Infectious diseases have been, alongside cardiovascular diseases and cancer, the main threat to human health. Acute and chronic respiratory diseases, especially pulmonary tuberculosis, but also malaria, AIDS and acute infections of the digestive tract are responsible for a large portion of mortality, both in developing and developed countries. Moreover, the role of infectious agents in the genesis of various severe ailments, such as cardiovascular diseases, certain carcinomas and stomach ulcers, is more and more being brought to light.

Fighting infectious diseases has many aspects – all of them characterized by their dynamic nature. First, infections travel. The plague did so extensively already in the Middle Ages and up to the end of the nineteenth century. The Spanish flu at the end of World War I cost the lives of several million people all over the world. At present, high mobility of people through travel and migration and an ever-increasing exchange of goods are driving the rapid spread of infections around the world. The first aspect of the fight against these infections is, therefore, what is commonly called “epidemic control”. This means fast information on new cases, on incidences and mortalities, on strains and transmission routes of the infectious pathogen, if possible centralized in a supranational institution such as the World Health Organization (WHO). It also means making rapid decisions on intervention and treatment strategies, for example, isolation and prophylaxis or treatment with antivirals, for example, stockpiling drugs. The efficacy of modern methods of epidemic control was demonstrated during recently emerging diseases like the bovine spongiform encephalopathy (mad cow disease), the severe acute respiratory syndrome (SARS) and avian influenza (A/H5N1), which finally did not reach large proportions of the population, especially compared to the diseases mentioned in the beginning. It is to be hoped that A/H1N1 can also be contained by rigorous control.

A second aspect of the fight against infectious diseases is the changing environment in which disease transmission is taking place. The transmission of an infection in a community or between communities is influenced by many characteristics of modern societies such as growing urbanization accompanied by changing structures of cities as well as of the country side, different housing conditions, growing social inequalities that imply growing health inequalities, pollution and malnutrition that may weaken the immune system, and consequences of climate change. Classical
hygiene, both public and personal, still plays a pivotal role in environmental prevention, but needs to be complemented by measures that respond to the aforementioned factors.

A third aspect of dealing with infectious diseases is large-scale primary prevention, of which immunization is by far the most important tool. Starting with vaccination against smallpox, this public health measure has helped to reduce the burden of vaccine-preventable infections enormously. In many scientific studies, both the effectiveness and possible adverse effects of large-scale immunizations have been investigated.

However, fighting infectious diseases is like shooting at a moving target. Pathogens are continuously evolving, among others under the pressure of large-scale infection control measures like antibiotic treatment and vaccination. This aspect generates renewed challenges to infectious disease control and creates the need for continued efforts in the development of monitoring and control. While antibiotic and antiviral resistance have emerged and led to increasing problems in the control of infections like tuberculosis and hospital infections around the world, molecular biology and bioinformatics have, on the other hand, provided us with tools that allow increasingly detailed insight into the transmission patterns and dynamics of pathogens. Molecular sequencing in combination with epidemiological studies has elucidated transmission routes among individuals, risk groups and populations.

The successful implementation of infectious disease control depends critically, if not predominantly, on thorough knowledge of epidemiologic facts. Epidemic control is based on surveillance and detailed knowledge of the paths of transmission in a population. Environmental prevention rests on epidemiological studies of environmental risk factors. The planning and monitoring of immunization measures requires a deep understanding of their mechanisms and effects on transmission dynamics in a given community. Mathematical modelling is employed to compute and estimate parameters that are important for understanding the transmission dynamics. Mathematical modelling can be used to simulate outbreaks and to assess the effectiveness of different prevention and intervention strategies. Results from modelling studies help with interpreting epidemiological data and support evidence-based decisions for targeting interventions for effective disease control.

The aim of our book is to present the reader with a general picture and the main ideas of the subject. We do not aim at covering the complete field of infectious disease epidemiology, but more to introduce the reader to different methodological aspects of epidemiology that are specific for infectious diseases. Furthermore, we give insight into the epidemiology of some classes of infectious diseases characterized by their main modes of transmission. With this choice of topics we hope to bridge the gap between scientific research on the clinical, biological, mathematical, social and economic aspects of infectious diseases and their applications in public health. We would like the reader to understand the impact of infectious diseases on modern society and the instruments that policy makers have at their disposal to deal with these challenges. Hardly a day goes by without news headlines concerning infectious disease control. At the time of writing these lines, the spectre of a pandemic of influenza A[H1N1] is raising its head and containment seems a lost
cause. At the same time, heated debates are taking place in many societies about the pros and cons of vaccinating young girls against human papillomavirus, while in the Netherlands one of the largest outbreaks of Q fever ever observed in humans is unfolding. It seems as if the momentum of the challenges posed by infectious diseases to our ability to control them is increasing rather than decreasing, maybe due to the increasing pace of changes in human societies and their natural environments. In order to meet these challenges we need solid scientific knowledge and an understanding of all aspects of infectious diseases and their controls. With this book we hope to provide the reader with the basic groundwork for this knowledge and understanding. We hope that it will contribute to an evidence-based and responsible communication of infectious disease topics to avoid misunderstandings and overreaction of the public.

The book is written for students of the health sciences, both of curative medicine and public health, and for experts that are active in these and related domains. It may also be of interest for the educated layman since the technical level is kept relatively low. It has evolved from a rich experience of continuous teaching and research in many places, but particularly at the School of Public Health of Bielefeld University, Germany, where an international summer school in our field has been held every year since 1999. We hope that it will fill a gap and prove useful by “infecting” the reader with fascination for the features and the dynamics of infectious disease epidemiology.

The first two parts of the text are general, treating the background and general methods for studying infectious diseases, while the third part deals with specific transmission routes and related infectious diseases.
Acknowledgements

We would like to thank the doctoral student Arina Zanuzdana from the Department of Public Health Medicine of the School of Public Health, Bielefeld University for her great engagement as technical editor, Mrs. Regine Myska for her secretarial assistance, and Erich Wehmeyer for his help in improving the English language of the chapters. In addition, we are indebted to the many critical comments of our students and colleagues that will hopefully continue to improve the quality of our book in future editions.

Bielefeld, Germany
Utrecht, The Netherlands
Le Châtelet (Manglieu), France

Alexander Krämer
Mirjam Kretzschmar
Klaus Krickeberg
# Contents

## Part I  Challenges

1. **The Global Burden of Infectious Diseases** .............................................. 3  
   Paulo Pinheiro, Colin D. Mathers, and Alexander Krämer

2. **Global Challenges of Infectious Disease Epidemiology** .......................... 23  
   Alexander Krämer and Md. Mobarak Hossain Khan

3. **Emerging and Re-emerging Infectious Diseases** .................................. 39  
   Thomas Löscher and Luise Prüfer-Krämer

4. **Infectious Disease Control Policies and the Role of Governmental and Intergovernmental Organisations** .......................... 69  
   Gérard Krause

## Part II  General Concepts and Methods

5. **Principles of Infectious Disease Epidemiology** ........................................ 85  
   Alexander Krämer, Manas Akmatov, and Mirjam Kretzschmar

6. **Social Risk Factors** ................................................................................. 101  
   Klaus Krickeberg and David Klemperer

7. **Molecular Typing and Clustering Analysis as a Tool for Epidemiology of Infectious Diseases** ........................................ 117  
   Sylvia M. Bruisten and Leo Schouls

8. **Epidemiologic Surveillance** ................................................................. 143  
   Ralf Reintjes and Klaus Krickeberg

9. **Outbreak Investigations** .......................................................................... 159  
   Ralf Reintjes and Aryna Zanuzdana

10. **Geographic Information Systems** .......................................................... 177  
    Patrick Hostert and Oliver Gruebner

11. **Methods and Concepts of Epidemiology** ............................................... 193  
    Rafael Mikolajczyk
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Mathematical Models in Infectious Disease Epidemiology</td>
<td>209</td>
</tr>
<tr>
<td></td>
<td>Mirjam Kretzschmar and Jacco Wallinga</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Immunity to Infectious Diseases</td>
<td>223</td>
</tr>
<tr>
<td></td>
<td>Timo Ulrichs</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Principles and Practice of Vaccinology</td>
<td>235</td>
</tr>
<tr>
<td></td>
<td>Richard Pebody and Mirjam Kretzschmar</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Health Economics of Infectious Diseases</td>
<td>249</td>
</tr>
<tr>
<td></td>
<td>Robert Welte, Reiner Leidl, Wolfgang Greiner, and Maarten Postma</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Part III</strong> Epidemiology of Particular Infectious Diseases</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Airborne Transmission: Influenza and Tuberculosis</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>Timo Ulrichs</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Infectious Childhood Diarrhea in Developing Countries</td>
<td>291</td>
</tr>
<tr>
<td></td>
<td>Charles P. Larson, Lars Henning, Stephen Luby, and ASG Faruque</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Bloodborne and Sexual Transmission: HIV/AIDS</td>
<td>309</td>
</tr>
<tr>
<td></td>
<td>Charlotte van den Berg, Karen Lindenburg, and Roel Coutinho</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Blood Borne and Sexual Transmission: Hepatitis B and C</td>
<td>333</td>
</tr>
<tr>
<td></td>
<td>Freke Zuure, Susan Hahné, Thijs van de Laar, Maria Prins, and Jim van Steenbergen</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Sexual Transmission: <em>Chlamydia trachomatis</em></td>
<td>357</td>
</tr>
<tr>
<td></td>
<td>Robert E. Johnson and Stuart M. Berman</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Vector-Borne Transmission: Malaria, Dengue, and Yellow Fever</td>
<td>381</td>
</tr>
<tr>
<td></td>
<td>Tomas Jelinek</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Nosocomial Transmission: Methicillin-Resistant <em>Staphylococcus aureus</em> (MRSA)</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td>M.J.M. Bonten and M.C.J. Bootsma</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Infectious Diseases and Cancer: HPV</td>
<td>409</td>
</tr>
<tr>
<td></td>
<td>Helen Trottier and Eduardo L. Franco</td>
<td></td>
</tr>
<tr>
<td><strong>Index</strong></td>
<td><strong>Index</strong></td>
<td>431</td>
</tr>
</tbody>
</table>
Manas Akmatov  Department of Experimental Mouse Genetics, Helmholtz Centre for Infection Research, Inhoffenstraße 7, 38124 Braunschweig, Germany, manas.akmatov@helmholtz-hzi.de

Charlotte van den Berg  Cluster Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, The Netherlands, cvdBerg@ggd.amsterdam.nl

Stuart M. Berman  Centers for Disease Control and Prevention, Atlanta, GA, USA, smb1@cdc.gov

M.J.M. Bonten  Department of Medical Microbiology and the Julius Center for Health Sciences and Primary Care; University Medical Center Utrecht, Utrecht, The Netherlands, mbonten@umcutrecht.nl

M.C.J. Bootsma  Faculty of Science, Department of Mathematics, Utrecht University, Utrecht, The Netherlands; Julius Center for Health Sciences and Primary Care University Medical Center Utrecht, Utrecht, The Netherlands, m.c.j.bootsma@uu.nl

Sylvia M. Bruisten  Cluster Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, The Netherlands, sbruisten@ggd.amsterdam.nl

Roel Coutinho  Center for Infectious Disease Control, RIVM, Bilthoven, The Netherlands, roel.coutinho@rivm.nl

A.S.G. Faruque  International Centre for Diarrhea Disease Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh, gfaruque@icddrb.org

Eduardo L. Franco  Division of Cancer Epidemiology, Departments of Oncology and Epidemiology and Biostatistics, McGill University, Montreal, Canada, eduardo.franco@mcgill.ca

Wolfgang Greiner  Bielefeld School of Public Health, Health Care Management (AG5), University of Bielefeld, Postfach 10 01 31, D-33501 Bielefeld, Germany, wolfgang.greiner@uni-bielefeld.de

Oliver Gruebner  Geography Department, Geomatics Lab, Humboldt-Universität zu Berlin, Berlin, Germany, oliver.gruebner@geo.hu-berlin.de
Susan Hahné  Center for Infectious Disease Control, RIVM, Bilthoven, Netherlands, susan.hahne@rivm.nl

Lars Henning  International Centre for Diarrhea Disease Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh; Swiss Tropical Institute, Basel, Switzerland, lars.henning@unibas.ch

Md. Mobarak Hossain Khan  Department of Public Health Medicine, School of Public Health, University of Bielefeld, Bielefeld, Germany, mobarak.khan@uni-bielefeld.de

Patrick Hostert  Geography Department, Geomatics Lab, Humboldt-Universität zu Berlin, Berlin, Germany, patrick.hostert@geo.hu-berlin.de

Tomas Jelinek  Berlin Center for Travel and Tropical Medicine, Jägerstrasse 67–69, 10117 Berlin, Germany, jelinek@bctropen.de

Robert E. Johnson  Centers for Disease Control and Prevention, Atlanta, GA, USA, rej1@cdc.gov

David Klemperer  School of Social Sciences, University of Applied Sciences, Regensburg, Germany, david.klemperer@soz.fh-regensburg.de

Alexander Krämer  Department of Public Health Medicine, School of Public Health, University of Bielefeld, Bielefeld, Germany, alexander.kraemer@uni-bielefeld.de

Gérard Krause  Department for Infectious Diseases Epidemiology, Robert Koch Institute, Nordufer 20, 13353 Berlin, Germany, krauseg@rki.de

Mirjam Kretzschmar  Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands; Center for Infectious Disease Control, RIVM, Bilthoven, The Netherlands, mirjam.kretzschmar@rivm.nl

Klaus Krickebberg  Formerly, Université de Paris V, France; Bielefeld, Germany, krik@ideenwelt.de

Thijs van de Laar  Cluster Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, Netherlands, tvdlaar@ggd.amsterdam.nl

Charles P. Larson  International Centre for Diarrhea Disease Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh; Centre for International Child Health, British Columbia Children’s Hospital and Department of Pediatrics, University of British Columbia, Vancouver, Canada, clarson@icddrb.org

Reiner Leidl  Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Institute of Health Economics and Health Care Management (IGM), Ingolstädter Landstr. 1, 85764 Neuherberg, Germany, leidl@helmholtz-muenchen.de

Karen Lindenburg  Cluster Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, The Netherlands, klindenburg@ggd.amsterdam.nl
Thomas Löscher  Department of Infectious Diseases and Tropical Medicine (DITM), University of Munich, Munich, Germany, loescher@lrz.uni-muenchen.de

Stephen Luby  International Centre for Diarrhea Disease Research, Bangladesh (ICDDR,B), Dhaka, Bangladesh, sluby@icddrb.org

Colin D. Mathers  Department of Measurement and Health Information Systems, World Health Organization, Geneva, Switzerland, mathersc@who.int

Rafael Mikolajczyk  Department of Public Health Medicine, School of Public Health, University of Bielefeld, Germany, rafael.mikolajczyk@uni-bielefeld.de

Richard Pebody  Health Protection Agency, Communicable Disease Surveillance Centre, London, England, richard.pebody@hpa.org.uk

Paulo Pinheiro  Department of Public Health Medicine, School of Public Health, University of Bielefeld, Germany, paulo.pinheiro@uni-bielefeld.de

Maarten Postma  Groningen Research Institute of Pharmacy (GRIP), Antonius Deusinglaan 1, University of Groningen, 9713 AV Groningen, Groningen, The Netherlands, m.j.postma@rug.nl

Maria Prins  Cluster Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, Netherlands, mprins@ggd.amsterdam.nl

Luise Prüfer-Krämer  Travel Clinic, Bielefeld, Germany, pruefer-kraemer@gmx.de

Ralf Reintjes  Department of Public Health, Hamburg University of Applied Sciences, Hamburg, Germany, ralf.reintjes@haw-hamburg.de

Leo Schouls  Laboratory for Infectious Diseases and Perinatal Screening, National Institute for Public Health and the Environment, Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven, The Netherlands, leo.schouls@rivm.nl

Helen Trottier  Division of Cancer Epidemiology, Departments of Oncology and Epidemiology and Biostatistics, McGill University, Montreal, Canada, helen.trottier@mcgill.ca

Timo Ulrichs  Koch-Metschnikow-Forum, Luisenstr. 59, 10117 Berlin, Germany, timo.ulrichs@bmg.bund.de

Jim van Steenbergen  Center for Infectious Disease Control, RIVM, Bilthoven, The Netherlands, jim.van.steenbergen@rivm.nl

Jacco Wallinga  Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands; Center for Infectious Disease Control, RIVM, Bilthoven, The Netherlands, jacco.wallinga@rivm.nl

Robert Welte  Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Institute of Health Economics and Health Care
Management (IGM), Ingolstädter Landstr. 1, 85764 Neuherberg, Germany, robert.welte@helmholtz-muenchen.de

Aryna Zanuzdana  Department of Public Health Medicine, School of Public Health, University of Bielefeld, Bielefeld, Germany, aryna.zanuzdana@uni-bielefeld.de

Freke Zuure  Cluster Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, Netherlands, fzuure@ggd.amsterdam.nl
Part I
Challenges
Chapter 1
The Global Burden of Infectious Diseases

Paulo Pinheiro, Colin D. Mathers, and Alexander Krämer

1.1 Introduction

Over the last century, infectious diseases have lost a lot of their threat to individuals’ health as well as to the health of populations living in industrialized countries. The continuous reduction and effective control of both mortality and morbidity from infectious diseases marks an impressive story of success in the history of public health in the developed world and has been linked to a wide range of improvements that occurred alongside the socioeconomic modernization of these societies. Although many factors (e.g., improved sanitation, development of antibiotics and vaccines, improved living conditions and food quality/availability, and improved health care and surveillance systems) that contributed significantly to the success have been identified, there are, however, still uncertainties about the underlying mechanisms and interactions that led to the decline of infectious disease mortality (Sagan 1987). The sustainable control of infectious diseases was also accompanied by an impressive rise of life expectancies which, in turn, gave chronic (non-communicable) diseases the opportunity to increase in quantity and importance for public health. This so-called epidemiological transition (Omran 1971, Olshansky and Ault 1986) may have resulted in the fact that infectious diseases have become somewhat marginalized in the public perception of the developed world.

From a global perspective, however, infectious diseases still play, and will continue to play, a significant role in public health since most of the regions of the world have not reached a level of modernization that is comparable with the industrialized world. Especially developing countries and countries in transition still face an enormous burden posed by communicable diseases on their populations’ health. Changes in environment and human behavior due to the globalization of the world and the evolutionary dynamics of microbial agents may, furthermore, produce new ecological niches that enable the emergence or re-emergence of infections, thus posing a persistent threat to the developed world too.
The subject is modern epidemiologic methods for infectious diseases, their origins and motivations, and their role and applications in public health. The authors are internationally renowned experts in the field of infectious disease epidemiology. The editors come from different scientific backgrounds but have been devoted to research in infectious disease epidemiology for many years. Alexander Krämer is an internist and epidemiologist who co-founded the first School of Public Health in the German-speaking region of Europe at the University of Bielefeld. Mirjam Kretzschmar is a mathematician and epidemiologist with many contributions to mathematical modelling of infectious diseases and its applications for public health.