Summary

The successive discovery of penicillin and many other antibiotics in the 1940s and 1950s, heralded a new era, promising humanity’s final triumph over infectious diseases. However, this view was soon challenged by the emergence and expansion of antimicrobial resistance. Recent surveillance data from the European Antimicrobial Resistance Surveillance System (EARSS, 1999-2009) showed that a high proportion of invasive Staphylococcus aureus isolates was methicillin-resistant. At the same time, resistance to third-generation cephalosporins was rapidly increasing among invasive Escherichia coli. Due to lack of clinical outcome data, it remained, however, unclear how antimicrobial resistance impinged on morbidity and mortality for Europe. To fill this void the Burden of Resistance and Disease in European Nations project was initiated, by a consortium of four different institutes including the Netherlands’ National Institute for Public Health and the Environment (RIVM), and funded by the Directorate General for Health and Consumer Protection of the European Commission. The analyses of the data collected through this project provided the basis for the majority of studies presented here (chapter 2-5). The aim of this thesis was to provide realistic estimates for the clinical impact (chapter 2-4) and the burden of disease (chapter 5) associated with methicillin-resistant S. aureus (MRSA) and third-generation-cephalosporin-resistant E. coli (G3CREC) causing bloodstream infections in the European region, and to demonstrate how expansion of antimicrobial resistance among these species influenced temporal trends in Europe (chapter 6). In the last chapter of this thesis, the novel methodological approaches of the presented investigations are discussed and the burden of disease associated with antimicrobial resistance is put into broader perspective (Discussion and conclusions).

Clinical impact of antimicrobial resistance for patients with bloodstream infections caused by S. aureus and E. coli

In chapter 2 and 3, we determined the excess 30-day mortality, hospital mortality, and length of stay attributable to MRSA and G3CREC bloodstream infections in Europe. A prospective, multi-centre, parallel, matched cohort study was carried out in thirteen different tertiary care centers in as many European countries. Thereby, infected patients were matched to uninfected controls based on length of hospital stay before infection of the case (Figure 1, page 133). This was done separately for patients with MRSA or G3CREC bloodstream infections (resistant cohort) and patients with methicillin-susceptible S. aureus (MSSA) or
third-generation-cephalosporin-susceptible *E. coli* (SEC) bloodstream infections (susceptible cohort). Through matching cases and controls within each cohort have similar risk profiles, allowing for a more meaningful comparison. In this manner, it was possible to determine the effect of infections with resistant and susceptible bacteria (risk of dying) separately and more accurately. The excess risk attributable to antimicrobial resistance was then established by subtracting the effect estimates previously derived for both cohorts.

Based on data from these cohort studies, the clinical impact of *S. aureus* bloodstream infections was assessed in chapter 2. Analyses showed that *S. aureus* bloodstream infection increased mortality as well as length of hospital stay compared to uninfected patients. Methicillin resistance contributed an additional 80% excess mortality at day 30 after infection compared to patients infected by MSSA. For hospital mortality or length of hospital stay an additional impact could not be discerned with confidence. In chapter 3, the clinical impact of G3CREC bloodstream infections was studied. For patients with *E. coli* bloodstream infection, mortality and length of hospital stay was also increased compared to patients without this infection. In addition, third-generation cephalosporin resistance increased in-hospital mortality more than two-fold compared to patients with SEC infection. Resistance prolonged hospitalization by 5 days. These results underline the clinical relevance of invasive *S. aureus* and *E. coli* infections and demonstrate the additional burden imposed by antimicrobial resistance.

Chapter 4 describes the effect of time to appropriate therapy on mortality from bloodstream infections caused by resistant and susceptible bacteria. It was found that patients with MRSA or G3CREC infections receive appropriate therapy much later than patients infected by susceptible bacteria. Appropriate antibiotic therapy improved survival for patients with MSSA or SEC bloodstream infection (hazard ratio MSSA 0.47; SEC 0.44). However, delayed adjustment to appropriate therapy did not improve outcome for patients infected with resistant bacteria. This discrepancy could only be explained by inferior activity of reserve antibiotics or irreversible progression of a systemic inflammatory response syndrome. It was concluded that early, adequate empirical treatment of vulnerable, septic patients is crucial. Local surveillance of antimicrobial resistance could help to improve the empirical choice of antibiotic compounds.

**Burden of disease associated with antimicrobial resistance**

In chapter 5, the magnitude of the health problem, i.e. the burden of disease, associated with antimicrobial resistance was estimated. The number of
bloodstream infections caused by MRSA and G3CREC was extrapolated from EARSS prevalence data and national health care statistics. Thereafter, the number of excess deaths and extra bed-days could be derived by applying the previously identified risk estimates. In 2007, 27,711 bloodstream infections were caused by MRSA (4.8/100,000 inhabitants) and 15,183 were caused by G3CREC (2.6/100,000). These bloodstream infections resulted in 8,215 excess deaths (1.4/100,000) and 376,000 extra bed-days in Europe. Hospital expenditure was calculated on the basis of a validated cost model developed by the World Health Organization, which provided costs per bed-day for each country. The costs for prolongation of hospital stay added up to 62.0 million euros for Europe. In the coming years, the burden of disease of antimicrobial resistance is expected to increase. This will be mainly due to the rapidly growing number of G3CREC bloodstream infections. The prevalence of MRSA infections seems to be decreasing for Europe as a whole.

Changing epidemiology of bloodstream infections in Europe
In chapter 6, temporal changes in five major causative pathogens, S. aureus, E. coli, Streptococcus pneumoniae, Enterococcus faecalis and Enterococcus faecium, were analyzed to describe how antimicrobial resistance modifies the incidence of bloodstream infections in Europe. Frequency of bloodstream infections, antimicrobial susceptibility and denominator data were extracted from the EARSS database. Laboratories were included if they reported data for all years between 2002 and 2008. Frequencies of bloodstream infections caused by all five major bacterial species have markedly increased in Europe. Within seven years, numbers increased by 47%, at an annual average of 6.4%. Notably, E. faecium (19.3% per year) and E. coli (8.7% per year) bloodstream infections showed the most significant increase. For E. coli this was mainly due to a rise in G3CREC isolates. The overall trends may be explained by an increasing vulnerability of the hospital population, while the rapid increase of resistant isolates may be associated with emergence and expansion of successful, antimicrobial resistant clones. Trends for resistant and susceptible strains were clearly dissociated within the same species (S. aureus and E. coli). This finding suggests that resistant strains are not replacing, but merely adding to infections caused by susceptible strains. As a consequence, expansion of antimicrobial resistance will result in additional cases of bloodstream infections, which will further strain limited healthcare resources.

Discussion and conclusions
Investigations presented in this thesis applied novel study designs, such as the
parallel matched cohort study, and recently developed analytical approaches, such as time to event analyses extended for competing events. We believe that this improved the accuracy of our estimates compared to previous studies pursuing the same goals. We demonstrated that time is crucial and needs to be included as factor in all analyses. Future studies on the impact of antimicrobial resistance should also acknowledge these time-related issues, including time from admission until infection, time from infection until therapy, and time from infection until death.

To conclude, the burden of disease of antimicrobial resistance appears to be modest compared to chronic diseases. Mortality rates estimated for patients with infections caused by antimicrobial-resistant bacteria are in a similar range as those reported for HIV, tuberculosis, and road traffic accidents in Europe. However, the latter three account for a much larger burden of disease when expressed in disability adjusted life years (DALYs). Notably, the absolute number of DALYS and deaths incurred by susceptible bloodstream infections are more than two times higher than those caused by MRSA and G3CREC in Europe, because of the higher incidence of susceptible infections. This indicates that there is a huge prevention potential if interventions target bloodstream infections that are amenable to infection control measures in hospitals. It is expected that in the coming years, the number of infections caused by G3CREC will increase. This trend could be accelerated by the observed emergence and expansion of successful ESBL-positive strains (Extended Spectrum Beta-lactamases are enzymes that confer resistance to a large number of antibiotics) in the community. While hospitals are also faced with sporadic outbreaks of carbapenemase-producing Enterobacteriaceae causing near-to-untreatable infections, the fear for a return to the pre-antibiotic era appears to be premature.