

Contributors xvii

Biographical xxvii

Introduction: Infectious Diseases, the Major Challenge of Twenty-First Century Medicine xxix

1. Pulmonary Tuberculosis and *Mycobacterium Tuberculosis*: Modern Molecular Epidemiology and Perspectives, 1

Sylvain Godreuil, Loubna Tazi, and Anne-Laure Bañuls

1.1. Introduction, 1

1.2. General Points on *Mycobacterium Tuberculosis* (MTB) and Pulmonary Tuberculosis (PTB), 2

1.2.1. Classification and Cellular Characteristics, 2

1.2.2. Transmission and Multiplication of MTB, 3

1.2.3. Clinical and Subclinical TB, 4

1.2.4. Diagnosis of MTB Species, 5

1.2.5. Treatment, Drug Resistance, and Control, 6

1.3. Genetics of MTB, Molecular Tools, and Population Structure, 7

1.3.1. Genome and Genetic Diversity of MTB, 7

| | | |
|-------------|---|-----------|
| 1.3.2. | Genetic Tools for Molecular Epidemiology, | 7 |
| 1.3.3. | How Should the Most Appropriate Molecular Marker be Chosen? | 10 |
| 1.3.4. | Population Structure of MTB and Epidemiological Consequences, | 11 |
| 1.4. | Use of Molecular Epidemiology for Understanding Tuberculosis Transmission and Pathogenesis, | 12 |
| 1.4.1. | MTB Families and Worldwide Distribution, | 13 |
| 1.4.2. | MTB in Developing Versus Developed Countries, | 14 |
| 1.4.3. | Clinical and Epidemiological Relevance of Molecular Epidemiology at the Local Level, | 15 |
| 1.4.4. | Use of Genotyping to Study the Impact of HIV/AIDS and Drug Resistance on Pathogenesis and Transmission, | 16 |
| 1.5. | Urgent Needs for TB Control, Limitations, and New Issues for Molecular Epidemiology, | 17 |
| 1.5.1. | Urgent Needs for TB Control and Molecular Epidemiology, | 17 |
| 1.5.2. | Limitations of Modern Molecular Tools, | 18 |
| 1.5.3. | Promising New Technologies, | 18 |
| 1.6. | Conclusion and Perspectives, | 20 |
| | Acknowledgments, | 20 |
| | Abbreviations, | 20 |
| | Glossary, | 20 |
| | References, | 22 |

2. Diseases that Threaten Livestock, 31

J. Blancou and P.-C. Lefévre

- 2.1. Introduction, 31**
- 2.2. Animal Diseases Under Control, 31**
 - 2.2.1. General Considerations, 31
 - 2.2.2. Description of the Diseases, 34
- 2.3. Diseases that Are an Economic Burden and Hamper International Trade in Animals and Animal Products, 36**
 - 2.3.1. General Considerations, 36
 - 2.3.2. Description of the Diseases, 37
- 2.4. Animal Diseases that may Threaten Human Health, 39**
 - 2.4.1. Description of the Diseases, 40
- 2.5. Surveillance and Control of Transmissible Animal Diseases: Progress Expected from Modern Technologies, 41**
- 2.6. Conclusion, 42**
- References, 43**

3. HIV/AIDS Infection in the World with a Special Focus on Africa, 45

C. Laurent, M. Peeters, and E. Delaporte

- 3.1. Introduction, 45**
- 3.2. Current State of the Epidemic, 45**
 - 3.2.1. Prevalences and Incidences in the World, 45
 - 3.2.2. Mode of Transmission, 47
 - 3.2.3. Impact of HIV Infection on Other Endemic Diseases, 47
 - 3.2.4. Demographic, Social, and Economic Consequences, 48
- 3.3. Molecular Epidemiology, 48**
 - 3.3.1. Classification of HIV, 48
 - 3.3.2. Distribution of HIV-1 in Africa, 50
 - 3.3.3. Implications of Recombination, 51
- 3.4. Implication of HIV Variability on Pathogenesis, Treatment, Diagnosis, and Vaccine Development in Africa, 51**
 - 3.4.1. Impact of HIV Variability on Diagnosis, 52
 - 3.4.2. Impact of HIV Variability and Antiretroviral Therapy, 52
 - 3.4.3. Impact of HIV Variability on Transmissibility and Pathogenesis, 53
 - 3.4.4. Impact of HIV Variability on Vaccine Development, 53
- 3.5. Access to Treatment, 53**
- 3.6. Conclusion, 54**
- References, 54**

4. Molecular-Phylogenetic Strategies for Characterization of Uncultured Pathogens, 57

Daniel N. Frank and Robert A. Feldman

- 4.1. Introduction, 57**
 - 4.2. A Phylogenetic Framework for Culture-Independent Pathogen Detection, 58**
 - 4.2.1. Molecular-Phylogenetic Analysis of Ribosomal RNA Genes, 58
 - 4.2.2. Application to Monomicrobial Infections, 60
 - 4.2.3. Application to Polymicrobial Infections, 62
 - 4.3. Whole Genome Characterization of Uncultured Pathogens, 66**
 - 4.3.1. Enrichment of Monocultures, 66
 - 4.3.2. Metagenomics, 67
 - 4.4. Future Perspectives, 68**
- References, 68**

5. Molecular or Immunological Tools for Efficient Control of Tuberculosis, 75

J.L. Herrmann and P.H. Lagrange

- 5.1. Introduction, 75**
- 5.2. Definitions: Clinical Characteristics of Tuberculosis, 75**
- 5.3. Molecular Epidemiology: Advantages and Drawbacks, 77**
- 5.4. Immunological Epidemiology, 79**
 - 5.4.1. The Immune Response in the Control of Tuberculosis, 79
 - 5.4.2. IFN- γ -Based Assays: Description—Gold Standard of Tuberculosis Infection, 80
 - 5.4.3. Impact of T-Cell or B-Cell Assays in the Diagnosis of Active Tuberculosis, 81
- 5.5. Conclusions, 82**
- Abbreviations, 83**
- Glossary, 84**
- References, 84**

6. Understanding Human Leishmaniasis: The Need for an Integrated Approach, 87

M. Hide, B. Bucheton, S. Kamhawi, R. Bras-Gonçalves, S. Sundar, J.-L. Lemesre, and A.-L. Banuls

- 6.1. Generalities on Leishmaniasis, 87**
 - 6.1.1. Geographic Distribution, 87

| | | |
|-------------|---|------------|
| 6.1.2. | The Players in Leishmaniasis, | 87 |
| 6.1.3. | The Life Cycle of the <i>Leishmania</i> Parasite, | 88 |
| 6.1.4. | Symptoms, | 89 |
| 6.1.5. | Prevention, Diagnosis, and Treatments, | 90 |
| 6.1.6. | Why an Integrated Approach? | 93 |
| 6.2. | Impact of Sand Fly Vectors on Leishmaniasis, | 93 |
| 6.2.1. | The Life Cycle of <i>Leishmania</i> in a Competent Sand Fly Vector, | 93 |
| 6.2.2. | Vector Competence, | 94 |
| 6.2.3. | Metacyclogenesis and Transmission, | 95 |
| 6.2.4. | Sand Fly Modulation of the Mammalian Host Immune Response, | 96 |
| 6.3. | Biodiversity and Genetics of Parasites: Implications in Virulence and Pathogenicity in Humans, | 96 |
| 6.3.1. | <i>Leishmania</i> Species and Epidemiological Diversity, | 96 |
| 6.3.2. | Different Pathogenic Potential of Species and Within Species: Experimental Data, | 98 |
| 6.3.3. | Genetic Markers and Parasitic Factors Involved in Pathogenicity in Humans, | 98 |
| 6.4. | The Immune Response and Genetic Factors from the Mammalian Host, | 100 |
| 6.4.1. | The Host Immune Response to <i>Leishmania</i> , | 100 |
| 6.4.2. | Host Genetic Factors in Resistance/Susceptibility to Leishmaniasis, | 102 |
| 6.5. | The Need for an Integrated Approach: The Kala-Azar Example in India, | 107 |
| 6.6. | Conclusion, | 108 |
| | Acknowledgments, | 108 |
| | Abbreviations, | 108 |
| | Glossary, | 109 |
| | References, | 111 |

7. Epidemics of Plant Diseases: Mechanisms, Dynamics and Management, 125

Serge Savary

| | | |
|-------------|--|------------|
| 7.1. | Botanical Epidemiology, | 125 |
| 7.2. | Phenomenology of Botanical Epidemics, | 126 |
| 7.3. | Processes in Botanical Epidemics, | 128 |
| 7.4. | Factors Influencing Epidemics, | 129 |
| 7.5. | Some Simple Models in Botanical Epidemiology, | 130 |
| 7.6. | Refinement of Models, | 131 |

- 7.7. Disease Management: A Brief Review of Principles, 132**
- 7.8. Concluding Remarks, 134**
- References, 134**

8. Malaria Vaccines, 137

Charles W. Todd, Venkatachalam Udhayakumar, Ananias A. Escalante, and Altaf A. Lal

- 8.1. Introduction, 137**
- 8.2. Malaria Vaccine Considerations, 139**
- 8.3. Required Efficacy of Malaria Vaccines, 140**
- 8.4. Duration of Protection, 141**
- 8.5. Field Epidemiology Studies, 141**
- 8.6. Selection of Vaccine Epitopes, 142**
- 8.7. The Vaccine Target: Epitopes or Strains? 142**
- 8.8. Cytoadherence and Variant Genes, 143**
- 8.9. Limitations to Malaria Vaccine Development, 143**
- 8.10. Adjuvants and Antigen Delivery Systems, 144**
- 8.11. Multistage, Multiepitope Malaria Vaccine Candidate Antigens, 144**
- 8.12. Description of FALVAC-1 Antigen, 145**
- 8.13. Designing Artificial Recombinant Antigens, 146**
- Abbreviations, 146**
- Glossary, 146**
- References, 147**

9. The SARS Case Study: An Alarm Clock? 151

Gabriel Turinici and Antoine Danchin

- 9.1. SARS: Definition and Clinical Aspects, 151**
- 9.2. Mathematical Models for Epidemic Spread Propagation, 157**
- 9.3. The Double Epidemic Model, 159**
- 9.4. Conclusion, 160**
- Acknowledgment, 161**
- References, 161**

10. Recombination and Its Role in the Evolution of Pathogenic Microbes, 163

Philip Awadalla, Xin-zhuan Su, and Kate McGee

- 10.1. Introduction, 163**
- 10.2. The Evolutionary Costs and Benefits of Recombination, 163**

- 10.3. Evolutionary Significance of Recombination in Pathogenic Microbes, 164**
- 10.4. Recombination and Its Effects on Evolutionary Inferences within a Species, 166**
- 10.5. Detecting and Estimating Recombination, 167**
- 10.5.1. Nonparametric Analyses, 167
- 10.5.2. Parametric Methods, 168
- 10.6. Conclusions, 170**
- References, 171**

11. Evolutionary History of the Malaria Parasites, 175

Francisco J. Ayala

- 11.1. Malaria's Human Toll, 175**
- 11.2. Evolutionary Origins of *Plasmodium*, 175**
- 11.3. Human to Monkey or Monkey to Human? 178**
- 11.4. Population Structure of *P. falciparum*, 180**
- 11.5. Malaria's Eve Hypothesis, 181**
- 11.6. The Neolithic Revolution, Agriculture, and Climate Change, 183**
- 11.7. Concluding Remarks, 184**
- Acknowledgments, 185**
- Glossary, 185**
- References, 185**

12. Ecology Of Infectious Diseases: An Example with Two Vaccine-Preventable Infectious Diseases, 189

H. Broutin, N. Mantilla-Beniers, and P. Rohani

- 12.1. Introduction, 189**
- 12.2. Concepts and Methods, 190**
- 12.2.1. Mathematics—Modeling, 190
- 12.2.2. Population Ecology, 190
- 12.2.3. Comparative Approach—The Search for Emerging Themes? 192
- 12.3. An Example with Two Directly Transmitted Diseases: Measles and Pertussis Dynamics, 192**
- 12.3.1. Pertussis and Measles: Two Vaccine Preventable Diseases, 192
- 12.3.2. Persistence—CCS and Impact of Vaccination, 193
- 12.3.3. “City–Village” Spread, 195
- 12.4. Conclusion, 196**
- Acknowledgments, 196**
- References, 196**

13. Influenza Evolution, 199

Robin M. Bush

- 13.1. Introduction, 199**
- 13.2. The Influenza Virus, 199**
 - 13.2.1. Influenza Genome, 200
 - 13.2.2. The Diversity of Influenza A Subtypes, 200
- 13.3. Antigenic Shift and Antigenic Drift, 200**
- 13.4. Host Specificity, 200**
- 13.5. Avian Influenza, 201**
- 13.6. Swine and Equine Influenza, 202**
- 13.7. Human Influenza, 202**
 - 13.7.1. Epidemic Influenza, 202
 - 13.7.2. Pandemic Influenza, 206
- 13.8. The Current Avian H5N1 Outbreak, 208**
- 13.9. Evolution and Intervention, 208**
- References, 209**

14. Experimental Evolution of Pathogens, 215

Vaughn S. Cooper

- 14.1. Experimental Design, 216**
- 14.2. Measuring Adaptation, 216**
- 14.3. Experimental Evolution of Vesicular Stomatitis Virus (VSV), 218**
- 14.4. In Vivo Evolution of *Salmonella Typhimurium*, 219**
- 14.5. Experimental Evolution of *Candida Albicans* Antibiotic Resistance, 220**
- 14.6. Future Prospects, 222**
- Acknowledgments, 223**
- Glossary, 223**
- References, 223**

15. Evolution of Antigenic Variation, 225

Steven A. Frank

- 15.1. Introduction, 225**
- 15.2. Why Do Parasites Vary? 226**
 - 15.2.1. Extend Length of Infection, 226
 - 15.2.2. Infect Hosts with Prior Exposure, 226
 - 15.2.3. Infect Hosts with Genetically Variable Resistance, 226
 - 15.2.4. Vary Attachment Characters, 226
- 15.3. Mechanisms that Generate Variation, 227**
 - 15.3.1. Mutation and Hypermutation, 227
 - 15.3.2. Stochastic Switching Between Archival Copies, 228
 - 15.3.3. Intragenomic Recombination, 229
 - 15.3.4. Mixing Between Genomes, 229

| | |
|---|--|
| 15.4. Interactions with Host Immunity, 230 | |
| 15.4.1. Natural Selection of Antigenic Variants, 230 | |
| 15.4.2. Pathogen Manipulation of Host Immune Dynamics, 231 | |
| 15.4.3. Sequence of Variants in Active Switching from Archives, 231 | |
| 15.5. Experimental Evolution, 233 | |
| 15.5.1. Antigenicity and Structure of FMDV, 233 | |
| 15.5.2. Antibody Escape Mutants, 233 | |
| 15.5.3. Cell Binding and Tropism, 234 | |
| 15.5.4. Fitness Consequences of Substitutions, 235 | |
| 15.6. Measuring Selection with Population Samples, 235 | |
| 15.6.1. Positive and Negative Selection, 235 | |
| 15.6.2. Positive Selection to Avoid Host Recognition, 236 | |
| 15.6.3. Phylogenetic Analysis of Nucleotide Substitutions, 236 | |
| 15.6.4. Predicting Evolution, 237 | |
| 15.7. Shape, Charge, Binding Kinetics, and Evolution, 237 | |
| Abbreviations, 237 | |
| Glossary, 237 | |
| References, 238 | |

16. Hantavirus Coevolution with Their Rodent Hosts, 243

Vincent Herbreteau, Heikki Henttonen, Kumiko Yoshimatsu, Jean-Paul Gonzalez, Yupin Suputtamongkol, and Jean-Pierre Hugot

| | |
|--|--|
| 16.1. Introduction, 243 | |
| 16.2. Generalities on Hantaviruses, 244 | |
| 16.2.1. Hantavirus Taxonomy, 244 | |
| 16.2.2. Geographic Distribution, 250 | |
| 16.2.3. Morphology, 250 | |
| 16.2.4. Transmission, 250 | |
| 16.2.5. Diagnosis and Symptoms, 251 | |
| 16.3. Serological Presence without Cases in Thailand, 251 | |
| 16.3.1. Serological Investigations in Rodents, 252 | |
| 16.3.2. Serological Investigations in Humans, 254 | |
| 16.4. Phylogeny of Hantaviruses, 254 | |
| 16.4.1. Material and Methods, 254 | |
| 16.4.2. Results, 255 | |
| 16.5. Discussion, 259 | |
| 16.5.1. Clades, Groups, Robustness of Nodes, and Molecular Data, 259 | |
| 16.5.2. Biogeography of Hantaviruses and Their Hosts, 260 | |

16.6. Conclusion, 261

16.6.1. Presence Without Cases Versus Cases Without Notification? 261

Abbreviations, 262

Glossary, 262

References, 262

17. Phylogenetic Methods for the Analysis of Parasites and Pathogens, 265

Jamie R. Stevens

17.1. Introduction, 265**17.2. The Phylogenetic Process, 267**

17.2.1. Source Material, 267

17.2.2. DNA Sequencing and Alignment, 267

17.2.3. Phylogenetic Methods, 272

17.2.4. Methods of Assessing the Robustness of Phylogenetic Relationships, 276

17.2.5. Additional Considerations, 276

17.3. Methods of Comparing Phylogenies, 282

17.3.1. Methods of Assessing Congruence Between Phylogenies, 282

17.3.2. Methods for Studying Coevolution, 282

17.4. Dating Phylogenetic Trees, 285

17.4.1. Molecular Clocks, 285

17.4.2. Biogeography and Fossils, 286

17.5. Conclusion, 287

Acknowledgments, 288

Glossary, 288

References, 289

18. Parasites that Manipulate Their Hosts, 299

Frédéric Thomas, Janice Moore, Robert Poulin, and Shelley Adamo

18.1. Introduction, 299**18.2. Historical Overview, 299****18.3. Selected Examples of Manipulation, 301**

18.3.1. Manipulation of Predator–Prey Encounters, 301

18.3.2. Manipulation of Habitat Choice, 303

18.3.3. Other Kinds of Manipulation, 303

18.3.4. Manipulation by Vector-Borne Parasites, 303

18.3.5. Are Humans Manipulated by Parasites? 303

18.4. How Does the Presence of a Parasite Alter Host Behavior? 305

18.4.1. Direct Effects, 306

18.4.2. Indirect Methods, 307

- 18.4.3. Importance of Understanding the Physiological Basis of Host Behavioral Change, 307
- 18.4.4. Implications about Parasitic Manipulation from Recent Mechanistic Studies, 307
- 18.4.5. New Methods in the Study of How Parasites Manipulate Their Hosts, 308
- 18.5. Adaptive Versus Nonadaptive Changes, 308**
- 18.6. Cost(s) of Manipulation for Parasites, 308**
- 18.7. Mafia-Like Strategy of Manipulation, 309**
- 18.8. Multiple Parasites within Manipulated Hosts, 310**
- 18.9. How Complex are “Parasitically Modified Organisms”? 310**
- 18.10. Intraspecific Variation in Manipulative Processes, 311**
- 18.11. Manipulative Parasites and Ecosystem Functioning, 311**
- 18.12. Concluding Remarks, 313**
 - Glossary, 313
 - References, 314

19. Human Genetic Diversity and the Spread of Infectious Diseases, 321

M. Tibayrenc

- 19.1. Introduction: Key Concepts, 321**
- 19.2. Exploring the Genetic Background of Human Genetic Susceptibility to Infectious Diseases, 322**
 - 19.2.1. Methodology, 322
 - 19.2.2. A Limited Harvest, 322
 - 19.2.3. Problems Encountered, 323
- 19.3. Human Diversity Revealed by Neutral/Historical Genetic Markers, 323**
 - 19.3.1. The Isoenzyme Revolution, 324
 - 19.3.2. A Now Classical Pattern, 325
- 19.4. Genetically Driven Phenotypic Diversity, 327**
 - 19.4.1. The Abyss Between Genotype and Phenotype, 327
 - 19.4.2. Phenotypic Traits that have an Obvious Genetic Basis, 327
- 19.5. Are Races and Ethnic Groups Biologically Meaningful and Medically Relevant? 327**
 - 19.5.1. The Biological Nature of Ethnic Groups/Races, 327
 - 19.5.2. Population and Ethnic Diversity with Regard to Transmission and Severity of Infectious Diseases, 329

- 19.6. Our Genetic Inheritance has been Sculpted by Infectious Diseases, 330**
- 19.7. Major International Programs that will Boost Our Understanding of Human Genetic Diversity, 330**
- 19.7.1. The Human Genome Project (HGP): Something Like Landing on the Moon, 330
- 19.7.2. A Welcome Enterprise: The Human Genome Diversity Project (HGDP), 331
- 19.7.3. The HapMap Project: Could It Miss Its Target? 331
- 19.8. Conclusion, 331**
- Abbreviations, 332**
- Glossary, 332**
- References, 334**

20. Molecular Epidemiology and Evolutionary Genetics of Pathogens, 337

M. Tibayrenc

- 20.1. Introduction: Molecular Epidemiology (ME) and Evolutionary Genetics Are Inseparable, 337**
- 20.1.1. ME Mission Statement, 338
- 20.3. The Modern Hypermarket of Molecular Technologies, 338**
- 20.3.1. Four Key Starting Points, 338
- 20.3.2. Classification of Markers, 339
- 20.4. Survival Kit for Evolutionary Genetic Interpretation, 342**
- 20.4.1. ME's Full Task, 342
- 20.4.2. Two Complementary Tools for ME: Population Genetics and Phylogenetic Analysis, 342
- 20.4.3. Pathogen Species, Subspecies, Strains, and Clones, 345
- 20.5. Conclusion, 349**
- Abbreviations, 349**
- Glossary, 350**
- References, 353**

21. The Need for Megatechnologies: Massive Sequencing, Proteomics and Bioinformatics, 357

David G. Biron, Austin L. Hughes, Hugh D. Loxdale, and Hercules Moura

- 21.1. Introduction, 357**
- 21.2. The Pre-Genomic Era, 358**

| | | |
|--------------|--|-----|
| 21.2.1. | Molecular Epidemiology and Infectious Diseases, | 358 |
| 21.2.2. | Population Genetics of Hosts and/or Infectious Agents, | 359 |
| 21.2.3. | Pre-Genomic Era and “Bioterrorism”, | 360 |
| 21.3. | Genomic Era, 360 | |
| 21.3.1. | Genome Projects, | 360 |
| 21.3.2. | New Scientific Fields Emerged During the Genomic Era, | 360 |
| 21.3.3. | Genomic Era and Bioterrorism, | 362 |
| 21.4. | Post-Genomic Era, 362 | |
| 21.4.1. | Proteomics, | 362 |
| 21.4.2. | Bioinformatics, | 368 |
| 21.4.3. | Post-Genomic Era and Bioterrorism, | 371 |
| 21.5. | Conclusion, 371 | |
| | Abbreviations, 372 | |
| | Glossary, 372 | |
| | References, 374 | |

22. Mathematical Modeling of Infectious Diseases Dynamics, 379

M. Choisy, J.-F. Guégan, and P. Rohani

| | | |
|--------------|---|-----|
| 22.1. | Introduction, 379 | |
| 22.2. | The Philosophy of Mathematical Modeling, 380 | |
| 22.2.1. | Model Complexity, | 380 |
| 22.2.2. | Model Formulation and Hypothesis Testing, | 381 |
| 22.2.3. | Stochastic Versus Deterministic Models, | 382 |
| 22.3. | The Nature of Epidemiological Data, 382 | |
| 22.4. | Childhood Micro-Parasitic Infections, 382 | |
| 22.5. | A Simple Epidemic Model, 383 | |
| 22.5.1. | Transmission Process, | 383 |
| 22.5.2. | Between-Compartment Flux of Individuals, | 383 |
| 22.5.3. | Basic Reproduction Number and Threshold Effects, | 383 |
| 22.5.4. | Deterministic Setup and Dynamics Analysis, | 383 |
| 22.5.5. | Stochastic Dynamics and Probability of an Epidemic in a Small Population, | 387 |
| 22.6. | A Simple Endemic Model, 388 | |
| 22.6.1. | Deterministic Dynamics, | 388 |
| 22.6.2. | Statics and the Average Age at Infection, | 389 |
| 22.6.3. | Stochastic Dynamics and Disease Persistence, | 390 |

| | |
|--|--|
| 22.7. Endemo-Epidemic Models, 391 | |
| 22.7.1. Varying Contact Rate, 392 | |
| 22.7.2. Age-Structured Models, 392 | |
| 22.7.3. Spatially Structured Models, 393 | |
| 22.7.4. Stochastic Endemic Models, 393 | |
| 22.8. Data Analysis, 394 | |
| 22.8.1. Parameter Estimations, 394 | |
| 22.8.2. Tools for Time Series Analysis, 396 | |
| 22.9. Applications to Vaccination Policies, 399 | |
| 22.9.1. Mass Vaccination Strategy, 399 | |
| 22.9.2. Pulse Vaccination Strategy, 400 | |
| 22.10. Conclusion, 401 | |
| 22.10.1. What we Have Seen, 401 | |
| 22.10.2. What We Have Not Seen, 402 | |
| 22.11. Summary, 402 | |
| Acknowledgments, 403 | |
| References, 403 | |

23. Using a Geographic Information System to Spatially Investigate Infectious Disease, 405

A. Curtis, J.K. Blackburn, and Y. Sansyzbayev

| | |
|--|--|
| 23.1. Introduction, 405 | |
| 23.1.1. What Is a GIS? 406 | |
| 23.1.2. Why Geography Is Important, 408 | |
| 23.2. The Basic GIS: Individual Components, 410 | |
| 23.2.1. Spatial Data Input, 410 | |
| 23.2.2. Spatial Precision in the Data, 412 | |
| 23.2.3. Data Entry into the GIS: Geocoding, Entering Coordinates, Heads-up Digitizing, 412 | |
| 23.3. Data Manipulation, 415 | |
| 23.3.1. Querying Data, 416 | |
| 23.3.2. Spatial R ₀ : Spatial Querying, 416 | |
| 23.3.3. Caution with Aggregation and Disaggregation, 416 | |
| 23.4. Spatial Analysis, 417 | |
| 23.4.1. Kernel Density Analysis, 417 | |
| 23.4.2. Measures of Spatial Autocorrelation and Spatial Forms of Regression, 417 | |
| 23.4.3. Spatial Analysis Software, 418 | |
| 23.5. Spatial Visualization, 419 | |
| 23.5.1. Map Production, 419 | |
| 23.5.2. Protecting Confidentiality While Preserving Spatial Relationships, 419 | |
| 23.5.3. Choropleth Maps, 419 | |
| 23.5.4. The Importance of Basic Cartographic Rules, 420 | |
| 23.5.5. Cartographic Animation, 420 | |
| 23.6. The Future of GIS, 421 | |
| Acknowledgments, 421 | |

Abbreviations, 421**Glossary, 421****References, 422****24. Vector Control by Surveillance Networks: The ECLAT Program and Chagas, 425***J.-P. Dujardin and C.J. Schofield***24.1. Introduction, 425****24.2. Origin and Spread of Human Chagas Disease, 426****24.3. The Dispersal of the Main Vectors, 427****24.4. From Disease to Public Health Problem, 428**

24.4.1. The Nature of the Disease, 428

24.4.2. The Disease of Poverty, 428

24.4.3. Socioeconomic Impact, 429

24.5. Control and Surveillance, 430

24.5.1. Control Strategies, 430

24.5.2. Vigilance Strategies, 430

24.6. Vigilance and Research, 431

24.6.1. Research and Vigilance, 431

24.6.2. Endangered Continuity, 431

24.6.3. The Role of Research, 431

24.6.4. The ECLAT Network, 431

24.6.5. The ECLAT Lesson, 432

24.7. Conclusion, 432**References, 433****25. Contributions of Morphometrics to Medical Entomology, 435***J.-P. Dujardin and D.E. Slice***25.1. Introduction, 435**

25.1.1. From Dimensions to Biology, 435

25.1.2. Tradition and Modernity, 435

25.2. Causes of Metric Variation? 436

25.2.1. Physiological Causes, 436

25.2.2. Pathological Causes, 437

25.2.3. Adaptive Causes, 437

25.2.4. Genetic Causes, 437

25.3. Size and Shape, 437

25.3.1. The Search for a Global Estimator of Size, 438

25.3.2. Shape As Size-Free Variation, 438

25.3.3. Shape As Geometry, 439

25.3.4. Which Shape? 441

25.4. Morphometrics and Medical Entomology, 441

25.4.1. Systematics, 441

25.4.2. Geographic Variation, 442

- 25.4.3. Comparisons of Morphometric with Genetic Variation, 442
- 25.4.4 Topics Specific to Triatominae, 443

25.5. Authors Contribution

to Morphometrics Software, 444

- 25.5.1. Software for Multivariate Analyses, 444
- 25.5.2. Software for Landmark-Based Data Analyses, 444
- 25.5.3. Comprehensive Software, 444

25.6. Conclusion, 445

References, 445

26. Surveillance of Vector-Borne Diseases Using Remotely Sensed Data, 449

D.E. Gorla

26.1. Vector-Borne Disease Surveillance, 449

26.2. Remote Sensing and Vector-Borne Diseases, 450

26.3. Identification of Vector Habitats, 453

26.4. Monitoring Environmental Changes for Disease Surveillance, 454

- 26.4.1. The Case of Chagas Disease in the Amazon, 454

26.5. Early Warning Systems for Vector-Borne Disease Outbreaks, 455

Acknowledgment 456

References, 456

27. Archaeological Epidemiology of Infectious Diseases: Fossil DNA, 459

Felipe Guhl and Arthur Aufderheide

27.1. Introduction, 459

27.2. Techniques and Procedures for Detecting Infectious Agents in Archaeology, 460

- 27.2.1. Mummies, 460
- 27.2.2. Coprolites, 462
- 27.2.3. Histological Methods, 463
- 27.2.4. Immunological Methods, 463
- 27.2.5. Fossil DNA, 464
- 27.2.6. Molecular Biology Methods, 464
- 27.2.7. Paleoparasitology, 466
- 27.2.8. Paleopharmacology and Ethnography, 466

27.3. Epidemiology of Ancient Infectious Diseases, 466

- 27.3.1. Smallpox, 466
- 27.3.2. Chagas Disease, 467
- 27.3.3. Malaria, 467

- 27.3.4. Influenza Virus, 467
- 27.3.5. Tuberculosis, 467
- 27.3.6. Leprosy, 467
- 27.3.7. Plague, 467
- 27.3.8. Treponematosis, 468

27.4. Clues Regarding American Humans, 468

- 27.4.1. The First Inhabitants, 469
- 27.4.2. The First Parasites, 470
- 27.4.3. The First Infectious Diseases, 470

27.5. New Perspectives, 470

Acknowledgments, 471

Abbreviations, 471

Glossary, 471

References, 472

**28. Insights Into Structure and Evolution of
Bacterial Species That Are Revealed
by Molecular Methods, 475**

P. Roumagnac, L. Gagnevin, O. Pruvost, and M. Achtman

28.1. Introduction, 475

28.2. Methods that Index DNA Polymorphism, 476

- 28.2.1. DNA Fingerprinting, 477
- 28.2.2. Sequence Comparisons, 482

28.3. Applications of Molecular Methods, 484

- 28.3.1. Clock Rates of Different Markers, 484
- 28.3.2. Geographical Considerations, 485
- 28.3.3. Hierarchical and Nested Approach, 486
- 28.3.4. Population Genetics, 486

28.4. Conclusions, 486

Acknowledgments, 487

References, 487

**29. Exploring Genetic Relatedness, Patterns of
Evolutionary Descent, and the Population
Genetics of Bacterial Pathogens Using
Multilocus Sequence Typing, 495**

Brian G. Spratt, William P. Hanage, and Christophe Fraser

29.1. Introduction, 495

29.2. Bacterial Population Structure and MLST, 496

- 29.2.1. Displaying Relationships Between Isolates, 497

- 29.2.2. Defining Clonal Complexes, Clonal Ancestry and Patterns of Descent, 498

- 29.2.3. Comparing Split Decomposition, Minimum Spanning Trees and eBURST, 502
- 29.2.4. Displaying the Overall Structure of a Population, 504
- 29.3. MLST Data As a Resource for Bacterial Population Genetics, 504**
- 29.4. Measuring Rates of Recombination from MLST Data, 505**
- 29.5. Concluding Remarks, 506**
- Glossary, 506**
- References, 507**

30. Topical Debates

Evaluation of Risks and Benefits of Consumption of Antibiotics: From Individual to Public Health, 509

Fernando Baquero

- 30.1. Antibiotics and Human Health, 509**
- 30.2. The Determinants of Health: Conservation Medicine, 509**
- 30.3. From Fears to Possibilities, 510**
- 30.4. How Important Is Antibiotic Resistance As a Risk for Public Health? 510**
- 30.5. Health Versus Resistance, 510**
- 30.6. Changes in Antibiotic Consumer's Behavior: Egoism Versus Altruism, 511**
- 30.7. The Role of Worry in Individual Patient's Behavior, 511**
- 30.8. The Role of Worry in the Prescriber's Behavior, 511**
- 30.9. Individual Versus Society Components in Shaping Individual Risks, 511**
- 30.10. Appropriate Demand of Antibiotics and the Individual Risk, 512**
- 30.11. "MY" Utilization of Antibiotics: A Personal Decision, 512**
- 30.12. The Individual Health Risks of Antibiotic Use, 512**
- 30.13. The Individual Health Benefits of Antibiotic Use, 513**
- 30.14. The Problem of Minimums: Minimal Benefits Versus Minimal Risks, 513**
- 30.15. The Problem of Presumed Minimal Benefits that Might Become Significant Ones, 513**
- 30.16. The Design of Observational-Ecological Experiments to Determine Attributable Risks and Benefits of the Use of Antibiotics, 514**
- 30.16.1. Facing Individual Variability: Blocking Strategies, 514

- 30.16.2. Facing the Heterogeneity of Antimicrobial Agents, 514
- 30.16.3. Assumptions to be Tested and Possible Outcomes, 515
- 30.16.4. Experiences in Other Fields, 515

30.17. Conclusion, 515

References, 515

31. Epidemic Diseases in the Past: History, Philosophy, and Religious Thought, 517

D. Buchillet

31.1. Plague, 517

31.2. Smallpox, 519

31.3. Cholera, 521

31.4. Conclusion, 523

References, 523

32. Fundamentals, Domains, and Diffusion of Disease Emergence: Tools and Strategies for a New Paradigm, 525

Jean-Paul J. Gonzalez, Philippe Barbazan, François Baillon, Julien Capelle, Damien Chevallier, Jean-Paul Cornet, Florence Fournet, Vincent Herbreteau, Jean-Pierre Hugot, Meriadeg Le Gouilh, Eric Leroy, Bernard Mondet, Narong Nitatpattana, Stephane Rican, Gérard Salem, Wailarut Tuntrapasarat, and Marc Souris

Foreword, 525

32.1. From Nosology to Concept, 526

32.1.1. Emerging Diseases, 526

32.1.2. Understanding the Fundamentals of Emergence, 527

32.2. Tools and Strategies: An Integrative Approach, 532

32.2.1. Choosing the Appropriate Strategies and Identifying Corresponding Tools, 532

32.2.2. The Emergence Play: Actors and Decors of a Drama, 533

32.2.3. Requiring and Acquiring Data: From Who, to Where and How? 533

32.2.4. Model and Simulation, 534

32.3. Emergence of Exemplary Diseases or Systems, 534

32.3.1. Assessing the Risk of Disease

Emergence in a Changing World, 535

32.3.2. Comprehension of Mechanisms of Emergence and Their Control, 538

32.3.3. Climate-Dependent Arboviroses, 542

- 32.3.4. Rain, Rodent, and Rice: Leptospirosis Epidemics in Thailand, 546
- 32.3.5. New Pathogens, New Diseases: A Faunistic Approach to Reservoirs and Their Hosts, 549

32.4. Concluding Remarks, 565

- 32.4.1. To Favor Prevention not Treatment, 565
- 32.4.2. The Emerging Viral Diseases Are Also a Growing Concern for the Northern Countries, 565
- 32.4.3. Development and the Economy of Prevention, 566
- 32.4.4. Diseases Will Emerge, 566

Acknowledgments, 566

References, 566

33. Epidemiology in a Changing World: The Need for a Bigger Picture! 569

J.-F. Guégan and G. Constantin de Magny

33.1. Introduction, 569

33.2. The Interactions Between Human Populations and Natural Systems, 570

- 33.2.1. Human Psychology and Our Mental Perception of the Environment, 570
- 33.2.2. A Changing World, Changing Human Mentalities, and the Role of Science, 571
- 33.2.3. Global Environmental Changes: New Health Threats for the Foreseeable Future, 573

33.3. Dynamic Properties of Microbes, Their Hosts and the Environment, 574

- 33.3.1. The Ecological Context of Infectious Diseases: The Three-Piece Puzzle 574
- 33.3.2. Ecosystem Dynamics and Health, or the Snowball Syndrome, 576
- 33.3.3. The Emergence of Conservation Medicine, 577

33.4. The Ecology of Infectious Diseases in Practice, 577

- 33.4.1. What Came First: Biology or Socioeconomy? 578
- 33.4.2. Enhanced Global Warming and the Spread of Infectious Diseases, 579
- 33.4.3. Ecosystem Changes and Health, 581
- 33.4.4. Land Use, Agricultural Development, Intensified Farming, and Health, 581
- 33.4.5. Human Population Growth and Behavioral Practices, 583
- 33.4.6. International Travel and Trade, 583

- 33.5. Conclusion and Suggested Research Perspectives, 585**
- 33.6. Summary, 586**
- Acknowledgments, 587**
- References, 587**

34. Contributions of Social Anthropology to Malaria Control, 591

Jaffré Yannick

- 34.1. Introduction, 591**
 - 34.1.1 A Poverty-Related Disease? 591
- 34.2. Six Proposals of Research and Control, 593**
- 34.3. Anthropology for Improving the Offer of Health Care, 599**
- 34.4. Three Operational Approaches, 599**
- References, 600**

35. The Neglected Diseases and Their Economic Determinants, 603

Alvaro Moncayo and Mario Ortiz Yanine

- 35.1. The “Neglected” Diseases, Criteria for Classification, 603**
- 35.2. The Diseases, 604**
 - 35.2.1. African Trypanosomiasis, 604
 - 35.2.2. Malaria, 604
 - 35.2.3. Leishmaniasis, 606
 - 35.2.4. American Trypanosomiasis (Chagas Disease), 607
 - 35.2.5. Dengue, 608
 - 35.2.6. Tuberculosis, 609
 - 35.2.7. Schistosomiasis, 610
- 35.3. The “Neglected” Diseases Burden, 611**
- 35.4. The Economic Situation and Trends in the Affected Countries and Regions, 612**
 - 35.4.1. Latin America, 1990–2003, 612
 - 35.4.2. Africa, 1985–2003, 612
 - 35.4.3. Southeast Asia, 1990–2001, 613
- 35.5. Economic Barriers for Development of Drugs, Vaccines and Vector Control Tools Against the “Neglected Diseases”, 613**
- 35.6. Future Perspectives, 615**
 - Abbreviations and Acronyms, 616**
 - References, 616**

36. The Challenge of Bioterrorism, 619

Stephen A. Morse

- 36.1. Introduction, 619**

- 36.2. Definitions, 619**
- 36.3. Threat Agents, 619**
- 36.4. Impact of Biotechnology, 626**
- 36.4.1. Modification of Threat Agents, 626
- 36.4.2. Modified Low Virulence or Nonpathogenic Organisms, 626
- 36.4.3. Recreation or In Vitro Synthesis of Viral Pathogens, 627
- 36.4.4. Unintended Consequences of Biotechnology, 628
- 36.5. Scenarios, 628**
- 36.6. Responses to Bioterrorism: Laboratory, 628**
- 36.7. Responses to Bioterrorism: Epidemiology and Surveillance, 630**
- 36.8. Molecular Epidemiology and Microbial Forensics, 632**
- 36.9. Basic and Applied Research, 632**
- 36.10. Limiting Access to Dangerous Pathogens, 633**
- 36.11. Summary, 634**
- Glossary, 634**
- References, 634**

37. Needs for an Integrative Approach of Epidemics: The Example of Cholera, 639

R. Piarroux and D. Bompangue

- 37.1. Introduction, 639**
- 37.2. *Vibrio Cholerae* and Its Natural Environment, 640**
- 37.2.1. *Vibrio Cholerae*, 640
- 37.2.2. Biotope of *Vibrio Cholerae*, 640
- 37.2.3. VPIΦ, CTXΦ Bacteriophages and Pathogenic Strains of *V. cholerae*, 641
- 37.3. Cholera, 641**
- 37.3.1. Clinical Manifestations, 641
- 37.3.2. Guidelines for Collective Management of a Cholera Epidemic, 642
- 37.4. Man and Cholera Epidemics in the Nineteenth and Twentieth Centuries, 643**
- 37.5. Man, Society, and Cholera at the Beginning of the Twenty-First Century: Our Personal Experience of Cholera Management, 646**
- 37.5.1. The Cholera Epidemic in Grand Comoro, 646
- 37.5.2. Cholera Epidemic in Kasai, 648
- 37.5.3. Cholera, Media, and Humanitarian Agencies, 650
- 37.6. Conclusion, 651**
- References, 652**

38. Infectious Diseases: Market of the Future?, 655

Jan Verhoef and Ad Fluit

- 38.1. Introduction, 655**
- 38.2. The Information and Communication Technology Revolution, 656**
- 38.3. Internet Changing the Health Care Delivery Landscape, 656**
- 38.4. The Looming Biotech Revolution, 658**
 - 38.4.1. Resistant and Multiresistant Bacteria, 658
- 38.5. Rapid Diagnosis of Infection, 658**
- 38.6. Laboratory Automation, 659**
- 38.7. Market, 660**
- 38.8. Future Market, 661**
 - 38.8.1. Molecular Diagnostics, 661
 - 38.8.2. Microarrays and Lab-on-a-Chip Devices, 662
- 38.9. Anticipated Developments, 663**
 - 38.9.1. Real-Time PCR, 663
 - 38.9.2. Raman Spectroscopy, 663
 - 38.9.3. Whole Genome Sequencing, 663
 - 38.9.4. DNA Chip Technology, 663
- 38.10. Novel Antibiotics, 663**
- 38.11. New Classes of Antibiotics, 664**
- 38.12. Pharmacogenomics, 665**
- 38.13. Conclusion, 666**
References, 667

39. Mobilizing the Scientific Community for the Patient's Benefit: At the Crossroads of Fundamental and Applied Science, 669

K. Victoir

- 39.1. What Are Neglected Diseases?, 669**
 - 39.1.1. Identification of Patient Needs and the Barriers to Overcome, 670
 - 39.1.2. Developing and Promoting a Needs-Based R&D Agenda, 672
 - 39.1.3. Funding, 673
 - 39.1.4. A Multidisciplinary Approach, 673
- 39.2. Conclusion, 675**
Acknowledgments 676
References, 676

40. Infectious Diseases and Arts, 677

Pierre Vidal, Myrtille Tibayrenc, and Jean-Paul Gonzalez

Foreword, 677

40.1. The Fine Arts: Pictorial Representations, 678

- 40.1.1. The Roots of Art and Infectious Disease, 679
- 40.1.2. The Plague: Art, Terror, and Religion, 679
- 40.1.3. Art at the Service of Medical Science, 680
- 40.1.4. Tuberculosis, Self-Portraits of the Diseased, 683
- 40.1.5. The Syphilitic Female Model: A Turning Point in Art History, 686
- 40.1.6. Images of Disease: Photography and Photographers, 691
- 40.1.7. Graphic Arts, 694

40.2. Literature, 695

- 40.2.1. The Bible, 695
- 40.2.2. Homer: The Iliad (Song I), 696
- 40.2.3. The Black Death, 696
- 40.2.4. Cholera, the Blue Plague, 707
- 40.2.5. The White Plague, 716
- 40.2.6. Syphilis, 719
- 40.2.7. Smallpox, Ebola, and Other Pestilences, 722

40.3. Cinematographic Art: Movies and Diseases, 729

- 40.3.1. The Ebola Fever Movies and Television Movies, 735
- 40.3.2. Alien “The Series”, 736

40.4. The Arts and Infectious Disease, in Conclusion, 736

References, 738

Index, 741