover the etiological agents of several devastating human diseases, like anthrax (1876), tuberculosis (1882), and cholera (1883). Based on these findings, his teacher Friedrich Henle and Robert Koch himself formulated four criteria for causation, which established the modern day paradigm for infectious diseases: i) identification of the micro-organism in abundance in lesions of the diseased hosts, ii) being able to isolate and culture the micro-organism, iii) cause indistinguishable lesions by introducing the purified agent in a healthy host, and iv) being able to isolate an identical micro-organism from a newly inoculated, diseased host. Now that the cause for infectious diseases was recognized for the first time, research into the development of effective cures was the logical next step.

The discovery of effective antibacterial compounds
Before the availability of antibacterial therapeutics, mortality and morbidity associated with infectious diseases were high. In 1909, the first effective chemical compound with the potential to cure a bacterial disease was discovered. Studying staining technique of cells between 1878 and 1887, the German physician Paul Ehrlich laid the conceptual basis for his ideas about ‘Zauberkugeln’ or ‘magic bullets’. Through his observation of differential affinities of aniline dyes to different cell components, he hypothesized that substances could be synthesized that specifically target and destroy infecting microbes without affecting the host’s cells. From 1891 onwards, Ehrlich and his team started to study the therapeutic potential of different dyes, but without success. Since organic arsenic derivatives were already in clinical use to treat African sleeping sickness, a parasitic disease, their pursuit for a magic bullet subsequently focused on arsenic compounds. And finally they managed to create the first man-made antibacterial: Salvarsan, ‘the arsenic that saves’. It was indeed a ‘magic bullet’ that had notable curative properties against syphilis. This was a common disease at that time, with severe late complications and mortality rates around 17%. Salvarsan had, however, an unfavourable side effect profile and could still inflict considerable harm to patients.
In the early 1930s, in line with Ehrlich’s experiments, the German Friedrich Bayer company discovered the second effective antibacterial agent: Prontosil rubrum, an aniline dye coupled to a sulphonamide. The chemist Josef Klarer and the bacteriologist Gerhard Domagk showed that this dye had a high selectivity for streptococci and a remarkable little toxicity to the host. Thereby, Prontosil was able to cure life threatening diseases, like postpartum puerperal fever, which used to be fatal in about 25% of the cases.

The third antibacterial agent to be discovered was not a chemotherapeutic, but an antibiotic, which is defined as ‘a substance produced by micro-organisms antagonistic to the growth or life of others.’ Already in 1928, Alexander Fleming observed how a mould, *Penicillium notatum*, inhibited the growth of staphylococci on solid media. He proved that the compound produced by the mould, which he named penicillin, affected many different disease-causing organisms in vitro and
was non-toxic to animals. However, he was unable to produce a stable substance in sufficient quantity ready for clinical trial.\textsuperscript{14,15} By 1939, coinciding with the beginning of the Second World War, Howard Florey and Ernst Chain, from Oxford, were able to purify penicillin and produce a stable and active compound.\textsuperscript{15} One year later, they reported of the successful treatment of ten seriously infected patients. Thereby, they confirmed the remarkable clinical effectiveness against different types of infections, caused by staphylococci and streptococci, and the wide safety margins of this new drug compared to the sulphonamides.\textsuperscript{16} This exerted wide interest in this miracle drug, but due to difficulties with culture, isolation and purification methods, and the threat of a German invasion in England, large-scale production of penicillin was delayed till 1943.\textsuperscript{15,17}

**Emergence of antimicrobial resistance**

Penicillin was seen as a true miracle drug with broad indications, and since it was available without prescription, its use rapidly increased in the early fourties.\textsuperscript{18} Only three years after the first approved use of penicillin in 1941, penicillin resistant *Staphylococcus aureus* isolates were already described\textsuperscript{19} and by 1948 resistance proportions of over 50\% were reported.\textsuperscript{20} The resistance was mediated through penicillinase. This enzyme, produced by staphylococci, hydrolyses the beta-lactam ring of penicillin, thereby inactivating the drug. A penicillinase-fast penicillin, called methicillin, that could overcome these resistance problems, was introduced in 1960.\textsuperscript{21} Only one year later, the first methicillin-resistant *S. aureus* (MRSA) were discovered in two clinical isolates from England.\textsuperscript{22} Over time, reports of clinical isolates expressing methicillin resistance became more frequent and nowadays MRSA has become endemic in hospitals all over the world\textsuperscript{23-25}, reaching resistance proportions as high as 80\%.\textsuperscript{25} Treatment options for serious MRSA infections are now limited to antibiotics of a few different classes, such as the glycopeptides, oxazolidinones, lipopeptides or streptogramins. These are all expensive, reserve antibiotics that are less active against staphylococci compared to beta-lactam antibiotics.\textsuperscript{26}

The first effective antibiotic treatment against infections by gram-negative bacteria was streptomycin, an aminoglycoside, which was discovered in 1943.\textsuperscript{27} Clinical isolates expressing streptomycin resistance were detected only three years after its introduction.\textsuperscript{28} In 1961 new broad-spectrum penicillins with anti-gram-negative properties were synthesized; the aminopenicillins, among which ampicillin became very popular.\textsuperscript{29} However, it soon turned out that gram-negative bacteria were able to secret a wide range of broad spectrum beta-lactamases
that were able to hydrolyze these compounds.\textsuperscript{30} In the mid 1970’s new extended spectrum cephalosporin antibiotics became available. Among these especially the third- and fourth-generation cephalosporins were developed for their excellent activity against gram-negative pathogens.\textsuperscript{31-33} Resistance against third-generation cephalosporins was already found during initial clinical trials in 1981.\textsuperscript{34} Nevertheless, reports of hospital outbreaks did not deter the successful marketing of these drugs for severe clinical infections. In the last two decades, third-generation cephalosporin resistance became an increasing problem in hospitals worldwide, mainly due to the rapid spread of extended spectrum beta-lactamases (ESBL).\textsuperscript{35-38} Third-generation cephalosporin resistance among invasive \textit{Escherichia coli} isolates has now reached levels up to 25\% in European countries.\textsuperscript{25} Treatment options for serious infections with third-generation-cephalosporin-resistant \textit{E. coli} (G3CREC) are confined to reserve antibiotics such as carbapenems.\textsuperscript{39}

\section*{Epidemiology and impact of antimicrobial resistance in Europe}

\subsection*{Surveillance of antimicrobial resistance}

Although there had been incidental studies describing the prevalence of antimicrobial resistance in clinical isolates, it remained unclear how widespread the problem was until the early seventies.\textsuperscript{40,41} A first overview of the resistance problem in \textit{S. aureus} for Europe was provided by Voss \textit{et al}. The authors carried out a prospective multi-centre study in 43 laboratories in ten countries, using a uniform method for methicillin resistance screening and subsequent confirmation by a reference laboratory.\textsuperscript{42} Although lacking geographical representativeness, the estimates about the occurrence of MRSA in Europe turned out to be rather accurate. Faced with the elusive dimension of antimicrobial resistance as a threat to public health in Europe, the need for a more structured approach to surveillance was expressed, during a conference held on the occasion of the Danish European Union presidency in Copenhagen in 1998.\textsuperscript{43} In the definition of surveillance it is emphasized that this should entail ‘on-going and systematic data collection, analysis and interpretation of outcome-specific data essential to the planning, implementation and evaluation of public health practice, closely integrated with timely dissemination of these data to those who need to know’.\textsuperscript{44}

Between 1990 and 2000, different initiatives were started for surveillance of antimicrobial resistance in the European region. A large proportion of these
projects were pharmaceutical company-sponsored surveillance efforts.\textsuperscript{45} Two decades later, many, especially sponsored collaborations, ceased to exist due to a combination of factors. The primary goal of most industry-sponsored networks was to show the activity and potential usefulness of novel proprietary drugs. However, the companies’ interest in antimicrobial resistance surveillance soon diminished, because of expanding resistance, an increasing number of off-patent drugs and the small number of new drugs advancing through the development pipeline. Moreover, most existing networks applied a top-down approach, whereby strains had to be sent to central laboratories for standardized antimicrobial susceptibility testing. This was associated with high costs, which ultimately became untenable. For the last ten years, the European Antimicrobial Resistance Surveillance System (EARSS) has been the most comprehensive surveillance system in Europe.\textsuperscript{46} It has systematically collected antimicrobial susceptibility data of invasive infections caused by seven major pathogens and is still continuing as EARS-Net. The network has grown from 320 laboratories in 13 countries to almost 800 laboratories in 33 countries, recording routine susceptibility test results from tertiary care as well as primary and secondary care hospitals. In most participating countries geographical representativeness is high, as more than 70\% of the population is covered.\textsuperscript{47} Data from the EARSS made clear that there are large differences in antimicrobial resistance proportions between countries in Europe. One of the largest resistance problems include MRSA, whereby over a quarter of countries reported resistance proportions above 25\% and resistance proportions reached 52\% in 2010.\textsuperscript{25,47} Temporal analyses showed that the level of antimicrobial resistance is dynamic as well; G3CREC is one of the most important emerging resistance problems. Proportions have increased consistently in almost all countries since the start of surveillance, reaching levels as high as 25\% in Bulgaria.\textsuperscript{25,47,48} These surveillance data have shed light on the prevalence and geographical and temporal variance of antimicrobial resistance. However, lack of clinical data precluded assessment of the morbidity and mortality associated with antimicrobial resistance. Although patient-level risk estimates have been provided by observational studies, these were often imprecise, due to single centre designs and an insufficient number of included cases. At the same time, pooled analysis of available data was hampered by heterogeneity between studies.\textsuperscript{49,50} Thereby, these clinical effect measures were inadequate for assessment of the etiological fraction of mortality attributable to antimicrobial resistance for Europe.
Burden of disease associated with MRSA and G3CREC

Although many published studies claim to estimate the burden of disease associated with antimicrobial resistance, most actually provide patient-based risk estimates. True burden of disease measures provide information about the size of the health problem and should be expressed as an incidence per population (conventionally per 100,000 per year), like the incidence of a disease, or a cause-specific mortality rate. In 1993, the World Bank published the first comprehensive report quantifying the health effects for more than 100 diseases and injuries. In the following years, the World Health Organization (WHO) provided regular updates, however, the burden of disease associated with antimicrobial resistance was never included. This is due to the lack of empirical data about the incidence of infections caused by resistant pathogens, as well as the counterfactual challenge to generate accurate and precise estimates about the impact of infections caused by resistant compared to susceptible agents. Information about the magnitude of a health problem is, however, a prerequisite for decisions of health system managers, policy-makers, and public health specialists, who need to prioritize public health spending constrained by limited resources.

Complementary to the clinical approach, measurement of economic consequences of antimicrobial resistance-related infections should provide decision-makers with an indication of the impact on healthcare expenditure. The economic impact of antimicrobial resistance can be divided in direct costs, due to extra medical care, like surgical interventions, and indirect costs including additional infection control efforts and adjusted antibiotic policies resulting in the prescription of more expensive, second or third line antibiotics for empirical treatment.

The Burden of Resistance and Disease in European Nations project

To fill the knowledge gap about the health and economic impact of antimicrobial resistance in Europe, the Burden of Resistance and Disease in European Nations (BURDEN) project was initiated. It was coordinated at the University Medical Centre Freiburg, Germany and the consortium further consisted of the Netherlands’ National Institute for Public Health and the Environment (RIVM), the Scientific Institute of Public Health, Brussels, Belgium and the University of Dundee, UK. Funding was provided by the Directorate General for Health and Consumer Protection (DG-Sanco) and the project was carried out between January 2007 and December 2009.

The working group (WP7) at RIVM had the specific objective to provide realistic estimates about the burden of disease associated with bloodstream infections
(BSIs) caused by MRSA and G3CREC in European hospitals. The decision to focus on BSIs was guided by the fact that a large part of the disease burden attributable to antimicrobial resistance is caused by hospital-associated infections, of which BSIs are among the most clinically relevant and often life-threatening events. Moreover, the availability of prevalence data for BSIs from the EARSS would enable extrapolation of the study results to the European level. *S. aureus* and *E. coli* are the two most frequent causes for BSIs among hospitalized patients in Europe and beyond.\textsuperscript{58,59} Since these species also harbour multi-resistance phenotypes, WP7 focused on these two specific pathogens.

In order to improve precision and external validity of the estimates about the clinical impact of MRSA and G3CREC BSIs, a prospective multi-centre cohort study design was chosen. Additional funding provided by the RIVM and the University Medical Centre Groningen (UMCG), made it possible to set up cohort studies in thirteen different hospitals. Successful implementation of a prospective cohort study in this many different centres required careful selection of hospitals and thorough training and support of onsite investigators (OSIs). Through a tender procedure eligible hospitals, based on diagnostic accuracy and representativeness for the national level of antimicrobial resistance, could be selected from different countries across Europe. In each participating centre an OSI was responsible to prospectively collect the required clinical data. To simplify and standardize data collection for all these centres, a web-based data entry tool was developed and a detailed study protocol and project manual was written. Moreover, three workshops were organized. In the first workshop OSIs were familiarized with the data entry tool and research protocol. The second workshop, which took place after a pilot phase of two months, provided the opportunity to solve final ambiguities and refine the research protocol and data entry tool. In the last workshop, feedback was provided and the implications of the study results were discussed. Throughout the year of data collection, daily help desk support was provided as well, which proved highly critical to the success of consistent data collection across so many different healthcare institutions. The analyses of the data provided by these cohort studies became the central component of this dissertation.

**Thesis outline**

The aim of this thesis is to provide insight into the health and economic consequences associated with BSIs caused by MRSA and G3CREC in Europe. In chapter 2-5 of this thesis, four studies are described which utilized the information collected from the study cohorts in the BURDEN project. In chapter 2 the clinical
impact of methicillin-resistance in *S. aureus* BSIs was evaluated, by estimating the excess 30-day mortality, excess hospital mortality and excess length of hospital stay (LOS) attributable to antimicrobial resistance. Focusing on the same outcome measures, chapter 3 gives estimates for the clinical impact of third-generation cephalosporin resistance in *E. coli* BSIs. In order to unravel the potential interference of a delay in appropriate therapy in the association between BSI and outcome, chapter 4 describes a time-to-event analysis from the first positive blood culture till appropriate therapy and the impact on 30-day mortality. In chapter 5, the effect estimates presented in chapter 2 and 3 are combined with prevalence data from the EARSS in order to quantify the burden of disease associated with MRSA and G3CREC BSIs in Europe. In this chapter we also present future trajectories of the burden of disease. Surveillance data from the EARSS were used to study how the epidemiology of BSIs caused by *S. aureus* and *E. coli* relates to BSIs caused by three other major species (*Streptococcus pneumoniae, Enterococcus faecalis* and *Enterococcus faecium*) in chapter 6. For these species, the influence of expanding antimicrobial resistance on temporal trends was explored as well. Finally, in chapter 7, all results are summarized, the novel methodological approaches of the presented investigations are discussed and the burden of disease associated with antimicrobial resistance is put into broader perspective.
Reference List


