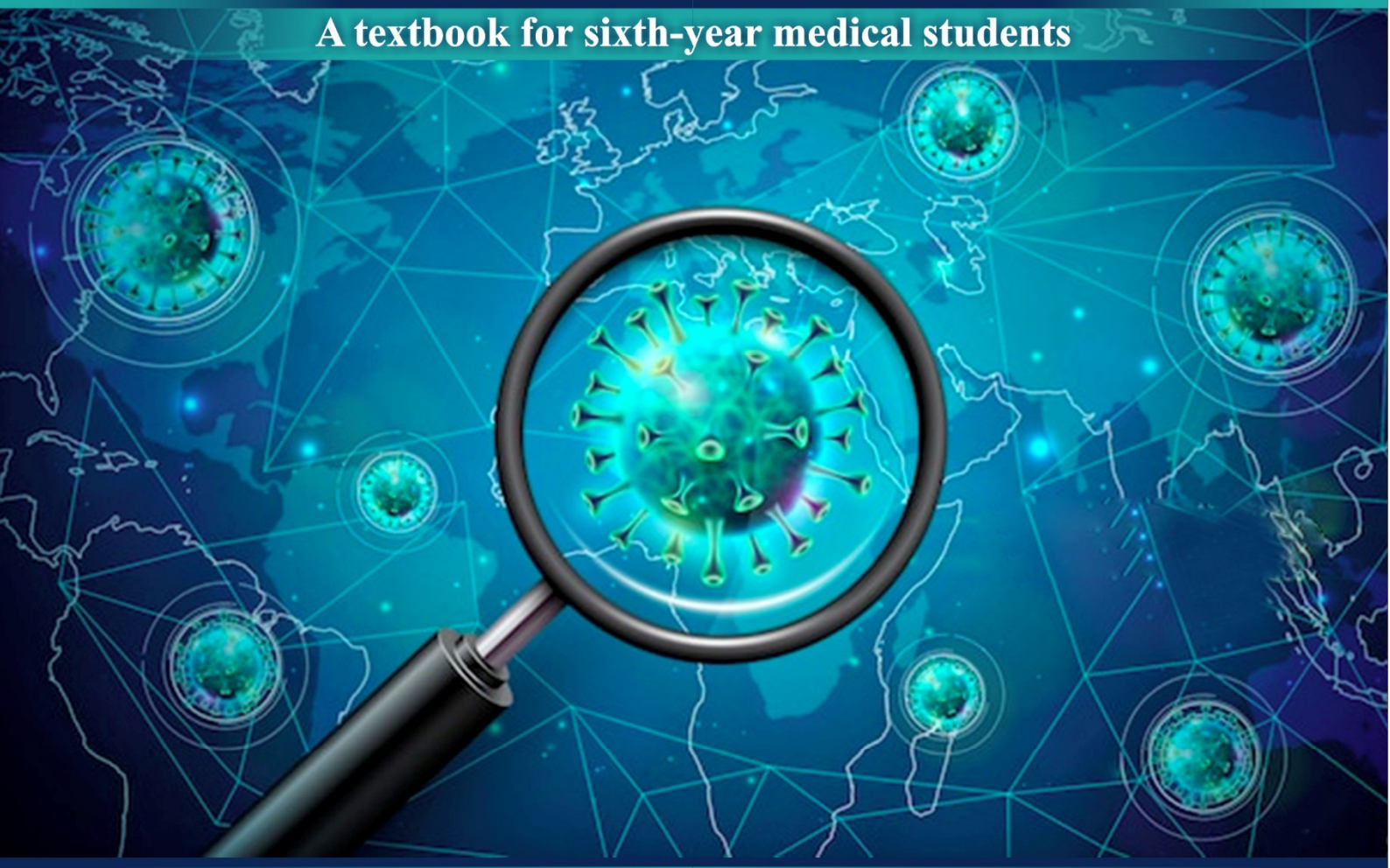
„VICTOR BABEŞ" UNIVERSITY
OF MEDICINE AND PHARMACY
FROM TIMIŞOARA

Ionuț-Dragoș Căpraru

EPIDEMIOLOGY
IN MEDICAL PRACTICE

Principles, Pathogens, and Chronic Diseases

A textbook for sixth-year medical students



HIPPOCRATE

„Victor Babeş" Publishing House
Timişoara, 2026

Editura „Victor Babeş”
Piaţa Eftimie Murgu nr. 2, cam. 316, 300041 Timişoara
Tel./ Fax 0256 495 210
e-mail: evb@umft.ro
https://www.umft.ro/ro/organizare-evb/

Director General: Prof.univ.dr. Sorin Ursoniu

Colecţia: HIPPOCRATE
Coordonastor colecţie: Prof. univ. dr. Andrei Motoc

Referent ştiinţific: Prof. univ. dr. Cătălin Marian

Indicativ CNCSIS: 324

© 2026
Toate drepturile asupra acestei ediţii sunt rezervate.
Reproducerea parţială sau integrală a textului, pe orice suport, fără acordul scris al autorilor este interzisă şi se va sancţiona conform legilor în vigoare.

ISBN 978-606-786-658-2

To my son Mihai,

who inspires me to share my knowledge with those who will become the specialists of tomorrow.

Preface

This book has grown out of the lectures in general epidemiology and in the epidemiology of communicable and non-communicable diseases delivered to sixth-year medical students at the "Victor Babeș" University of Medicine and Pharmacy of Timișoara. Its purpose is to gather, in a single and coherent text, the material that students encounter in the lecture hall, so that they may prepare for their examinations and — more importantly — for their future practice with a complete and readable reference in hand.

Epidemiology occupies a special place in the training of the future physician. It is the discipline that lifts the doctor's gaze from the individual patient to the population, teaching him or her to think in terms of sources of infection, routes of transmission, susceptible groups, risk factors and preventive strategies. The clinician who understands epidemiology treats not only the case in front of them but also contributes, through early diagnosis, correct reporting, isolation measures and vaccination, to the protection of the whole community. The COVID-19 pandemic, the resurgence of measles in Europe, the silent burden of viral hepatitis and the steadily growing weight of chronic non-communicable diseases have all reminded us — sometimes brutally — that no branch of medicine can function without an epidemiological foundation.

The book is organised in five parts. **Part I — General Epidemiology** presents the object and history of the discipline, the fundamental concepts (the infectious process, the epidemiological focus, the epidemiological process), the three determining factors — the source of infection, the routes and mechanisms of transmission, and the receptive population — together with the favouring factors and the forms of manifestation of the epidemiological process, and closes with the theory of prevention and its levels. **Part II — Epidemiological Methods** provides the instruments with which all of this is established: the measurement of disease frequency and burden, the architecture of epidemiological studies from the case series to the randomised trial, bias, confounding and causal inference, the principles and the specific pitfalls of screening, and the organisation of surveillance, of outbreak investigation and of the international legal framework of health security. **Part III — Special Epidemiology of Infectious Diseases** applies the general framework to the principal communicable diseases: influenza and other respiratory viral infections, HIV/AIDS, the classical respiratory-entry infections of childhood (measles, rubella, scarlet fever, diphtheria, mumps, whooping cough, meningococcal disease), the viral hepatitides, the digestive-entry infections (cholera, typhoid fever, bacterial dysentery, poliomyelitis, food poisoning) and tetanus as the model of a tegumentary-entry infection, followed by six chapters devoted to subjects that have become inseparable from contemporary practice: COVID-19 and the lessons of the pandemic, vaccinology and immunisation programmes, healthcare-associated infections, antimicrobial resistance, tuberculosis, and the group of zoonoses, vector-borne diseases and sexually transmitted infections. **Part IV — Epidemiology of Chronic Non-Communicable Diseases** is devoted to the modern epidemic

of chronic diseases — obesity, coronary heart disease, hypertension, diabetes mellitus and cancer — and to the strategies of prevention and control that the World Health Organization has placed at the centre of global public health policy. **Part V — Epidemiology at the Bedside** closes the volume by returning the whole apparatus to the individual patient: pre-test and post-test probability, the number needed to treat, the critical reading of a paper, and shared decision-making.

Five appendices follow: a glossary of the terms used throughout, the essential formulae, a table of incubation periods and isolation measures, the structure of the national immunisation programme, and a set of self-assessment questions covering each part.

A word on how to read this text. The core of every chapter reproduces and develops, in continuous prose, the content of the lectures; this is the material required for the examination. Two kinds of addition surround it. Clearly marked **boxes** contain supplementary material — historical notes, mechanisms, worked examples and updated classifications — placed beside the lecture content to set it in a broader context. And the closing section of each chapter, together with the new chapters of Parts II and III, presents the **current international evidence**: the most recent figures of the World Health Organization, of ECDC, of UNAIDS, of the International Diabetes Federation and of the Global Burden of Disease studies, together with the landmark and recent trials that have changed practice. These sources are cited in the text by numbers in square brackets and listed at the end of each chapter, so that the reader may go to the original — a habit that this book would like to leave behind more than any particular figure it contains.

Where figures, thresholds or drug doses are quoted, the reader should remember that recommendations evolve continuously: for clinical decisions, the current national methodological norms and international guidelines must always be consulted. The epidemiological data cited correspond to the most recent reports available at the time of writing, in the summer of 2026.

A note on sources and acknowledgements. The teaching material on which this book rests belongs to the Discipline of Epidemiology of the "Victor Babeș" University of Medicine and Pharmacy of Timișoara. The lecture courses that form its backbone — the introduction to epidemiology, the transmission of infectious diseases and the forms of manifestation of the epidemiological process, and the special epidemiology of influenza, of the respiratory-entry infections, of the viral hepatitides and of the digestive-entry infections — were conceived and delivered by **Assoc. Prof. Emilian - Damian Popovici, M.D., Ph.D.** and **Assoc. Prof. Luminita Baditoiu, M.D., Ph.D.**, Head of the Department of Epidemiology, to whom I express my gratitude for the didactic tradition within which this text has been written and which it seeks to continue. The present volume develops that material into continuous prose, adds the supplementary boxes described above, and assumes full responsibility for the wording, the selection and any errors of the resulting text.

I hope that this book will serve students not as a collection of facts to be memorised, but as an invitation to epidemiological thinking — the habit of asking, before every case of disease: where did it come from, how did it travel, whom else may it reach, and how can it be prevented?

Timișoara, 2026

Ionut – Dragos Capraru

Table of Contents

Preface i

PART I. GENERAL EPIDEMIOLOGY 1

Chapter 1. Introduction to Epidemiology 2

1.1. Definition and object of study 2
1.2. A brief history of epidemiology 3
1.3. Contemporary features of epidemiological processes 5
1.4. Eradication 6
1.5. The fundamental concepts of infectious disease epidemiology 7
1.6. Anti-infectious resistance, contamination and infection 9
1.7. Prevention and its levels 10
1.8. The contemporary landscape: what the global figures show 11
1.9. The levels of prevention in the light of recent evidence 12

Chapter 2. The Source of Infection 14

2.1. Definition and classification of diseases according to the source 14
2.2. The human source of infection 14
2.3. The animal source of infection 16
2.4. The secondary source of infection 17
2.5. Natural focality (natural focus infections) 17
2.6. The reservoir of infection in contemporary epidemiology 18
2.7. The carrier state: contemporary examples 19

Chapter 3. The Transmission Routes and Mechanisms 20

3.1. Definition and general classification 20
3.2. Direct transmission 20
3.3. Indirect transmission — general features 20
3.4. Aerogenous transmission 21
3.5. Transmission through water 22
3.6. Transmission through the soil 22
3.7. Transmission through food 23
3.8. Transmission through objects 24
3.9. Transmission through dirty hands 24
3.10. Transmission through vectors 25
3.11. Transmission routes: what the past decade has changed 25

Chapter 4. The Receptive Population. Immunity 28

4.1. Receptiveness and resistance 28
4.2. Individual and collective immunity 28
4.3. The classification of immunity 29
4.4. The individual factor and the spectrum of infection 29
4.5. The immunological structure of the population 30
4.6. Population immunity: measurement, erosion and modern evidence 30

Chapter 5. The Favouring Factors of the Epidemiological Process 33
5.1. The place of the favouring factors 33
5.2. The natural environmental factors 33
5.3. The economic and social factors 34
5.4. The favouring factors today: climate, conflict, urbanisation, information 35

Chapter 6. The Forms of Manifestation of the Epidemiological Process 37
6.1. The criteria for assessing the forms of manifestation 37
6.2. The sporadic form 38
6.3. The endemic form 39
6.4. The epidemic form 39
6.5. The pandemic form 40
6.6. The forms of manifestation in the light of modern epidemic theory 40

PART II. EPIDEMIOLOGICAL METHODS 43

Chapter 7. Measuring Health and Disease in Populations 44
7.1. Why measurement is the foundation of epidemiology 44
7.2. Measures of disease frequency 44
7.3. Crude, specific and standardised rates 46
7.4. The sources of epidemiological data 47
7.5. Interpreting variation: the three questions of descriptive epidemiology 48

Chapter 8. Epidemiological Study Designs and Causal Inference 49
8.1. The architecture of epidemiological research 49
8.2. Descriptive and ecological studies 49
8.3. The case-control study 50
8.4. The cohort study 50
8.5. Experimental studies: the randomised controlled trial 51
8.6. Bias, confounding and interaction 52
8.7. Chance, precision and the interpretation of statistics 53
8.8. From association to causation 53

Chapter 9. Screening and Early Detection 55
9.1. Definition and place among the levels of prevention 55
9.2. The validity of a screening test 55
9.3. Criteria for instituting a screening programme 56
9.4. The specific biases of screening evaluation 57
9.5. Screening programmes of demonstrated value 57
9.6. Screening in communicable diseases 58
9.7. The ethics of screening 59

Chapter 10. Surveillance, Outbreak Investigation and International Health Regulations 60
10.1. Public health surveillance 60
10.2. The investigation of an outbreak 61
10.3. Preparedness and the international legal framework 63

PART III. SPECIAL EPIDEMIOLOGY OF COMMUNICABLE DISEASES.....65

Chapter 11. Influenza and Other Respiratory Viral Infections 66
11.1. Definition and aetiological agent 66
11.2. Antigenic variability: drift and shift 66
11.3. The epidemiological process 67
11.4. The manifestations of the epidemiological process 68
11.5. Prevention and control 69
11.6. Infections with parainfluenza viruses 69
11.7. Influenza today: surveillance, the avian threat and the state of the vaccines 70

Chapter 12. The HIV/AIDS Infection 72
12.1. Definition and epidemiological importance 72
12.2. Features of the aetiological agent 72
12.3. The epidemiological process 73
12.4. Prevention and control 74
12.5. HIV in the present decade: figures, biomedical prevention and the unfinished agenda 75

Chapter 13. Respiratory-Entry Viral and Bacterial Infections.....78
13.1. Measles 78
13.2. Rubella 79
13.3. Scarlet fever 80
13.4. Diphtheria 82
13.5. Epidemic parotitis (mumps) 83
13.6. Whooping cough (pertussis) 84
13.7. Meningococcal meningitis 86
13.8. The respiratory-entry infections today: resurgence, new evidence and the Romanian situation 87
13.9. Two further respiratory-entry infections of current importance 89

Chapter 14. The Viral Hepatitides 92
14.1. Definition, entities and epidemiological importance 92
14.2. Features of the pathogens 92
14.3. Entries, eliminations, sources 94
14.4. Transmission routes and mechanisms 94
14.5. The receptive population and the favouring factors 95
14.6. The manifestation forms of the epidemiological process 95
14.7. Prevention and control 96
14.8. Viral hepatitis today: the elimination agenda and its arithmetic 98

Chapter 15. Infections with a Digestive Entry 101
15.1. Cholera 101
15.2. Typhoid fever 103
15.3. Bacterial dysentery (shigellosis) 104
15.4. Poliomyelitis 106
15.5. Food poisoning 108
15.6. The digestive-entry infections today 110
15.7. The viral and bacterial gastroenteritides of everyday practice 112

Chapter 16. Infections with a Tegumentary Entry: Tetanus 114
16.1. Definition and importance 114
16.2. The aetiological agent 114
16.3. The epidemiological process 114
16.4. Prevention and control 116
16.5. Tetanus and the other tegumentary-entry infections today 117

Chapter 17. COVID-19 and the Lessons of the Pandemic 119
17.1. Why COVID-19 belongs in a textbook of epidemiology 119
17.2. The aetiological agent and its variability 119
17.3. The epidemiological process 119
17.4. The manifestation of the epidemiological process 120
17.5. Prevention and control: what the pandemic taught 121

Chapter 18. Vaccinology and Immunisation Programmes 123
18.1. The place of vaccination in preventive medicine 123
18.2. Types of vaccine 123
18.3. Immunisation schedules and the Romanian National Immunisation Programme 124
18.4. Vaccine safety and adverse events 125
18.5. Vaccine hesitancy and confidence 125
18.6. New and forthcoming vaccines 126

Chapter 19. Healthcare-Associated Infections 128
19.1. Definition and importance 128
19.2. The epidemiological process in the hospital 128
19.3. The main types and their prevention 129
19.4. Prevention and control programmes 130

Chapter 20. Antimicrobial Resistance 132
20.1. A slow pandemic 132
20.2. Mechanisms and epidemiology of resistance 132
20.3. Resistance in the classical diseases of this book 133
20.4. Containment: what actually works 134

Chapter 21. Tuberculosis 136
21.1. Definition and importance 136
21.2. The aetiological agent 136
21.3. The epidemiological process 137
21.4. Diagnosis in the epidemiological perspective 138
21.5. Prevention and control 138

Chapter 22. Zoonoses, Vector-Borne Diseases and Sexually Transmitted Infections ... 141
22.1. Zoonoses: the general framework 141
22.2. Vector-borne diseases in Europe 142
22.3. Sexually transmitted infections 143

PART IV. SPECIAL EPIDEMIOLOGY OF NON-COMMUNICABLE DISEASES..145

Chapter 23. General Characteristics of Chronic Non-Communicable Diseases 146

23.1. Definition 146
23.2. The global burden 146
23.3. The epidemiological peculiarities of chronic diseases 146
23.4. Common risk factors and the strategy of prevention 147
23.5. The current global figures and the framework of action 147
23.6. The strategy: from declarations to "best buys" 148

Chapter 24. Obesity 150

24.1. Definitions 150
24.2. Aetiology 150
24.3. The measurement of obesity 150
24.4. The hazards of obesity 151
24.5. Prevention and control 151
24.6. Obesity today: magnitude, mechanisms and the new pharmacology 152

Chapter 25. Coronary (Ischaemic) Heart Disease 154

25.1. Definition and clinical presentations 154
25.2. Magnitude and burden 154
25.3. Descriptive epidemiology: person, time, place 154
25.4. Aetiology and risk factors 155
25.5. Prevention 156
25.6. Coronary disease today: global risk, modern evidence and the Romanian burden 157

Chapter 26. Hypertension 160

26.1. Definition and classification 160
26.2. The magnitude of the problem 160
26.3. Where the problems lie — the "rule of halves" 161
26.4. What is needed 161
26.5. The management plan 162
26.6. Hypertension today: the global report and what it demands 162

Chapter 27. Diabetes Mellitus.....165

27.1. Definition and classification 165
27.2. Diagnostic criteria 165
27.3. Magnitude 166
27.4. Aetiology 166
27.5. Diabetes and pregnancy 166
27.6. Descriptive epidemiology 167
27.7. Prevention 167
27.8. Diabetes today: the Atlas figures, prevention trials and modern therapy 168

Chapter 28. Cancer.....171

28.1. Definition and magnitude 171
28.2. Descriptive epidemiology 171
28.3. Aetiology 172
28.4. Cancer prevention 173

28.5. Cancer today: GLOBOCAN, prevention that works, and the elimination of a cancer 173

Chapter 29. The Global Response to the Chronic Disease Epidemic **176**

29.1. Misunderstandings and realities 176

29.2. The global goal 176

29.3. What works 177

29.4. Where the global response stands, and what remains to be done 177

29.5. A concluding note for the student 178

PART V. EPIDEMIOLOGY AT THE BEDSIDE **180**

Chapter 30. Clinical Epidemiology and Evidence-Based Practice **181**

30.1. Why this chapter closes the book 181

30.2. Diagnosis: probability before and after the test 181

30.3. Treatment: expressing benefit in usable numbers 181

30.4. Prognosis and natural history 182

30.5. Reading a paper: a practical sequence 182

30.6. From evidence to guidelines, and back to the patient 183

30.7. Conclusion: the epidemiological habits of mind 183

APPENDICES **185**

Appendix A. Glossary of Epidemiological Terms **186**

Appendix B. Essential Formulae **189**

Appendix C. Incubation Periods and Isolation of the Principal Diseases Studied **190**

Appendix D. The Romanian National Immunisation Programme (structure) **191**

Appendix E. Self-Assessment Questions **192**

General Bibliography and Further Reading **194**

PART I. GENERAL EPIDEMIOLOGY

Chapter 1. Introduction to Epidemiology

1.1. Definition and object of study

Epidemiology is the medical branch that studies the distribution of diseases among the population, analysing deaths and infirmities as well as the factors that determine and favour the onset of diseases. The word itself betrays its object: it derives from the Greek *epi* (upon), *demos* (people) and *logos* (science, discourse) — literally, the science of what falls upon the people.

The essential feature that distinguishes epidemiology from the clinical disciplines is its **unit of study**. Whereas the clinician examines and treats the individual patient, the epidemiologist works with the **population** — understood, especially in infectious disease epidemiology, as the receptive mass of people susceptible of becoming affected. A diagnosis in clinical medicine is attached to a person; a diagnosis in epidemiology is attached to a community: an outbreak, an endemic territory, a risk group, a cohort exposed to a given factor.

From this population perspective follow the practical tasks of the discipline: measuring the frequency of disease (morbidity, mortality and their derivatives), identifying the factors that determine and favour disease occurrence, recognising the groups at highest risk, and designing, applying and evaluating the measures of prevention and control.

Taken in its entirety, epidemiology as a science encompasses several major fields:

- **infectious disease epidemiology**, historically the founding branch of the discipline;
- **non-infectious disease epidemiology**, dealing with chronic non-communicable diseases;
- **pharmacoepidemiology**, which studies the use and the effects of drugs at the population level;
- **iatrogenicity epidemiology**, concerned with disease produced by medical care itself, and other applied fields.

Non-infectious disease epidemiology consists in the early identification of a disease in its preclinical and biochemical stage; its practical solution consists in mobilising at-risk people for long-term specialised examinations. It must be admitted, however, that people much too frequently prefer the often illusive "show" of curative medicine to preventive medicine, which would be less costly, more efficient and more beneficial for public health in all its aspects.

The main goals of infectious disease epidemiology are: highlighting an epidemiological process from the onset to the extinguishing stage; taking prevention and control measures; and encouraging high-quality clinical practices by introducing and applying the concepts of clinical epidemiology.

Didactically, the discipline is divided into two large chapters:

- **general epidemiology**, which studies the laws, factors and forms of manifestation common to all epidemiological processes, together with the general principles of prevention and control — the subject of Part I of this book;
- **special epidemiology**, which applies the general framework to each disease or group of diseases — the subject of Parts III and IV.

Epidemiology cooperates with a wide variety of sciences: with almost all medical branches, but also with zoology (the animal source of infection), environmental science, biostatistics and medical information science. Mathematical models are also employed in modern epidemiology — the reader will remember the prominent role that modelling played in the public debate during the COVID-19 pandemic.

Box 1.1. Epidemiology beyond infectious diseases (supplementary). The classical definition given above has been progressively broadened. A widely used modern formulation (Last's *Dictionary of Epidemiology*) defines epidemiology as "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems" [1]. Three elements deserve emphasis: (1) *distribution* — answering the questions who? where? when?; (2) *determinants* — the causes and risk factors, answering the question why?; (3) *application* — epidemiology is not contemplative but actionable, feeding directly into public health decisions. Under this definition, epidemiology studies not only diseases but any health-related state: injuries, disabilities, health behaviours, the use of health services, and even positive states such as vaccination coverage or longevity.

1.2. A brief history of epidemiology

The history of the discipline can be divided, for teaching purposes, into five stages: Antiquity, the Middle Ages, the Renaissance, the Pasteur stage and the modern stage.

Antiquity

The observation that disease is linked to the environment is ancient. **Hippocrates** (c. 460–370 BC), in his treatise *On Airs, Waters and Places*, noticed the connection between disease and environmental conditions, advising the physician arriving in an unknown city to study its winds, its waters and the way of life of its inhabitants — an authentically epidemiological programme, formulated more than two millennia before the microbial era. In ancient Egypt, the iconography of the god **Ptah** is suggestive: his appearance has been linked to the connection between death and the rat — the animal reservoir of plague, a disease that would devastate the ancient and medieval world in successive waves.

The Middle Ages and the Renaissance

The medieval pandemics of plague — of which the Black Death of 1347–1351 is the most infamous, killing an estimated third of Europe's population — imposed the first organised anti-epidemic measures: the isolation of the sick, the *lazarettos*, and the forty-day detention of ships

and travellers from which the very word **quarantine** (*quaranta giorni*) derives. The plague of Florence was memorably described by Boccaccio in the *Decameron*, a scene later painted by Sabatelli. In the Renaissance, **Paracelsus** established that diseases are caused by external agents — a decisive break with the purely humoral doctrine of disease.

Box 1.2. Fracastoro and the theory of contagion (supplementary). In 1546, the Veronese physician **Girolamo Fracastoro** published *De contagione et contagiosis morbis*, in which he proposed that epidemic diseases are caused by minute, self-multiplying "seeds of disease" (*seminaria contagionum*) transmitted by direct contact, by contaminated objects (for which he coined the term *fomites*, still in use today) and at a distance. Three centuries before bacteriology, Fracastoro thus anticipated the germ theory of disease.

The pre-Pasteur stage

Two figures dominate this period. **Ambroise Paré**, the great military surgeon of the sixteenth century, attested the transmission of the "rotten hospital infection" through the contact between the sick person and the healthcare staff — the first clear description of what we now call healthcare-associated infection transmitted by the hands of personnel. Three centuries later, **Ignaz Semmelweis** (1818–1865) demonstrated, in the obstetric clinic of Vienna, the transmission of puerperal fever through the "cadaveric matter" carried on the hands of doctors and students coming from the autopsy room. The measures he imposed — isolation of puerperal infection cases, a strict hand-washing protocol with chlorinated lime water before entering the delivery room, and the boiling of all instruments — reduced maternal mortality spectacularly, and remain to this day the conceptual foundation of hand hygiene, the single most effective measure against hospital infections.

Box 1.3. John Snow and the birth of field epidemiology (supplementary). No history of epidemiology, however brief, may omit **John Snow** (1813–1858), the London anaesthetist considered the father of modern field epidemiology. During the cholera epidemic of 1854 in Soho, by plotting the cases on a map and comparing the mortality of households supplied by different water companies, Snow demonstrated that cholera was transmitted through water contaminated with faecal matter — and famously had the handle of the Broad Street pump removed — decades before Koch isolated *Vibrio cholerae*. His investigation remains the model of every outbreak investigation: describe the cases in time, place and person; formulate a hypothesis of transmission; test it; intervene. In the same period, **William Farr**, registrar of vital statistics in England, laid the foundations of modern health statistics and of the surveillance of mortality.

The Pasteur stage

The second half of the nineteenth century transformed epidemiology from an observational into an aetiological science. **Louis Pasteur** demonstrated the infectious aetiology of nosocomial diseases and laid the groundwork of aseptic medicine; his studies on attenuation opened the way to vaccination against rabies and anthrax. **Robert Koch**, the creator of modern bacteriology, identified the microorganisms responsible for anthrax (1876), tuberculosis (1882) and cholera (1883), and formulated the postulates that still bear his name, establishing the criteria by which a microorganism may be accepted as the cause of a disease. **Joseph Lister**

introduced the concept of antisepsis in surgery, dramatically reducing operative mortality. At the beginning of the twentieth century, prevention and control behaviour was generalised in the field of intrahospital infections through continuous sanitation, the introduction of sterilisation through physical methods, and the application of asepsis, antisepsis and disinfection.

The modern stage

The modern stage is marked by the generalisation of epidemiological concepts and the implementation of rigorous study methods in epidemiology — the cohort study, the case-control study, the randomised controlled trial. **Alexander Fleming** discovered penicillin in 1928, opening the stage of antibacterial treatments and, with it, an entirely new chapter of prevention (antibioprophylaxis) but also, in time, a new epidemiological problem: antimicrobial resistance.

Box 1.4. The epidemiological method conquers chronic disease (supplementary). After the Second World War the epidemiological method, forged on infectious diseases, was successfully turned upon chronic diseases. In 1948 the **Framingham Heart Study** began following an entire American town, introducing into medicine the very concept of *risk factor* for cardiovascular disease. In 1950, **Richard Doll and Austin Bradford Hill** published their landmark case-control study linking smoking to lung cancer, followed by the prospective British Doctors Study. Bradford Hill's criteria for causal inference (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, analogy — 1965) remain the classical framework for judging causality in epidemiology. The eradication of smallpox (certified 1980) and the COVID-19 pandemic (2020–2023) frame, at the two extremes of triumph and challenge, the contemporary period of the discipline.

1.3. Contemporary features of epidemiological processes

The epidemiology of the present day differs profoundly from that of a century ago, and its features must be known because they shape the entire strategy of surveillance and control.

The decrease of morbidity in some infectious diseases has been achieved through immunoprophylaxis, antibioprophylaxis and the higher standard of living. In parallel, **mortality has decreased** in some infectious diseases, especially through the modernisation of therapeutic means and methods. Some diseases have become benign — scarlet fever, for instance, through therapeutic progress.

Other diseases, however, **continue to display very high morbidity**:

- respiratory viral infections and influenza — because of the high antigenic variability of the causal viruses;
- the viral hepatitides — because of the high number of unidentified sources of infection;
- pulmonary tuberculosis;
- HIV/AIDS, and others.

New aspects have also emerged: a larger number of **atypical disease forms**, with important clinical and epidemiological implications, because atypical cases escape diagnosis and isolation; a larger number of **carriers of resistant germs** (tuberculosis being the classical example); and the **diversification of the factors of the epidemiological process**.

Imported diseases are infectious or parasitic conditions brought from an affected territory into one with no or only rare occurrences. They are mainly due to the generalised movement of people and goods — tourism, migration, trade — which today can carry a pathogen between any two points of the globe within twenty-four hours, less than the incubation period of virtually every infectious disease.

Emerging diseases are recent clinical entities, either generally or in a certain territory: legionellosis, HIV/AIDS, SARS, chronic fatigue syndrome, Lyme disease, the viral haemorrhagic fevers. **Re-emerging diseases** are conditions that were at some point under control but are currently experiencing a new recrudescence: diphtheria, whooping cough, tuberculosis.

Box 1.5. Emergence in the twenty-first century (supplementary). The list of emerging infections has lengthened considerably since the concept was coined: SARS (2003), pandemic influenza A(H1N1)pdm09 (2009), MERS (2012), the West African Ebola epidemic (2014–2016), Zika virus and its congenital syndrome (2015–2016), and above all **COVID-19**, caused by SARS-CoV-2, declared a Public Health Emergency of International Concern on 30 January 2020 and a pandemic on 11 March 2020. Some three quarters of emerging infections are **zoonotic** in origin, which explains the current emphasis on the **One Health** approach — the integrated surveillance of human, animal and environmental health. Antimicrobial resistance, sometimes described as a "slow pandemic", is treated by WHO as an emergency of the same order.

1.4. Eradication

The ultimate ambition of the fight against a communicable disease is its eradication. Eradication has three stages:

1. **Decrease** — morbidity decreases to a minimum;
2. **Nosological annihilation (elimination)** — the disease disappears from some territories, but the pathogen is still present, at first with unaltered virulence and pathogenicity features and later with altered features;
3. **Actual eradication** — the disease and the pathogen disappear worldwide.

The only disease eradicated worldwide so far is **smallpox**; **poliomyelitis** is pending eradication.

Box 1.6. Smallpox, poliomyelitis and the criteria of eradicability (supplementary). Smallpox was certified eradicated by the World Health Assembly in **1980**, after the last natural case had occurred in Somalia in 1977 — the greatest single triumph of public health. The features that made smallpox eradicable are instructive: an exclusively human reservoir, no carrier state, an easily recognisable clinical picture, solid post-infectious immunity and an effective, thermostable vaccine. Poliomyelitis has approached the same goal: wild poliovirus type 2 was certified eradicated in 2015 and type 3 in 2019, and wild type 1 transmission has remained confined to a single endemic pocket (Afghanistan–Pakistan); the persistence of circulating vaccine-derived polioviruses, however, shows how demanding the "last mile" of an eradication programme is. Dracunculiasis (guinea-worm disease) is the main non-vaccine candidate for eradication. By contrast, diseases with animal reservoirs or environmental persistence (tetanus, for example) can never be eradicated — only controlled.

1.5. The fundamental concepts of infectious disease epidemiology

Three fundamental concepts are used in infectious disease epidemiology, distinguished by the increasing complexity of the forms studied: the **infectious process**, the **epidemiological focus** and the **epidemiological process**.

The infectious process

The infectious process consists in the complexity of local or general biological reactions and histopathological changes caused by the interaction between the microorganism (the pathogen) and the macroorganism, under the given environmental conditions. It is, in other words, the phenomenon studied at the level of one host: the encounter between one pathogen and one organism.

The epidemiological focus

The epidemiological focus includes the infectious process together with all its links with previous and subsequent infectious processes. It can consist of a single case of disease recently occurred in a community, or of several cases from or among which a direct relation can be established. The focus therefore has both a biological and a territorial dimension: it comprises the case (or cases), the persons and elements of the environment contaminated from it, and the space within which transmission can occur.

The case relation is the connection that can be established among disease occurrences within the maximum incubation period of the disease. The transmission link is followed from a **primary case** to two or more **secondary cases**; if a secondary case passes the disease on, it becomes a primary case for the subsequent occurrences. Reconstructing these chains of transmission — today assisted by molecular typing of the isolated strains — is one of the central operations of any outbreak investigation.

The factors of the epidemiological focus

For the occurrence of any epidemiological focus, two categories of factors must be present: determining factors and favouring factors.

The **determining factors** are three, and their conjunction is obligatory — the removal of any one of them interrupts the process:

1. **The source of infection** — the organism or the environment that hosts the pathogen, in which the pathogen multiplies, and from which the pathogen is eliminated into the outer environment;
2. **The transmission route** — the route taken by the pathogen from the source of infection to the receiving organism, as well as the manner in which this route is covered, which is influenced by the external physical environment factors;
3. **The receiving (receptive) population** — the mass of people prone to the disease.

The **favouring factors** comprise:

1. **natural environmental factors** — weather and climate, geographic factors, cosmic factors, earth (telluric) factors;
2. **economic and social factors** — the economic, cultural and educational standard, occupational factors, crowding, economic and social disruptions;
3. **biological factors** — vector invasions, rodents, other animals and birds, biological weapons, and others.

The favouring factors do not always have a decisive effect on the formation of the epidemiological focus, but they may have a significant effect on the form of manifestation of the epidemiological process — as will be seen in Chapter 6, the same disease may smoulder sporadically or explode epidemically according to the favouring conditions.

The epidemiological process

The epidemiological process consists in all the physiopathological processes and mechanisms, as well as the economic and social disruptions, occurring in a population that has been threatened by a pathogen, throughout the spread of the disease among that population. Structurally, it consists in a sequence of connected epidemiological foci; the concrete unit of the epidemiological process is the epidemiological focus.

The three concepts are therefore nested like concentric circles: the infectious process (one host) is contained in the epidemiological focus (one case or one cluster with its connections), and the succession of foci constitutes the epidemiological process (the disease moving through the population).

Box 1.7. The infectionist and the epidemiologist (supplementary). The two professional perspectives are complementary and must not be confused. The **infectious disease specialist** starts from the patient: diagnosis, treatment, individual prognosis. The **epidemiologist** starts from the population: for the same case, he or she asks where the infection was contracted, who else was exposed, which measures will interrupt transmission, and what the case reveals about the immunity of the community. The complete management of any communicable disease case requires both: treatment of the patient *and* investigation and neutralisation of the focus.

1.6. Anti-infectious resistance, contamination and infection

The pathogen, in its attempt to get into the body, is confronted with the **anti-infectious resistance** of the host, which comprises two large components.

Non-specific resistance is made up of three categories of factors:

- **the cutaneous-mucous barrier**, offering mechanical and biological protection — the intact skin and mucosae, their secretions, their normal flora;
- **the cyto-tissular barrier** — the inflammatory reaction, fever, phagocytosis, interferon production;
- **the blood humoral barrier** — the production of complement, properdin, natural opsonins, lysins and other humoral factors.

Specific anti-infectious resistance comprises:

- **inherited specific resistance**, which includes species-related (specific) natural resistance, relative resistance due to hereditary features, and transplacental resistance passively transmitted from the mother to the infant;
- **acquired (gained) specific resistance**, which can occur naturally — after going through the infection — or artificially, through active and/or passive immunisation.

If the pathogen overcomes all these obstacles, it will start to multiply; the body responds to the multiplication or to the metabolism products of the pathogen through a series of biological reactions. The period of time in which the pathogen has entered the body but has not multiplied is called **contamination** [2]. The place in the body where the pathogen produces morbid manifestations is called an **infection focus**, from which the pathogen spreads into the body through various routes.

When biological reactions occur in the body, this indicates that **infection** has set in. As long as there are only the biological and histopathological changes characterising that disease, we speak of a **latent infection**. With the occurrence of clinical signs, we speak of **disease (manifest infection)**, which may have:

- a **typical** manifestation — with all the signs of the disease;
- an **atypical** manifestation — with just some of the signs of the disease (the viral hepatitides offer the classical example).

The distinction has major epidemiological weight: latent and atypical infections elude diagnosis, remain unisolated, and constitute the hidden, mobile part of the reservoir of infection — the submerged portion of the epidemiological "iceberg" to which we shall return.

1.7. Prevention and its levels

Prevention represents the totality of medical, economic, social and political actions undertaken to preserve and promote health — that is, to reduce the risks of the appearance and spread of a disease. It comprises the totality of methods and means used to ensure knowledge of health risks, to neutralise their action, to detect high-risk population groups, to avoid the establishment of epidemiological processes, and to detect pre-disease and disease states in the earliest possible stages.

Prophylactic (preventive) medicine is the branch of medicine based on the application by doctors of prophylaxis measures. Its importance grows continuously in the context of modern medicine, in which costs are increasing, elderly people are increasingly representative in the population, and we are faced with the emergence and re-emergence of diseases.

The steps (levels) of prevention

Primordial prophylaxis has the role of combating the emergence and consolidation of social, cultural and economic habits that increase the risks of disease in the population. It includes improving living conditions and hygiene, ensuring drinking water and food, combating smoking and alcohol consumption, and campaigns to reduce speed on the roads. Its target is not the risk factor in the individual, but the very appearance of the risk factor in society.

Primary prophylaxis controls the risk factors, in order to prevent the occurrence of disease at the individual or population level. It includes measures to maintain an optimal body weight, combating sedentarism, immunising the population against some communicable diseases, and similar interventions. It is carried out both through programmes protecting people at risk and through population-wide programmes.

Secondary prophylaxis includes the measures for the early detection and correction of reversible imbalances that occur before the disease manifests clinically, during the incubation or latency period. It is based on **screening** tests, using the most accurate methods for early detection — as little invasive as possible, inexpensive, and applicable at the population level; the detection of cervical cancer in its early stages by the Papanicolaou method is the classical example.

Tertiary prophylaxis refers to the medical activities that prevent or reduce the complications of disease. It is part of the therapy of chronic pathology and includes measures to reduce suffering, injuries and disabilities, and to support the patient's adaptation to his or her new condition.

Quaternary prophylaxis is the protection of the patient against medicine itself: against polypharmacy and the excess of invasive procedures — against overdiagnosis and overtreatment.

Types of prevention

Depending on the **degree of specificity**, we distinguish:

- **general prevention** — respecting personal and collective hygiene, health education, decontamination, disinsection and deratisation measures, surveillance of risk groups, and related measures;
- **special prevention** — antibacterial or antiviral chemoprophylaxis, and standard immunoglobulins administered post-exposure;
- **specific prevention** — specific active and/or passive immunisation (vaccines and specific immunoglobulins).

Depending on the **pathology addressed**, we distinguish the prevention of communicable diseases — influenza, the viral exanthemas of early childhood, whooping cough, poliomyelitis, tetanus, rabies, viral hepatitis A and B — and the prevention of non-communicable diseases: metabolic, cardiovascular, respiratory, digestive and oncological diseases, among others.

The medical specialties with an important role in preventive medicine are family medicine, epidemiology, public health and hygiene; but it must be underlined that **every clinician** has a preventive component in his or her activity — every consultation is an opportunity for vaccination, screening and counselling.

Box 1.8. The levels of prevention applied to one disease (supplementary). The five levels are best fixed in memory on a single example — cervical cancer. *Primordial:* social policies discouraging early sexual debut and smoking, health education in schools. *Primary:* HPV vaccination of girls (and boys) before exposure. *Secondary:* screening by Papanicolaou cytology and/or HPV-DNA testing, with treatment of precancerous lesions. *Tertiary:* oncological treatment and follow-up of diagnosed cancer, preventing recurrence and complications. *Quaternary:* avoiding unnecessary interventions in low-risk women (for example, over-frequent screening or aggressive treatment of lesions that would regress spontaneously). One disease, five distinct preventive strategies — and the earlier the level, the greater the benefit for the population.

1.8. The contemporary landscape: what the global figures show

The concepts of this chapter acquire their proportions only when they are set against the current global figures, and the student should carry a small number of orders of magnitude in mind.

The epidemiological transition has been completed almost everywhere. Non-communicable diseases now cause about **43 million deaths a year, some 75% of all deaths worldwide**, of which 18 million occur before the age of 70; 73% of all NCD deaths, and 82% of the premature ones, occur in low- and middle-income countries [3]. The classical opposition between "diseases of poverty" and "diseases of affluence" has therefore lost its meaning: the poor countries now carry both burdens simultaneously, and within rich countries the chronic diseases have migrated to the disadvantaged groups.

Communicable diseases have not, however, been defeated. Tuberculosis alone caused about **1.23 million deaths in 2024**, with an estimated 10.7 million people falling ill, and returned to being the leading single infectious cause of death [4]. HIV — 40.8 million people living with the infection, 1.3 million new infections and 630,000 deaths in 2024 [5] — and the viral hepatitides — 254 million living with hepatitis B, 50 million with hepatitis C, 1.3 million deaths annually [6] — constitute, together with malaria, the great chronic infections of humanity. Measles, the disease with which every immunisation programme is measured, caused about **95,000 deaths in 2024, on an estimated 11 million infections**, and 59 countries experienced large or disruptive outbreaks — nearly three times the number in 2021 [7].

The list of contemporary features given in Section 1.3 must therefore be read as a description of the present, not of the past: emergence (COVID-19, mpox, high-pathogenicity avian influenza), re-emergence (measles, diphtheria, pertussis, cholera), imported disease (an inevitable consequence of the movement of 1.5 billion international travellers a year), and the diversification of the factors of the epidemiological process (climate change, urbanisation, ageing, antimicrobial resistance, misinformation).

To these classical categories the past decade has added two structural phenomena which will accompany the professional life of today's students. The first is **antimicrobial resistance**, already attributable to more than a million deaths a year and associated with nearly five million, with forecasts of 1.91 million attributable deaths annually by 2050 [8] — the subject of Chapter 20. The second is the **syndemic interaction** between communicable and non-communicable disease, demonstrated during the COVID-19 pandemic, in which obesity, diabetes and hypertension multiplied the lethality of an infectious agent, and in which the disruption of health services by the epidemic in turn worsened the control of chronic disease.

1.9. The levels of prevention in the light of recent evidence

Two developments of the past decade deserve to be recorded alongside the classical scheme of Section 1.7.

Primordial and primary prevention have acquired quantified instruments. WHO's "best buys" — fiscal and regulatory measures on tobacco, alcohol and unhealthy foods, salt reduction, elimination of industrial trans-fats, and accessible treatment of hypertension and diabetes in primary care — are today accompanied by cost-effectiveness estimates that allow ministries to rank them. Vaccination, historically the model of specific primary prevention, has been credited by a modelling analysis for the fiftieth anniversary of the Expanded Programme on Immunization with having averted of the order of **154 million deaths in fifty years**, the majority in children under five [9].

Quaternary prevention has moved from the margin to the centre of the debate. The recognition of overdiagnosis in cancer screening (Chapter 9), of polypharmacy in the elderly, and of low-value care in general has made the protection of the patient against unnecessary

medicine a mainstream concern, expressed in initiatives such as *Choosing Wisely* and in the deprescribing literature. It is the ethical counterweight to the enthusiasm of prevention: the physician who screens, tests and treats without evidence of benefit is not practising prevention but generating disease.

References

1. Porta M (ed.). *A Dictionary of Epidemiology*. 6th ed. Oxford University Press; 2014.
2. Heymann DL (ed.). *Control of Communicable Diseases Manual*. 21st ed. APHA; 2022.
3. World Health Organization. Noncommunicable diseases — key facts. Geneva: WHO; 2025 (data for 2021).
4. World Health Organization. *Global tuberculosis report 2025*. Geneva: WHO; 2025.
5. UNAIDS. *Global HIV statistics — fact sheet 2025* (data for 2024). Geneva: UNAIDS; 2025.
6. World Health Organization. *Global hepatitis report 2024: action for access in low- and middle-income countries*. Geneva: WHO; 2024.
7. World Health Organization. Measles deaths down 88% since 2000, but cases surge. Geneva: WHO; 28 November 2025.
8. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. *The Lancet*. 2024. doi:10.1016/S0140-6736(24)01867-1
9. Shattock AJ, Johnson HC, Sim SY, et al. Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization. *The Lancet*. 2024. doi:10.1016/S0140-6736(24)00850-X

Chapter 2. The Source of Infection

2.1. Definition and classification of diseases according to the source

The **source of infection** is the body or the environment in which the pathogen is hosted, in which it multiplies and from which it is released into the outer environment through various routes, contributing to the onset, persistence and spread of an infectious disease among the population mass.

The definition contains three cumulative conditions, and all three must be fulfilled: the source *hosts* the pathogen, the pathogen *multiplies* in or on it, and the pathogen is *eliminated* from it into the environment. An organism that merely harbours a pathogen without eliminating it is an epidemiological dead end, not a source.

According to the source of infection, infectious diseases are classified into two main groups:

- **anthroponoses** — human-specific diseases, transmitted from human to human: rubella, measles, syphilis, gonorrhoea, scarlet fever, the viral hepatitides;
- **zoonoses** — animal-specific diseases that can accidentally be transmitted to humans as well: anthrax, brucellosis.

Some authors speak of a separate group of diseases in which the share of the animal source of infection is close to that of the human source. These diseases are called **anthropozoonoses**; influenza is one such example.

The practical value of this classification is strategic: in anthroponoses, control measures are aimed at the human reservoir (case finding, isolation, treatment, vaccination of the population), whereas in zoonoses no measure applied to humans alone can extinguish the reservoir — control must extend to the animal population (veterinary surveillance, animal vaccination, control of rodents), in the spirit of the modern *One Health* approach.

2.2. The human source of infection

As a source of infection, humans can be classified into the following groups: humans with a typical disease; humans with an atypical disease; humans with a chronic disease; and humans as germ carriers.

Humans with a typical disease

The sick person with a typical clinical picture is a source of infection with various degrees of germ release, depending on the evolutionary stage of the disease. Thus, the sick person eliminates the pathogen:

- **during the incubation period** — in typhoid fever, whooping cough, rubella, measles, mumps, influenza and the viral respiratory infections; this pre-symptomatic

contagiousness is of the greatest epidemiological importance, because the future patient circulates freely and cannot yet be recognised as a danger;

- **during the latency (state) period** — in all types of infectious diseases;
- **during convalescence** — the sick person can remain a source of infection in diseases such as typhoid fever and dysentery.

Paradoxically, the typical patient is the *least* dangerous of the human sources in one respect: precisely because the disease is recognisable, the patient is diagnosed, isolated and treated, and the surrounding contacts are investigated.

Humans with an atypical disease

The person with an atypical (subclinical, abortive) form is a source of infection that is difficult to identify; the disease may go unnoticed, and the person thus remains unisolated, which has major clinical and epidemiological implications. Atypical forms are frequent at the extremes of age and in partially immune persons — for instance, vaccinated individuals in whom immunity has waned — and they maintain transmission chains that the surveillance system does not see.

Humans with a chronic disease

Persons with a chronic infectious disease preserve their capacity as a source of infection during recrudescences and relapses. Consequently, a chronic disease can also be a source of infection, generally contributing to the **endemisation** of a territory; malaria, dysentery and the viral hepatitides are the classical examples. The chronically infected person eliminates the pathogen over months or years, seeding the territory with repeated contaminations.

Humans as germ carriers

The **carrier** is any healthy or apparently healthy person who hosts and releases germs into the external environment, either continuously or intermittently [1]. Carriers are classified according to their relation with the disease into:

- **pre-infectious carriers** — actually sick people in the incubation period, releasing germs a few days before the invasion (typhoid fever, whooping cough, rubella, measles, mumps, influenza, the viral respiratory infections);
- **post-infectious carriers** (previously sick people), subdivided into:
  - **convalescent carriers** — with temporary carriage of 1–3 weeks, occurring in typhoid fever, dysentery, scarlet fever, diphtheria;
  - **chronic carriers** — with longer-term carriage that can span months, years or a lifetime; chronic carriage is favoured by dystrophy, diseases of the gall bladder, chronic colitis, sinusitis, and urinary and genital diseases, the pathogen remaining stationed in the gallbladder, the bone marrow, the blood and other sites;

- **healthy carriers** — immune organisms which have acquired this status following immunisation (whether occult or artificial). They can release germs in full health for 1–3 weeks and are generally found in the environment around a source of infection — they are, so to speak, the immunological shadow of the focus.

According to the way in which germs are released, carriers can be classified into:

- **permanent carriers** — continuously releasing germs;
- **intermittent carriers** — excreting germs at certain intervals;
- **closed (encysted) carriers** — not excreting germs; they become dangerous only if the closed focus opens (for example, the drainage of a chronic abscess).

All the carrier categories mentioned above are very important in epidemiology, and measures must be taken to limit their epidemiological role. These measures generally consist in:

- clinical, epidemiological and laboratory identification of carriers, followed by the elimination (sterilisation) of the carrier state;
- setting strict hygiene rules that carriers must follow — the so-called *moral isolation* of the carrier: the carrier is not physically isolated, but must know his or her condition and observe the conduct that protects those around;
- observing a strict, correct and complete therapy during the disease, which reduces the probability of evolving towards carriage;
- temporarily or permanently removing carriers from workplaces with high epidemiological risk — children's collectivities, the food sector, the drinking water supply.

Box 2.1. The carrier in history: "Typhoid Mary" (supplementary). The most famous illustration of the epidemiological weight of the healthy carrier is Mary Mallon ("Typhoid Mary"), a cook in New York at the beginning of the twentieth century. A chronic biliary carrier of *Salmonella typhi* who had never been clinically ill, she caused a documented series of typhoid outbreaks in the households where she worked. Identified by the sanitary engineer George Soper through a classical epidemiological investigation — the tracing of a common element across apparently unconnected foci — she demonstrates every principle of this chapter: the invisibility of the healthy carrier, the elective localisation of chronic carriage in the biliary tract, the special danger of carriers employed in the food sector, and the necessity (and human difficulty) of restrictive measures.

2.3. The animal source of infection

The features mentioned for the human source of infection also apply to the animal one, with the mention that pathogens can additionally be transmitted from animals to humans through biting, scratching and touching. Animal furs and, generally, the products of animal slaughtering used for human consumption can be involved in the transmission of diseases from animals to humans.

The incidence of these diseases is higher among people exposed to prolonged contact with animals or birds: animal and bird breeders, veterinarians, forestry personnel, slaughterhouse workers and related occupations — the zoonoses are, to a large extent, occupational diseases.

The animal categories involved are:

- **domestic or wild animals and birds** — in salmonellosis, influenza, rabies, anthrax, toxoplasmosis, tularaemia;
- **wild peridomestic animals (synanthropes)** — rats and mice, in leptospirosis and plague;
- **fish and aquatic creatures** — in the minor salmonelloses and botulism.

2.4. The secondary source of infection

The **secondary source of infection** is the organism or the environment that hosts the pathogen, in which the pathogen multiplies, and which represents at the same time a transmission route of the pathogen. The concept therefore designates those elements which cumulate the attributes of source and route. Examples: an organism — the *Anopheles* mosquito, in which the malaria parasite completes part of its life cycle while the insect also carries it to the human host; an environment — milk, in which certain bacteria (for example staphylococci or salmonellae) not only survive but actively multiply before being ingested.

2.5. Natural focality (natural focus infections)

A **natural focus infection** is an infectious disease occurring in a certain geographic area in which a certain biocoenosis exists — a self-maintaining ecological community of reservoir animals, vectors and pathogens, independent of man. Humans become sick by entering such a geographic area, and the contamination and disease are caused by wild animals, domestic animals, or rats and mice.

Examples of diseases with natural focality: plague, rabies, anthrax, yellow fever, Japanese B encephalitis, Russian spring–summer (taiga) encephalitis, toxoplasmosis, typhus, Q fever and others.

The theory of natural focality — developed by the Russian parasitologist E. N. Pavlovsky — has direct practical consequences: such diseases cannot be eradicated, because their reservoir is ecological, not human; prevention rests on knowing the map of natural foci, on protecting the persons who enter them (vaccination, protective clothing, repellents) and on surveillance at the boundary between the natural focus and human settlements. Tick-borne encephalitis and Lyme borreliosis, both present in Europe, are contemporary illustrations familiar to every practitioner.

2.6. The reservoir of infection in contemporary epidemiology

Three developments have enlarged the classical account of the source of infection given above, and each has direct practical consequences.

Zoonotic spillover and the One Health approach. It is now estimated that around 60% of known human infectious diseases and about three quarters of emerging infections are of animal origin. The consequence for the doctrine of this chapter is that the "animal source of infection" is no longer a marginal category but the principal frontier of emergence. The **One Health** approach — the integrated surveillance and management of human, animal and environmental health [2] — has accordingly moved from the veterinary literature to the centre of international health law, being written into the WHO Pandemic Agreement adopted in 2025 (Chapter 10).

The current panzootic of high-pathogenicity avian influenza A(H5N1) clade 2.3.4.4b illustrates the whole doctrine in real time: a virus whose classical reservoir is wild aquatic birds has spread to poultry worldwide, to a very wide range of wild and domestic mammals, and — since March 2024 — to dairy cattle in the United States, from which human infections have occurred [3]. Between March 2024 and May 2025, 70 laboratory-confirmed human cases were documented in the United States; 41 had been exposed to dairy cattle and 24 to commercial poultry; the illnesses were predominantly mild, with conjunctivitis in 89%, four hospitalisations and one death; and, decisively for the epidemiology, **no human-to-human transmission was detected** [4]. The episode is a textbook demonstration of an animal source producing sporadic human disease without — so far — acquiring the transmissibility that would make it an anthroponosis.

The molecular identification of the source. The classical categories of this chapter — sick person, carrier, animal — could until recently be linked to cases only by epidemiological reasoning. **Whole-genome sequencing** now permits the reconstruction of transmission chains with a precision that was unattainable a generation ago: it distinguishes an outbreak strain from unrelated coincidental cases, it identifies the food vehicle by matching isolates from patients and from products, and it can show the direction of transmission between individuals. Public health microbiology has thereby become an instrument of the source investigation itself, and the epidemiologist's hypothesis is today confirmed or refuted in the sequencing laboratory.

Environmental and non-human reservoirs are increasingly recognised. Wastewater surveillance detects the circulation of poliovirus, SARS-CoV-2, influenza and measles independently of any identified case; *Legionella* in the water systems of buildings, *Aspergillus* in the air of hospitals under construction, and multi-resistant Gram-negative bacteria in sink traps and drains constitute reservoirs that no measure directed at persons will ever eliminate, and that must be managed as engineering problems.

2.7. The carrier state: contemporary examples

The categories of Section 2.2 remain valid, and modern medicine has supplied them with new illustrations of great practical importance:

- **chronic carriage** of the hepatitis B virus (254 million persons worldwide, most unaware of their status) and chronic infection with hepatitis C (50 million) [5] are the largest chronic carrier reservoirs in the world, and the reason why the WHO elimination strategy begins with screening rather than treatment;
- **asymptomatic and presymptomatic transmission** of SARS-CoV-2 (Chapter 17) demonstrated at global scale the epidemiological principle taught here — that the source which cannot be recognised is the source which cannot be isolated;
- **asymptomatic carriage of multi-resistant organisms** (MRSA, carbapenemase-producing Enterobacterales) by hospitalised patients and by healthcare workers is the modern equivalent of the classical carrier state, and screening on admission of high-risk patients is its modern equivalent of "clinical, epidemiological and laboratory identification";
- **latent tuberculosis infection**, present in around a quarter of the world's population, is a reservoir of a different kind — not currently contagious, but from which the future cases arise, and which preventive therapy is designed to extinguish.

References

1. Heymann DL (ed.). *Control of Communicable Diseases Manual*. 21st ed. APHA; 2022.
2. World Health Organization, FAO, WOAH, UNEP. *One Health Joint Plan of Action (2022–2026)*. Geneva; 2022.
3. Food and Agriculture Organization, WOAH, WHO. Updated joint FAO/WOAH/WHO public health assessment of recent influenza A(H5) virus events in animals and people. 2025.
4. Rolfes MA, Kniss K, Kirby MK, et al. Human infections with highly pathogenic avian influenza A(H5N1) viruses in the United States from March 2024 to May 2025. *Nature Medicine*. 2025;31:3889–3898. doi:10.1038/s41591-025-03905-2
5. World Health Organization. *Global hepatitis report 2024*. Geneva: WHO; 2024.

Chapter 3. The Transmission Routes and Mechanisms

3.1. Definition and general classification

The **transmission route** is the route taken by the pathogen from the source of infection to the receiving organism, as well as the way this route is covered, which is ultimately influenced by the external physical environment factors [1].

The transmission can be **direct** or **indirect**. The distinction rests on whether elements of the external environment are interposed between the source and the receiver — and it commands the entire strategy of prevention: direct transmission is interrupted by acting on human contact and behaviour, indirect transmission by acting on the vehicles (air, water, food, objects, hands, vectors).

3.2. Direct transmission

In direct transmission, no element from the external environment is interposed between the source of infection and the receiving organism. Its principal modalities are:

- **cutaneous contamination** — scabies;
- **cutaneous contamination through biting** — rabies;
- **neonatal contamination** — the herpetic infection of the newborn, contracted during passage through the birth canal;
- **transplacental contamination** — rubella during the first trimester of pregnancy, the model of congenital infection;
- **sexual contamination** — syphilis and the other sexually transmitted infections;
- **contamination through blood transfusions** — malaria, hepatitis B virus, HIV/AIDS;
- **aerogenous contamination at close range** — the projection of secretion droplets on the nasopharyngeal mucosa of the receiver from a distance of less than 1 metre.

Direct transmission characterises pathogens with low resistance in the external environment, which cannot survive a prolonged journey outside the host; this fragility is, epidemiologically, their weak point, and behavioural measures (protected sexual contact, safe injection, hand hygiene, distance) their specific antidote.

3.3. Indirect transmission — general features

In indirect transmission, one or several elements from the external physical environment are interposed between the source of infection and the receiving organism: **air, water, soil, food, objects, residues, dirty hands and vectors**.

Two notions deserve emphasis. First, indirect transmission may be **simple** — a single vehicle — or **complex**, when several elements act successively as a relay (faeces → soil → water → vegetables → dirty hands → mouth). Secondly, one transmission route can contaminate

another (**chain transmission**): whenever a route contaminates a further route, the epidemiological possibilities of the pathogen multiply. Diseases with complex indirect transmission are the domain par excellence of the faecal–oral mechanism.

3.4. Aerogenous transmission

Transmission by air is classified among the direct mechanisms when it occurs by projection on the host's nasopharyngeal mucosa from less than 1 metre, and among the indirect mechanisms when it occurs by dissemination over longer distances. Although air is not a good environment for microbial multiplication, it is a highly favourable transmission agent — whooping cough, the meningitides, the viral respiratory infections, COVID-19 and hospital germs all travel by it.

The determining role is played by **Flügge's droplets**, expelled by speaking, coughing and sneezing: they can travel up to 2–4 metres by sneezing and 1–2 metres by coughing. The aerogenous transmission route is **the most efficient and the hardest to block** — one cannot boil, chlorinate or filter the air of daily life, and breathing cannot be suspended.

Flügge's droplets can dehydrate, forming **droplet nuclei (nucleosols)** which, due to the loss of weight, can remain suspended and travel over much longer distances, giving rise to special epidemiological events — the long-range aerosol transmission characteristic of tuberculosis, measles or varicella. The larger particles are less harmful from this point of view, because they deposit sooner due to their weight.

Air can also be polluted by **dust particles** — fragments of organic substances or soil on which pathological products have been deposited. The pathological products dehydrate, and the pathogens continue to adhere to the dust particles, travelling over even longer distances and contaminating both the external environment and people located far away from the starting point of the pathogen; germs resistant to desiccation (tubercle bacilli, staphylococci, spores) are the typical passengers of dust.

Box 3.1. Droplets, aerosols and the lesson of COVID-19 (supplementary). The classical dichotomy — "large droplets" falling within 1–2 metres versus "droplet nuclei" under 5 µm travelling far — has been substantially refined by the aerobiology of the COVID-19 pandemic. Exhaled particles form a continuum of sizes, and particles considerably larger than 5 µm can remain airborne in poorly ventilated indoor spaces, where infectious aerosol accumulates over time. Hence the modern emphasis, alongside masks and distance, on **ventilation, air filtration and the avoidance of crowded, closed, prolonged-contact settings** as anti-epidemic measures for respiratory infections. The practical hierarchy taught by the pandemic — outdoor safer than indoor, ventilated safer than unventilated, brief safer than prolonged — is the contemporary translation of the classical physics of Flügge's droplets and nucleosols.

3.5. Transmission through water

Due to industrial pollution and to the lack of correlation between urbanisation and the development of the drinking water supply, water has become a significant vehicle of propagation of infectious diseases within the complex indirect route.

The survival and multiplication of pathogens in water are conditioned by turbidity, ultraviolet radiation and, generally, the **self-purification ability** of the water. Clear, deep and cold waters have a low self-purification ability (little biological activity to destroy the intruding germs — hence the paradox that a limpid mountain water may keep a pathogen alive longer); at the opposite end stand the waters with high self-purification ability.

The contamination of surface water is produced by: animal carcasses, water from melting snow, the washing of the soil by rain, residual water, and used water coming from hospitals and from the animal-farming sector. Humans become ill through direct consumption of contaminated water, through its use in the household, through the washing of fruits and vegetables, and even through bathing.

The germs most frequently transmitted through water are: *Salmonella* spp., hepatitis A and E viruses, *Shigella* spp., *Pseudomonas aeruginosa*, the cholera vibrio, the polioviruses and other enteroviruses (Coxsackie, ECHO), *Mycobacterium tuberculosis*, and parasite eggs and cysts.

In many water-transmitted contaminations we are dealing with a **hydric epidemic**, whose classical features are:

- a large number of contaminations in a short time — the explosive character;
- morbidity matching the water distribution area — the map of the cases is the map of the network;
- the decrease in frequency of contaminations when the contaminated water is removed from consumption, often followed by a "tail" of secondary contact cases.

The methods of controlling waterborne diseases include: supplying the population with drinking water; the hygienic-sanitary and laboratory surveillance of water sources; water treatment to ensure potability; the periodic control of the personnel working in the centralised water supply system; avoiding the contamination of sources; and the continuous education of the population.

3.6. Transmission through the soil

The soil is not a good environment for germ multiplication; nevertheless, vegetative and — more often — sporulated forms can be transmitted through it. From the soil, germs can be inhaled or ingested through dirty hands; the soil can also contaminate other transmission routes (water, vectors), which leads to chain transmission.

The soil is permanently contaminated through faeces, residual and surface water, household waste, carcasses and various contaminated objects. It can host the aetiological agents of

dysentery, cholera, brucellosis, anthrax, tetanus and gas gangrene (*Clostridium perfringens*). The sporulated anaerobes deserve special mention: their spores survive in the soil for years or decades, making the soil the permanent reservoir of tetanus — one more reason why tetanus can never be eradicated, only prevented by vaccination.

3.7. Transmission through food

Food is involved in transmission in three categories: foods of animal origin, foods of vegetable origin and mixed foods.

Foods of animal origin

The contamination can be:

- **primary** — coming from sick animals or from animals carrying germs, the food being contaminated in the animal organism itself: **meat** — trichinosis, the salmonelloses, anthrax, tuberculosis; **milk** — brucellosis, typhoid fever, tuberculosis, staphylococcal and streptococcal infections;
- **secondary** — the most frequent, arising when food products are contaminated through the urine and faeces of sick or carrier animals, or through other factors of the complex indirect route, including sick or carrier humans, at any point of the chain from the slaughtering of the animal to the marketing of the product.

The distinction matters practically: primary contamination is fought by veterinary control of the living animal and of slaughtering; secondary contamination by hygiene along the entire food chain — transport, storage, processing, handling, sale.

Foods of vegetable origin

Contamination occurs through the irrigation of vegetable fields with residual water; through the use of animal faeces as manure; and from sick or carrier humans, from the harvesting of the crop to its marketing. Examples of diseases transmitted this way: typhoid fever and the paratyphoid fevers, cholera, viral hepatitis A, botulism (improperly preserved vegetables), and the toxinfections with *Salmonella* spp.

Mixed foods

Mixed foods — creams, salads, mayonnaises, beer — are both a good culture medium and a good transmission route; most of the germs mentioned above can be transmitted through them. Their danger lies in their composition (nutritive, water-rich, often uncooked) and in their preparation (much handling, no final thermal treatment), which explains their star role in food poisoning outbreaks, discussed in Chapter 15.

3.8. Transmission through objects

Objects become contaminated through direct contact with the secretions or excretions of sick or carrier persons, through blood, or through other factors of the complex indirect transmission route. **Any object can be contaminated** — linen, dishes, toys, instruments, door handles, telephones; in the hospital environment, contaminated objects and surfaces are a central link of nosocomial transmission.

Objects can carry:

- **bacteria** — *Staphylococcus* spp., *Streptococcus* spp., *Salmonella* spp., *Pseudomonas aeruginosa*, *Escherichia coli*, *Mycobacterium tuberculosis*, rickettsiae, as well as the sporulated anaerobic bacteria — the germs of gas gangrene and *Clostridium tetani*;
- **viruses** — adenoviruses and enteroviruses.

The measures directed against this route are decontamination and disinfection, the individualisation of objects of personal use, and sterilisation for medical instruments.

3.9. Transmission through dirty hands

The hands occupy a special position among the vehicles: they belong simultaneously to the potential victim and to the environment, and they touch everything — including, by ancient reflex, the face and the mouth. The possible scenarios are:

- **self-contamination** with the body's own germs, through one's own secretions and excretions;
- **contamination from a sick person or a germ carrier**, which can be **direct** (contact with the source itself) or **indirect** (contact with its pathological products);
- contamination of the hands **by other factors** of the complex indirect transmission route — objects, water, soil, food.

Pathogens can then be transmitted from the dirty hands either directly to one's own or another person's mucosae, or through the contamination of further factors of the complex indirect route — the hands are thus the universal interchange station of the faecal–oral mechanism.

Examples of diseases that can be transmitted through dirty hands: typhoid fever and paratyphoid fever, dysentery, food poisoning, viral hepatitis A, the zoonoses, and staphylococcal and streptococcal infections. Disease transmission through dirty hands can be prevented through measures of individual hygiene — hand washing with water and soap remains, from Semmelweis to the present day, the cheapest and most efficient single measure of prevention in the whole of medicine, in the community as in the hospital.

3.10. Transmission through vectors

Vectors are living carriers of pathogens, and they are classified according to two criteria.

According to the **method of transmission**:

- **passive (mechanical) vectors** — flies, cockroaches: they carry the pathogen on their body surface or in their digestive tract, without the pathogen multiplying in them; they are, so to speak, flying dirty hands;
- **active (biological) vectors** — the haematophagous species: lice, fleas, mosquitoes, ticks; in them, the pathogen multiplies and/or completes part of its life cycle, and transmission occurs through the act of blood feeding.

According to the **specificity of transmission**:

- **monovalent (specific) vectors** — transmitting a single disease: the tsetse fly (African trypanosomiasis);
- **polyvalent vectors** — transmitting several diseases: the louse (epidemic typhus, recurrent fever, trench fever);
- **universal vectors** — the housefly, able to carry mechanically practically any pathogen present in its environment.

The struggle against vector-borne diseases is fought largely outside the doctor's office: disinsection, deratisation, environmental sanitation, protection against bites (nets, repellents, clothing). Vector-borne diseases are also the most climate-sensitive of all infectious diseases, since temperature and humidity govern the geography and the activity of the vectors; the current expansion of *Aedes* mosquitoes into southern and central Europe, with autochthonous cases of dengue, chikungunya and West Nile fever, illustrates the renewed importance of this route on our continent.

3.11. Transmission routes: what the past decade has changed

The classification of transmission presented above is classical and remains sound; three areas, however, have been substantially revised by recent evidence, and the student who learns only the older account will be at a disadvantage.

The continuum of respiratory particles. The rigid dichotomy between "droplets" (large, ballistic, falling within 1–2 metres) and "droplet nuclei" (below 5 µm, airborne) was, as Box 3.1 noted, a convenient simplification, and the COVID-19 pandemic made its limitations impossible to ignore. Exhaled particles form a continuous spectrum of sizes; particles considerably larger than 5 µm can remain suspended in still indoor air; and the accumulation of infectious aerosol in poorly ventilated indoor spaces is now recognised as the principal mechanism of the superspreading events that drive respiratory epidemics. The practical hierarchy that follows applies to influenza, measles, tuberculosis and SARS-CoV-2 alike: **outdoors is safer than indoors; ventilated is safer than unventilated; brief contact is safer**

than prolonged; and a well-fitting respirator protects better than a loose surgical mask in high-risk settings. Ventilation — measured in air changes per hour, or monitored indirectly by indoor CO□ concentration — has consequently become an anti-epidemic measure in its own right [2], and one of the durable public health legacies of the pandemic.

Vectors and the changing map of Europe. The vector-borne diseases described in Section 3.10 were, in the European teaching of a generation ago, largely exotic. This is no longer true. *Aedes albopictus* is now established in much of southern and central Europe and has been implicated in locally acquired transmission of dengue and chikungunya in Mediterranean countries; West Nile virus produces annual summer epidemics in south-eastern Europe, Romania included, with the *Culex* mosquito as vector and birds as reservoir [3]; and the ticks that transmit Lyme borreliosis and tick-borne encephalitis have extended their season, their altitude and their latitude. The favouring factors of Chapter 5 — temperature, humidity, land use — are the drivers, and the practical consequence for the clinician is that a febrile syndrome in August, in a patient who has not left the country, may today have an aetiology that the textbooks of 1990 placed in the tropics.

Food and water in an industrialised food chain. The mechanisms of Sections 3.5 and 3.7 are unchanged, but their scale is not: a single contaminated ingredient distributed through international commerce can produce an outbreak dispersed across many countries, in which no local investigator sees more than a handful of cases. Such **diffuse outbreaks** are detectable only by the routine molecular typing of isolates and by the international comparison of sequences — the reason for the European molecular surveillance networks — and their investigation is a matter of tracing supply chains rather than of interviewing patients about a common meal. The classical hydric epidemic, on the other hand, remains fully contemporary wherever sanitation fails: cholera produced more than 600,000 reported cases and nearly 7,600 deaths across 33 countries in 2024, with deaths continuing to rise even as case numbers began to fall in 2025 [4].

Hands and healthcare. The oldest chapter of this discipline is also among the most current. In European acute-care hospitals, **4.3 million patients acquire at least one healthcare-associated infection each year**, and at least a fifth of these are considered preventable — the hands of staff, and the devices they insert, being the dominant transmission routes [5]. Chapter 19 develops the subject; here it is enough to note that everything Semmelweis demonstrated about the transmission route in 1847 remains the operative doctrine of hospital hygiene in 2026.

References

1. Heymann DL (ed.). *Control of Communicable Diseases Manual*. 21st ed. APHA; 2022.
2. World Health Organization. *Roadmap to improve and ensure good indoor ventilation in the context of COVID-19*. Geneva: WHO; 2021.

3. European Centre for Disease Prevention and Control. Vector-borne disease surveillance: West Nile virus, dengue, chikungunya — annual epidemiological reports. Stockholm: ECDC.
4. World Health Organization. Preventive cholera vaccination resumes as global supply reaches critical milestone. Geneva: WHO; 4 February 2026.
5. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals, 2022–2023. Stockholm: ECDC; 2024.

Chapter 4. The Receptive Population. Immunity

4.1. Receptiveness and resistance

The third determining factor of the epidemiological process is the **receiving (receptive) population** — the mass of people prone to the disease. Without receptive individuals, the most active source and the most efficient transmission route remain without effect; conversely, the accumulation of receptive individuals in a population is the silent preparation of the next epidemic.

The degree of receptiveness to infectious diseases differs. An organism can be **receptive** or **resistant** (specifically or non-specifically):

- **receptiveness** is the state of the organism that allows the pathogen to survive and multiply in it;
- **non-receptiveness (resistance)** gives the organism the ability to prevent the entry of the pathogen, to destroy it, or to eliminate it as quickly as possible.

Resistance has the two components already described in Chapter 1: the non-specific defence (the cutaneous-mucous, cyto-tissular and humoral barriers) and the specific defence — immunity.

4.2. Individual and collective immunity

The individual's immunity is the organism's property of not contracting an infection in the case of an infecting contact with a pathogen or its toxins.

Collective immunity is not merely the sum of the immune individuals at a given moment, but the capacity of the collectivity as a whole to resist being affected by the pathogen — to prevent or limit its spreading in the collectivity. The immune individuals act as so many interruptions of the transmission chains: when their proportion is high enough, the pathogen can no longer find, from each source, a next receptive host, and transmission dies out even though receptive individuals still exist. This is the phenomenon known today as **herd immunity (herd protection)**, and it is the theoretical foundation of mass vaccination programmes [1]: the vaccinated majority protects the unvaccinatable minority — infants too young for vaccination, persons with contraindications, the immunosuppressed.

Box 4.1. The herd immunity threshold and R□ (supplementary). The intensity of transmission of a disease is summarised by the **basic reproduction number R□** — the average number of secondary cases produced by one case introduced into a fully receptive population. The proportion of immune individuals needed to block sustained transmission (the herd immunity threshold) is approximately $1 - 1/R_0$. For measles, with R_0 of the order of 12–18, the threshold is 92–95% — which is why measles returns first, as vaccination coverage erodes, and why it functions as the sentinel of every immunisation programme; for rubella and mumps the threshold is lower, and for influenza, with modest R□ but high antigenic variability, lasting herd immunity is unattainable. R□ is not a biological constant of the germ alone: it incorporates the contact patterns of the population, and every measure that reduces contacts, from school closure to masks, lowers the *effective* reproduction number R below R□.

4.3. The classification of immunity

Immunity is classified as follows:

- **inborn (species-related) immunity** — the resistance belonging to the human species as such: humans do not contract distemper, and animals do not contract measles;
- **acquired immunity**, which can be obtained:
  - **actively**, when the organism produces its own antibodies and immune memory:
  - **spontaneously** — following the disease (post-infectious immunity);
  - **artificially** — following vaccination (post-vaccinal immunity);
  - **passively**, when the organism receives ready-made antibodies:
  - **spontaneously** — transplacentally, from the mother to the foetus (and through breast milk);
  - **artificially** — through the administration of serums and immunoglobulins.

The two modalities are complementary in practice: active immunisation installs slowly but lasts long; passive immunisation protects immediately but only for weeks — hence the classical association, in post-exposure prophylaxis (tetanus, rabies, hepatitis B of the newborn), of the specific immunoglobulin, which covers the immediate danger, with the vaccine, which builds the durable protection [2].

4.4. The individual factor and the spectrum of infection

The individual factor is especially important, because no infection that spreads in a collectivity occurs in an identical form in each individual. In some people the infection is manifested:

- **typically** — with the complete clinical picture;
- **atypically** — with an incomplete or unusual picture;
- **inapparently** — with immunological and biochemical changes only, without clinical signs.

The contagiousness index is the percentage of individuals in a receptive collectivity who, when exposed to the infection, develop the typical disease. It varies enormously between diseases and defines their epidemiological personality:

- for some diseases, 90–100% of those exposed develop the typical disease — **measles** is the classical example;
- other diseases have a high percentage of inapparent infection — in **poliomyelitis** there are several hundred inapparent infections for every typical or atypical sick person.

In poliomyelitis, therefore, the person has a high receptiveness for the *infection* but a low tendency to develop the *disease*. The inapparent infection is also immunising; consequently, if we assessed the number of immune individuals taking into account only those who have visibly gone through the disease, we would be making an exact calculation for measles and a grossly

incorrect one for poliomyelitis — in poliomyelitis, the sum of individuals immune after having had the recognisable disease is much smaller than the real collective immunity. This is the **iceberg phenomenon**: the visible cases are only the emerged tip; the mass of inapparent infections — invisible, contagious and immunising — floats below the waterline, and only serological surveys can measure it.

The durability of post-infectious immunity likewise differs among diseases: there are infections from which all individuals gain strong, long-term immunity — **measles** — and infections leaving only short-term, labile post-infectious immunity — **influenza**, in which reinfection is the rule.

4.5. The immunological structure of the population

The immunological structure of a population — the map of its immunity at a given moment — is determined by two categories of factors:

- **specific factors**: going through the disease; going through the inapparent infection; the application of chemoprophylaxis; the application of vaccination; other measures of specific prophylaxis;
- **non-specific factors**: age, food (nutrition), recent anergic diseases, the type of work, and the economic, cultural and sanitary level.

In some diseases, collective immunity is determined predominantly by the **specific** factors — measles, through vaccination and post-infectious immunity. In others, the determining role is played by the **non-specific** factors — dysentery, through hygiene, food and lifestyle. In others still, the two categories combine — cholera.

The practical consequence is that the epidemiologist must periodically evaluate the immunological structure of the population — through vaccination coverage surveys and serological studies — because every cohort of newborns, every wave of migration and every year of waning immunity quietly modifies it. When the proportion of receptive individuals exceeds the critical threshold, the conditions of the next epidemic are assembled, and only the moment of introduction of the pathogen remains unknown.

4.6. Population immunity: measurement, erosion and modern evidence

The immunological structure of a population, described in Section 4.5 as a theoretical construct, is today a measured quantity, and its measurement has become one of the routine tasks of public health.

Serosurveys — the systematic measurement of specific antibodies in representative population samples — reveal what notification data cannot: the true extent of past infection, including its inapparent portion, and the size of the susceptible pool. During the COVID-19 pandemic, serosurveys conducted worldwide showed that reported cases represented a small fraction of infections, and they became the instrument by which the transition from a naive to an immune

population was tracked. For the vaccine-preventable diseases, serosurveys identify the age cohorts in which immunity has fallen below the herd-protection threshold, and thus permit intervention *before* the epidemic that would otherwise reveal them.

Vaccination coverage is the second measure, and its recent history in Europe is a demonstration of the theory of this chapter. Global first-dose measles coverage stood at 84% in 2024 and second-dose coverage at 76%, against the 95% with two doses required to interrupt transmission; more than **30 million children remained under-protected**, and 59 countries experienced large outbreaks [3]. In Romania, MMR coverage fell between 2018 and 2024 from about 90% to 78% for the first dose and from 81% to 62% for the second, and the epidemic that followed exceeded 25,000 reported cases in 2024 — the largest since 1993 [4]. The arithmetic of Box 4.1 is not an abstraction: with an R□ of 12–18, measles requires 92–95% immunity, and a population at 62% two-dose coverage is not partially protected but structurally epidemic.

The mechanisms of erosion of collective immunity are four, and they should be distinguished because they call for different responses: the accumulation of unvaccinated birth cohorts (a demographic process, requiring routine coverage); the waning of vaccine-induced immunity over time (an immunological process, requiring boosters — pertussis and mumps are the examples); antigenic change in the pathogen (influenza, SARS-CoV-2 — requiring reformulation); and the loss of public confidence (a social process, requiring communication and the strengthening of primary care — Chapter 18).

Two refinements of the classical doctrine deserve mention. First, herd protection depends not only on the *proportion* immune but on the *distribution* of immunity: clusters of unvaccinated persons — in a school, a community, a region — sustain outbreaks even when national coverage appears adequate, because the pathogen circulates within the cluster rather than across the average. Secondly, herd protection requires that the vaccine reduce **transmission**, not merely disease: the conjugate vaccines against pneumococcus, meningococcus and *Haemophilus influenzae* type b protect the unvaccinated precisely because they reduce nasopharyngeal carriage, whereas a vaccine that prevents severe illness without preventing infection (as the COVID-19 vaccines largely proved to be against the Omicron lineages) protects the vaccinated individual but confers correspondingly less indirect protection on the community.

Finally, the phenomenon of **measles-induced immune amnesia** — the destruction by the measles virus of pre-existing immune memory to other pathogens, with an increased susceptibility to unrelated infections for two to three years afterwards — adds an argument to the case for vaccination that the classical account did not know: measles does not merely cause its own disease, it erases part of the immunological history of the child who survives it [5].

References

1. Fine P, Eames K, Heymann DL. "Herd immunity": a rough guide. *Clinical Infectious Diseases*. 2011. doi:10.1093/cid/cir007
2. Orenstein WA, Offit PA, Edwards KM, Plotkin SA (eds.). *Plotkin's Vaccines*. 8th ed. Elsevier; 2023.
3. World Health Organization. Measles deaths down 88% since 2000, but cases surge. Geneva: WHO; 28 November 2025.
4. World Health Organization Regional Office for Europe. Romania increases vaccination coverage for measles, mumps and rubella. Copenhagen: WHO/Europe; 26 June 2026.
5. Moss WJ, Griffin DE. Measles 2025. *New England Journal of Medicine*. 2025. doi:10.1056/NEJMra2504516

Chapter 5. The Favouring Factors of the Epidemiological Process

5.1. The place of the favouring factors

Alongside the three determining factors — source, transmission, receptive population — the epidemiological process is modulated by the **favouring (secondary) factors**: the natural environmental factors and the economic and social factors. They do not create the process, but they open or close the road for it; as stated in Chapter 1, they may not have a decisive effect on the *formation* of the epidemiological focus, yet they often decide the *form of manifestation* of the process — sporadic smouldering or epidemic explosion.

5.2. The natural environmental factors

The seasons can favour or prevent the occurrence of morbid processes:

- **the cold** favours the aerogenous infections — crowding indoors, reduced ventilation, the drying and cooling of the respiratory mucosa, the better survival of respiratory viruses in cold air;
- **the heat** favours the digestive infections — a higher intake of liquids and cellulose-rich foods, the faster multiplication of germs in food, the development of vectors and of rodents;
- **atmospheric pressure oscillations** — temperature drops followed by sudden rises are classically associated with influenza epidemics;
- **heavy rainfall and the water from melting snow** wash the soil and contaminate water sources, favouring the digestive infections;
- **natural disasters** — floods, earthquakes — destroy at a stroke the sanitary infrastructure (drinking water, sewerage, housing, medical services) and drive the epidemiological process towards its epidemic manifestation.

To these are added the climatic, geographic, geologic and hydrologic factors, which draw the permanent map of many diseases: the geography of natural foci, of vectors, of water sources.

Box 5.1. Climate change as an epidemiological factor (supplementary). The natural favouring factors are no longer stable background conditions: climate change is shifting them measurably. Warmer temperate winters extend the season and the altitude range of ticks (tick-borne encephalitis, Lyme borreliosis) and allow the establishment of *Aedes albopictus* across southern and central Europe, with autochthonous transmission of dengue and chikungunya recorded in Mediterranean countries and West Nile virus seasons of growing intensity in south-eastern Europe, Romania included. Heat waves and floods, increasingly frequent, act as recurrent amplifiers of food-borne and water-borne infections. Climate change is therefore treated today as a structural determinant of the epidemiology of communicable diseases [1].

5.3. The economic and social factors

The economic and social factors act upon **all** the determining factors — they multiply the sources (poverty and war multiply the unrecognised and untreated cases), widen the transmission routes (deficient water supply, crowding) and deepen receptiveness (malnutrition, exhaustion, low vaccination coverage). They are represented by:

- the social life conditions;
- the population's economic state;
- the working conditions;
- the conditions of living together (cohabitation);
- food;
- population movements;
- the sanitary and moral level;
- certain religious habits.

The classical correspondences between social conditions and pathology deserve memorising:

- **the insalubrious home** — influenza, the viral hepatitides, tuberculosis;
- **agglomerations (crowding)** — the aerogenous infections and the vector-borne infections;
- **improper eating**, quantitatively or qualitatively — decreases the body's resistance and favours the onset of diseases;
- **contaminated food** — food poisoning;
- **contaminated water** — the diseases with hydric transmission;
- **the job and the working conditions** — viral hepatitis B is a job-related disease for the medical staff;
- **social calamities — wars** — impose the epidemic manifestation form of the epidemiological process; the great epidemics of typhus, dysentery and cholera have always marched with armies and with refugees.

The world map of poverty overlaps to a striking degree with the world map of communicable disease: the regions with the lowest income concentrate the highest burden of infections, and within every country — including the wealthy ones — the socially disadvantaged groups bear the heaviest share. For the epidemiologist, the economic and social factors are thus not a sociological digression but a working instrument: every programme of prevention and control that ignores them fails.

5.4. The favouring factors today: climate, conflict, urbanisation, information

The classical list of Sections 5.2 and 5.3 requires four contemporary annotations, each supported by data that were not available when the course was first written.

Climate change has become a structural determinant. Rising temperatures extend the geographical range and the seasonal activity of vectors (Section 3.11); heat waves and floods produce recurrent amplifications of food- and water-borne infection; drought and crop failure act through malnutrition upon the receptive population. The *Lancet* Countdown reports document these pathways annually, and the practical consequence for the epidemiologist is that the "natural environmental factors" of the classical scheme are no longer a stable background but a moving one, requiring the periodic revision of risk maps.

Conflict and displacement remain the most powerful of the social favouring factors, exactly as the course states. The largest cholera epidemics of the present decade — Yemen, Haiti, Sudan, the Democratic Republic of the Congo — have all occurred where war or disaster destroyed water and sanitation; more than 600,000 cases and nearly 7,600 deaths were reported to WHO from 33 countries in 2024, and the deaths continued to rise even as reported cases declined in 2025 [2]. Diphtheria, measles and hepatitis E follow the same map. Populations in camps and in besieged cities reproduce, with distressing fidelity, the epidemiology of the nineteenth century.

Urbanisation and inequality. More than half of humanity now lives in cities, and a substantial share of urban growth occurs in informal settlements without adequate water, sanitation or housing — the classical conditions for the diseases of Part III. Within wealthy cities, the same gradient operates in miniature: occupational exposure, crowded housing and limited access to care concentrated both COVID-19 mortality and chronic disease among the disadvantaged. The economic and social factors of Section 5.3 are therefore not a historical relic but the strongest predictor of health in every country, at every level of development [3].

The informational environment is a new favouring factor. The classical list — climate, geography, economy, housing, work, nutrition — did not include the circulation of information, because until recently it did not act at epidemiological scale. It does now: WHO's designation of the COVID-19 "infodemic" [4], the measurable effect of vaccine misinformation on coverage, and the European measles epidemics that followed the loss of confidence in immunisation (Chapters 13 and 18) are evidence that beliefs propagate like pathogens and modify the receptive population as surely as any biological factor. The countermeasures — transparency, the acknowledgement of uncertainty, engagement with communities, the strengthening of trusted primary care — belong in the modern toolbox of epidemic control alongside chlorination and vaccination.

Romania in this framework. The country's health profile shows how the favouring factors translate into outcomes: life expectancy of 76.6 years in 2024, some 5.1 years below the EU

average; the third-highest preventable mortality in the EU (304 deaths per 100,000 in 2022) and the highest treatable mortality (215 per 100,000); daily smoking in about a fifth of adults; alcohol consumption of 12.3 litres per adult, among Europe's highest; and health expenditure of about €1,800 per capita, less than half the EU average, at 5.8% of GDP against the EU's 10.0% [5]. Every one of these is a favouring factor in the sense of this chapter, and together they explain more of the Romanian disease burden than any specific biological characteristic of the pathogens involved.

References

1. Romanelli C, Cooper D, Campbell-Lendrum D, et al. *Connecting global priorities: biodiversity and human health*. Geneva: WHO/CBD; 2015.
2. World Health Organization. Preventive cholera vaccination resumes as global supply reaches critical milestone. Geneva: WHO; 4 February 2026.
3. Marmot M. *The Health Gap: The Challenge of an Unequal World*. Bloomsbury; 2015.
4. World Health Organization. *Infodemic management: WHO competency framework*. Geneva: WHO; 2021.
5. OECD/European Observatory on Health Systems and Policies. *România: Profilul de țară din 2025 în ceea ce privește sănătatea* (State of Health in the EU). Paris/Brussels; 2025.

Chapter 6. The Forms of Manifestation of the Epidemiological Process

6.1. The criteria for assessing the forms of manifestation

The intensity of the epidemiological process is labelled through four forms of quantitative manifestation: **sporadic, endemic, epidemic and pandemic**. These forms are assessed according to a set of criteria: morbidity, mortality, lethality, fatality, diffusion ability and periodicity.

Morbidity expresses the number of cases of a certain disease occurring in a population living on a certain territory, over a certain period of time.

Mortality records the deaths occurring within a population occupying a certain territory, over a given period of time.

Lethality is expressed as the ratio of the number of deaths generated by a certain disease to the number of deaths from all causes, in a certain territory and over a certain period of time — it answers the question: what share of all deaths is due to this disease?

Fatality expresses the ratio of the cases of a certain pathology resulting in death, over a certain period of time, to the global number of cases of that pathology over the same period — it answers the question: what is the risk of dying for a person who has contracted the disease?

Box 6.1. Terminological note (supplementary). In the international epidemiological literature, the indicator called here *fatality* corresponds to the **case-fatality rate (CFR)** — deaths from the disease divided by cases of the disease — while the indicator called here *lethality* corresponds to the **proportionate mortality** — deaths from the disease divided by deaths from all causes. Morbidity is measured in practice through two distinct indicators which must never be confused: **incidence** (the new cases appearing in a period — the cinema film of the process) and **prevalence** (all existing cases at a given moment — the photograph). A disease with long duration can have a low incidence and a high prevalence (diabetes); an acute disease, a high incidence and a negligible prevalence at any single moment (influenza).

Diffusion ability (expansion) expresses the propagation speed of an infectious disease in a fully receptive population. The spreading speed depends on: the number of sources of infection, the number of transmission routes, the number of receptive individuals, the duration of incubation, and the economic and social factors. According to this criterion we distinguish:

- diseases with **no expansion tendency** — tetanus (no interhuman transmission);
- diseases with **slow expansion** — dysentery;
- diseases with **rapid expansion** — influenza, rubella.

Periodicity is the increase in morbidity at certain intervals, in the form of seasonal and multiannual oscillations.

Seasonal oscillations express the increase of morbidity in a certain season, regardless of the manifestation form of the epidemiological process during the rest of the year: the digestive-entry diseases — cholera — in **summer**; the respiratory-entry diseases — influenza — in **winter and spring**.

Multiannual oscillations are the recurrence of acute and extensive manifestations of the epidemiological process — an epidemic or a pandemic — in a collectivity or a territory, after a time of inter-epidemic tranquillity. During this interval, which can last years, the disease has either not manifested itself at all or has manifested itself only sporadically and endemically. Multiannual oscillations manifest themselves in a population that has again become receptive after the previous epidemic:

- either through the loss of the weak immunity remaining after the disease,
- or through the accumulation of population segments that have not yet been vaccinated (the new birth cohorts).

Classical examples: rubella, with a 3–5-year periodicity; influenza, with a 2–3-year periodicity. The mechanism is worth retaining in its generality: every epidemic consumes the receptive mass and leaves behind an immune population; the years of calm that follow are precisely the years in which births, migration and waning immunity rebuild the receptive mass — until the threshold is crossed and the cycle recommences. Vaccination programmes, when coverage is high, flatten these oscillations; when coverage falls, the oscillations return, as the measles epidemics of recent years in Europe have demonstrated.

6.2. The sporadic form

The sporadic form manifests itself in a small number of disease cases, recorded at large intervals of time, with no apparent link between them, and disseminated over a wide geographic area — tetanus and anthrax are typical examples.

The sporadic character may be the natural manifestation of some diseases, or it may be determined by the existence of a population mass refractory to the disease as a result of post-infectious and/or post-vaccinal immunity. The sporadic form may also occur in a receptive population when the transmitting vector is missing or when the infecting contact occurs only sporadically; and it may occur even in highly contagious diseases, when the sick persons became infected outside the collectivity and the correct prevention and control measures have been taken within the community.

The sporadic form is thus the epidemiological ideal for the diseases that cannot be eradicated — and, at the same time, a state that must be actively defended, not taken for granted.

6.3. The endemic form

In the endemic form there is a curve of relatively low and uniform morbidity: the disease is constantly present in the territory, without great oscillations. The endemic character of a disease can be transformed — either naturally or through prevention and control measures — into a sporadic form, or it may evolve towards an epidemic form; endemicity is therefore a state of unstable equilibrium, a permanent negotiation between the pathogen and the control measures.

The process by which a territory is made endemic, through the massive interest of the population in that particular infection, is known as **hyperendemisation**. In this phase there are many individuals with latent forms or inapparent infections, so that the clinically manifest infections appear as merely sporadic — the **iceberg model** once again: the surveillance system sees scattered cases, while beneath them a broad, invisible circulation of the pathogen is taking place.

6.4. The epidemic form

The epidemic form is represented by numerous cases of the disease occurring in a collectivity, on a given territory, in a limited period of time. The epidemic appears as a large-scale manifestation:

- in highly contagious diseases — influenza;
- when the population is 100% receptive;
- when the population is only partly receptive, but there is an influx of many sources of infection;
- when the germs display maximum virulence;
- when there are many transmission routes;
- when the favouring factors intervene.

In practice, we can encounter **explosive** or **slow** epidemics.

Explosive epidemics have a sudden outbreak and are characterised by a large number of cases in a short time. Their types, named after the vehicle, are: **hydric** epidemics; **food-related** epidemics (milk — food poisoning); **vector-based** epidemics; and **respiratory** epidemics — influenza. The explosive character betrays the massive, simultaneous contamination of many persons from a common vehicle; the epidemic curve rises almost vertically, and the identification of the common vehicle is the key of the investigation.

Slow epidemics are due to infecting contacts occurring intermittently, individually or in small population groups. They are usually transmitted through contact, and contamination occurs at the level of the transmission route with small doses of germs or with weakly virulent germs. Example: recurrent fever. The epidemic curve rises and falls gently, over weeks or months, reflecting successive generations of cases rather than a single common exposure.

6.5. The pandemic form

The pandemic form is an amplified manifestation of the epidemic, in which the disease foci expand successively and permanently, crossing the borders of countries and continents.

Pandemic manifestations are noticed currently in type A influenza and in HIV/AIDS, and were displayed by SARS-CoV-2 (COVID-19); in the case of the viral hepatitides, through their universal spreading — with some 300 million carriers of the hepatitis B virus — a slowly evolving pandemic manifestation is taking place. HIV/AIDS illustrates the modern pandemic of slow motion: thousands of new infections every day worldwide, accumulated over four decades into one of the great pandemics of history.

Box 6.2. The great pandemics as historical markers (supplementary). Each age has had the pandemics of its ecology: the Plague of Justinian (sixth century) and the Black Death (1347–1351) in the age of caravans and grain ships; cholera in seven successive pandemics of the industrialising nineteenth and twentieth centuries; influenza in 1918 ("Spanish flu", with tens of millions of deaths), 1957, 1968, 1977 and 2009; HIV/AIDS from 1981 onwards; COVID-19 from 2020, with over 770 million confirmed cases and some 7 million officially reported deaths (WHO) — the true excess mortality being estimated far higher. The lesson of this series is structural: pandemics are born at the meeting point of a new or renewed pathogen with a globally receptive and globally connected population, and the interval between them is not an era of safety but an interval of preparation — surveillance, laboratory networks, vaccine platforms, international health regulations.

6.6. The forms of manifestation in the light of modern epidemic theory

The four quantitative forms — sporadic, endemic, epidemic, pandemic — are descriptive categories inherited from the pre-mathematical era of epidemiology. Modern epidemic theory does not replace them; it explains them, and the correspondence is worth making explicit, because it converts a classification into a mechanism.

The reproduction number is the parameter that unifies the four forms. The **basic reproduction number R□** is the mean number of secondary cases produced by one case in a wholly susceptible population; the **effective reproduction number R_t** is the same quantity in the population as it actually is, with its immunity and its control measures. The relation to the classical categories is direct: while $R_t < 1$ the process declines and manifests itself sporadically or endemically; when R_t exceeds 1 the process is epidemic; and the transition between the two states is what an epidemic curve records. Multiannual oscillations are the natural behaviour of a system in which the susceptible pool is consumed by each epidemic and rebuilt by births and by waning immunity — precisely the mechanism described in Section 6.1, now expressible as a set of differential equations (the classical SIR model of Kermack and McKendrick, 1927) [1] whose oscillatory solutions reproduce the observed periodicity of measles, rubella and pertussis [2].

Overdispersion and superspreading. The classical account implicitly assumes that each case transmits to about the same number of others. In reality transmission is highly heterogeneous for many pathogens: a minority of infected persons produce the majority of secondary cases, in circumstances (crowded, closed, prolonged, poorly ventilated) rather than through any peculiarity of the individual. Overdispersion — quantified by the dispersion parameter k — explains why introductions of a pathogen frequently die out by chance even when R□ exceeds 1 [3], why explosive clusters appear against a quiet background, and why **backward** contact tracing (looking for the event that infected the case) can be more efficient than forward tracing alone. SARS-CoV-2, SARS-CoV-1 and measles all display it.

Serial interval and generation time determine the speed of an epidemic, and with it the feasibility of control: a disease whose serial interval is longer than the delay between symptom onset and isolation can be contained by contact tracing, while one that transmits before symptoms — as SARS-CoV-2 does — cannot be contained by isolating the symptomatic alone [4]. This single quantitative consideration explains why the strategy that had contained SARS in 2003 failed against COVID-19 in 2020.

Modern nomenclature. Two additions to the classical vocabulary should be known. A **syndemic** describes the synergistic co-occurrence of two or more epidemics in a population, each aggravating the other and both amplified by social conditions [5] — the interaction of COVID-19 with obesity, diabetes and deprivation being the demonstrative example. A **panzootic** is the animal equivalent of a pandemic, and the current spread of high-pathogenicity avian influenza A(H5N1) among wild birds and mammals across several continents is the most important contemporary instance, with its permanent implication for human pandemic risk (Chapter 11).

The pandemic form, legally defined. Since the 2024 amendments to the International Health Regulations, the pandemic form of Section 6.5 has acquired for the first time a formal legal category: the **"pandemic emergency"**, the highest level of alert, defined above the Public Health Emergency of International Concern and requiring, among other criteria, wide geographical spread and the capacity to cause substantial social and economic disruption [6] (Chapter 10). The epidemiological description taught in this chapter has thereby become the trigger of an international legal regime — a development that would have surprised the authors of the classical classification, and one more reason for the student to define the terms precisely.

References

1. Kermack WO, McKendrick AG. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society A*. 1927;115:700–721.
2. Anderson RM, May RM. *Infectious Diseases of Humans: Dynamics and Control*. Oxford University Press; 1991.
3. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. *Nature*. 2005. doi:10.1038/nature04153

4. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. *PNAS*. 2004. doi:10.1073/pnas.0307506101
5. Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. *The Lancet*. 2017. doi:10.1016/S0140-6736(17)30003-X
6. World Health Organization. International Health Regulations (2005): amendments adopted by the Seventy-seventh World Health Assembly, 2024.

PART II. EPIDEMIOLOGICAL METHODS

Chapter 7. Measuring Health and Disease in Populations

7.1. Why measurement is the foundation of epidemiology

Epidemiology begins where counting begins. Every statement of the discipline — that a disease is frequent or rare, that it is increasing or declining, that one group is at greater risk than another, that an intervention works — is at bottom a comparison of numbers. The physician trained only in the clinic thinks in cases; the physician trained in epidemiology thinks in **rates**, that is, in cases related to the population that produced them and to the time over which they occurred. This chapter presents the instruments of that measurement, which will be used throughout the rest of the book.

Three questions must be answered before any epidemiological figure can be interpreted: **who is counted** (the numerator: what is a case?), **among whom** (the denominator: which population, over what period?), and **compared with what** (the reference: another period, another territory, another exposure group?). A figure that does not answer all three is not an epidemiological measure but a fragment of information.

7.2. Measures of disease frequency

Incidence

Incidence measures the appearance of *new* cases. It is the dynamic measure — the film of the epidemiological process — and it is the measure of choice whenever the question concerns risk, causation, or the effect of an intervention.

The **cumulative incidence** (incidence proportion, attack rate, risk) is the number of new cases occurring during a specified period divided by the number of persons at risk at the beginning of that period [1]:

```
CI = (new cases during the period) / (persons at risk at the start of the period)
```

It is a proportion, dimensionless, between 0 and 1, and it must always be accompanied by the length of the period ("the 5-year cumulative incidence"). In outbreak investigations, cumulative incidence computed for a defined exposed group is called the **attack rate**, and the attack rate among persons infected by a primary case within the maximum incubation period is the **secondary attack rate** — the classical measure of contagiousness in households and closed collectivities.

The **incidence rate (incidence density)** relates the new cases not to persons but to **person-time** at risk:

```
IR = (new cases) / (total person-time at risk)
```

Its unit is cases per person-year (or per 100,000 person-years). Person-time correctly handles populations in which individuals are observed for different durations — cohorts with losses to follow-up, migration, or deaths — and it is the measure used in most cohort studies.

Prevalence

Prevalence measures the *existing* cases — the photograph of the population at a moment (point prevalence) or over an interval (period prevalence):

$$P = \text{(existing cases at a given moment)} / \text{(total population at that moment)}$$

Prevalence is not a measure of risk: it is determined jointly by incidence and by the duration of the disease. For a stable situation the relation is approximately:

$$P \approx I \times D$$

where D is the mean duration of the disease. Three consequences follow, and they explain many apparent paradoxes:

- a disease of short duration (influenza) has a high incidence and a low prevalence at any single moment;
- a chronic disease (diabetes, HIV infection under treatment) accumulates prevalence even when incidence is stable or falling — effective treatment, by prolonging survival, *increases* prevalence;
- prevalence is the right measure for planning services (how many patients must be cared for?), incidence for studying causes (what makes people fall ill?).

Measures of mortality

Crude mortality rate — deaths from all causes per 100,000 population per year — is the simplest but least comparable measure, because it depends heavily on the age structure of the population.

Cause-specific mortality rate — deaths from a given cause per 100,000 per year.

Case-fatality (fatality) — deaths from a disease divided by the cases of that disease, expressed as a percentage; a measure of the severity of the disease, not of its frequency in the population. As emphasised in Chapter 6, it must never be confused with **proportionate mortality (lethality)**, which is the share of a given cause among all deaths.

Infant mortality rate — deaths under one year of age per 1,000 live births — remains the classical sentinel indicator of the health and social development of a population, and **maternal mortality ratio** — maternal deaths per 100,000 live births — its counterpart for the obstetric services.

Excess mortality — the difference between observed deaths and the deaths expected from historical trends — became, during the COVID-19 pandemic, the reference measure of the true

impact of the crisis, precisely because it does not depend on testing capacity or on the accuracy of death certification [2, 3].

Composite measures of burden

Mortality alone underestimates diseases that disable without killing. The **disability-adjusted life year (DALY)** sums the **years of life lost (YLL)** through premature death and the **years lived with disability (YLD)**, weighted by severity:

```
DALY = YLL + YLD
```

One DALY represents one lost year of "healthy" life. The Global Burden of Disease (GBD) studies, published by the Institute for Health Metrics and Evaluation, estimate DALYs for hundreds of diseases and risk factors in more than 200 countries, and they have become the common currency of international health policy [4, 5]. Related measures are **HALE** (healthy life expectancy) and the **QALY** (quality-adjusted life year), the latter used mainly in health economics, where the cost per QALY gained is the standard criterion of cost-effectiveness.

7.3. Crude, specific and standardised rates

A crude rate mixes together populations of very different composition. Comparing the crude cancer mortality of Romania with that of Egypt says as much about the age pyramids of the two countries as about their cancer risk: cancer being predominantly a disease of old age, an older population will show a higher crude rate even if the risk at every age is identical.

Two solutions exist:

- **specific rates** — computed within homogeneous strata (age groups, sex, occupation). They are the honest description, but they are numerous and hard to compare at a glance;
- **standardisation (adjustment)** — the construction of a single summary figure freed of the confounding effect of the composition.

Direct standardisation applies the age-specific rates observed in each population to one common **standard population** (the European Standard Population, the WHO World Standard Population, or the Segi world population). The result — the age-standardised rate — answers the question: what mortality would this population have if it had the age structure of the standard? Only such rates may be compared across countries and across time.

Indirect standardisation applies the age-specific rates of a reference population to the age structure of the study population, to obtain the number of expected deaths; the ratio of observed to expected deaths is the **standardised mortality ratio (SMR)**, conventionally multiplied by 100 [6]. An SMR of 130 means a 30% excess mortality relative to the reference. Indirect standardisation is preferred for small populations, where the age-specific rates would be unstable — the study of occupational cohorts is its classical field.

Box 7.1. Reading a standardised rate correctly. Two rules protect the reader from the commonest errors. First, a standardised rate is an artificial number: it has no meaning in itself, only in comparison with another rate standardised to the *same* standard population — which is why every table must state the standard used. Secondly, standardisation removes the effect of the standardised variable only; a rate standardised for age still carries whatever differences in sex distribution, smoking, deprivation or diagnostic practice may exist between the populations compared. Standardisation is a descriptive convenience, not a substitute for the analytical control of confounding discussed in Chapter 8.

7.4. The sources of epidemiological data

The epidemiologist rarely collects data personally; the art lies in knowing what already exists, and what each source can and cannot tell.

Vital statistics — birth and death registration, with the cause of death coded according to the **International Classification of Diseases (ICD-11**, in force since 2022) [7] — provide the longest continuous series in public health. Their weakness is the quality of certification: "cardiac arrest" and "senility" written on a certificate destroy the information of a death.

Mandatory notification of communicable diseases is the backbone of infectious disease surveillance; in Romania it is regulated by the methodologies of the National Institute of Public Health (INSP/CNSCBT) and feeds the European surveillance system (TESSy) managed by ECDC.

Disease registries — cancer registries above all, but also registries for diabetes, congenital anomalies, transplantation and rare diseases — provide population-based incidence, staging and survival, and are the only valid source for cancer incidence.

Hospital discharge data (DRG), prescription and reimbursement databases from health insurance, laboratory information systems, and increasingly **electronic health records** offer very large volumes at low cost, at the price of being generated for administrative rather than epidemiological purposes.

Population surveys — the European Health Interview Survey (EHIS), the WHO STEPS surveys, HBSC for adolescents — measure what routine systems cannot see: behaviours, self-reported health, undiagnosed disease.

Sentinel and syndromic surveillance, including **wastewater surveillance** (polio for decades, SARS-CoV-2 and influenza increasingly), detect circulation independently of health-seeking behaviour and diagnostics; the last of these has become one of the durable methodological legacies of the COVID-19 pandemic.

7.5. Interpreting variation: the three questions of descriptive epidemiology

Descriptive epidemiology organises every observation along three axes — **person, place and time** — and a fourth question, always: is the variation real?

Before accepting an apparent difference or trend, four artefactual explanations must be excluded: a change in the **definition of the case** (the redefinition of AIDS, of myocardial infarction after troponins, of hypertension after 2017); a change in **diagnostic intensity or screening** (the epidemic of thyroid cancer in South Korea, produced by ultrasound screening rather than by any change in risk); a change in **reporting completeness** (the improvement of a surveillance system looks like an epidemic); and **chance**, in small numbers. Only when these are excluded does the epidemiologist proceed to substantive hypotheses — and to the analytical designs of the next chapter.

References

1. Porta M (ed.). *A Dictionary of Epidemiology*. 6th ed. Oxford University Press; 2014.
2. World Health Organization. 14.9 million excess deaths associated with the COVID-19 pandemic in 2020 and 2021. Geneva: WHO; 5 May 2022. Available at: who.int/news/item/05-05-2022
3. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *The Lancet*. 2022. doi:10.1016/S0140-6736(21)02796-3
4. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. *The Lancet*. 2024. doi:10.1016/S0140-6736(24)00367-2
5. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories, 1990–2021. *The Lancet*. 2024. doi:10.1016/S0140-6736(24)00757-8
6. Celentano D.D., Szklo M. *Gordis Epidemiology*. 6th ed. Elsevier; 2019.
7. World Health Organization. International Classification of Diseases, Eleventh Revision (ICD-11). Geneva: WHO; 2022.

Chapter 8. Epidemiological Study Designs and Causal Inference

8.1. The architecture of epidemiological research

Epidemiological studies are classified along two axes. The first distinguishes **descriptive** studies, which characterise the distribution of disease (who, where, when) and generate hypotheses, from **analytical** studies, which test hypotheses by comparing groups. The second distinguishes **observational** studies, in which the investigator only observes an exposure that occurred without his intervention, from **experimental** (interventional) studies, in which the investigator allocates the exposure.

The principal designs, in ascending order of evidential strength, are: case reports and case series; ecological studies; cross-sectional studies; case-control studies; cohort studies; randomised controlled trials; and the syntheses of these — systematic reviews and meta-analyses. To this classical hierarchy modern epidemiology adds designs that borrow from several families: nested case-control and case-cohort studies, case-crossover and self-controlled case series designs, natural experiments, and instrumental-variable approaches such as **Mendelian randomisation**, which uses genetic variants allocated at conception as a natural randomisation of lifelong exposure.

8.2. Descriptive and ecological studies

The **case report** and the **case series** describe one or several patients with an unusual condition or exposure. They cannot quantify risk, but they have repeatedly opened new chapters of medicine: five cases of *Pneumocystis* pneumonia in previously healthy young men, reported in the *MMWR* of 5 June 1981, were the first published trace of the AIDS pandemic [1]; a case series of hepatic angiosarcoma among workers exposed to vinyl chloride identified an occupational carcinogen.

The **ecological (correlational) study** compares aggregate measures — mean salt intake and stroke mortality across countries, vaccination coverage and measles incidence across counties. It is cheap, fast, and uses routinely available data, and it is often the first step in international comparisons. Its characteristic weakness is the **ecological fallacy**: an association observed between group averages does not necessarily hold for individuals, because the individuals with the exposure may not be those with the disease.

The **cross-sectional study** measures exposure and outcome simultaneously in a sample of the population, and is the design of prevalence surveys (EHIS, STEPS, seroprevalence surveys). Its limitation is intrinsic: since exposure and disease are ascertained at the same moment, the temporal sequence usually cannot be established, and **reverse causation** cannot be excluded (do sedentary people become obese, or do obese people become sedentary?).

8.3. The case-control study

The case-control study starts from the **outcome**: a group of persons with the disease (cases) is compared with a group without it (controls) with respect to the frequency of past exposure. It is the design of choice for rare diseases and for diseases with a long latency, and it is the workhorse of outbreak investigation, where it can produce an answer within days.

Its critical methodological point is the **selection of controls**: they must come from the same population that produced the cases, and be selected independently of exposure. The classical sources are population registers, hospital patients with unrelated conditions, neighbours or friends of cases — each with its own advantages and biases.

Because the investigator fixes the number of cases and controls, a case-control study cannot estimate incidence, and therefore cannot compute a relative risk directly. Its measure of association is the **odds ratio**:

$$\text{OR} = (a \times d) / (b \times c)$$

where a and b are exposed and unexposed cases, c and d exposed and unexposed controls. For rare diseases (prevalence under about 10%), the odds ratio approximates the relative risk — the **rare-disease assumption** [2].

The design's vulnerabilities are **recall bias** (cases search their memory harder than controls for possible causes) and **selection bias** in the recruitment of controls.

Box 8.1. The case-control study that changed the twentieth century. In 1950, Richard Doll and Austin Bradford Hill published in the *British Medical Journal* a case-control study of 709 patients with lung cancer and 709 matched controls in London hospitals, showing a strong association with cigarette smoking [3]. The finding was contested — case-control studies were then new and suspect — and the authors answered by launching, in 1951, the prospective **British Doctors Study**, following over 34,000 physicians for half a century; the 50-year results showed that persistent smokers lost about ten years of life expectancy, and that cessation before the age of 40 avoided almost all the excess risk [4]. The pair of studies is a model of the complementarity of the two designs: the case-control study finds the signal quickly, the cohort study confirms it with the correct temporal architecture.

8.4. The cohort study

The cohort study starts from the **exposure**: a group of persons free of the disease is classified according to exposure and followed forward in time to observe the appearance of the outcome. It may be **prospective** (the follow-up occurs after the study begins — Framingham, the British Doctors Study) or **retrospective/historical** (the exposure and the outcomes have already occurred and are reconstructed from records — the classical design of occupational epidemiology).

The cohort study measures incidence directly in the exposed and the unexposed, and therefore yields the full set of measures of association:

- **Relative risk (risk ratio):** RR = I_exposed / I_unexposed — how many times more frequent the disease is among the exposed. It measures the *strength of the association* and thus the aetiological argument.
- **Attributable risk (risk difference):** AR = I_exposed − I_unexposed — the excess incidence caused by the exposure, and thus the number of cases that would be prevented per unit population by removing it; the measure of *public health impact*.
- **Attributable fraction in the exposed:** AF = (I_e − I_u)/I_e = (RR − 1)/RR — the proportion of cases among the exposed attributable to the exposure.
- **Population attributable fraction (PAF):** the proportion of all cases in the population attributable to the exposure, which depends both on the RR and on the **prevalence of exposure**. A modest relative risk applied to a very common exposure (physical inactivity, mild hypertension) may produce a larger PAF — and hence a greater number of preventable cases — than a large relative risk on a rare exposure. This is the arithmetic behind Geoffrey Rose's celebrated "prevention paradox": *a large number of people at small risk may give rise to more cases than a small number at high risk* [5].

The strengths of the cohort design are the correct temporal sequence, the possibility of studying several outcomes of one exposure, and the direct estimation of incidence; its weaknesses are cost, duration, and losses to follow-up — the last being a source of bias whenever loss is related to both exposure and outcome.

8.5. Experimental studies: the randomised controlled trial

In the **randomised controlled trial (RCT)** the investigator allocates the intervention by chance. Randomisation is the only technique that distributes *unknown* as well as known confounders equally between groups, which is why the RCT is the reference design for evaluating interventions.

Its methodological pillars are: **randomisation** with **allocation concealment**; **blinding** (single, double or triple), which protects the ascertainment of outcomes from expectation; **intention-to-treat analysis**, which preserves the benefit of randomisation by analysing every participant in the group to which he was allocated, whatever he actually received; an adequate **sample size**, computed in advance for a clinically meaningful difference; and a **pre-registered protocol** with pre-specified primary outcomes — the safeguard against selective reporting.

In public health, the unit of randomisation is often not the individual but the community, the school, or the general practice: these are **cluster-randomised trials**, used for interventions that cannot be individually allocated (water and sanitation, mass vaccination strategies, health education). **Stepped-wedge** designs, in which all clusters eventually receive the intervention in randomised order, are increasingly used when withholding an intervention entirely would be unacceptable.

The RCT nevertheless has limits that the epidemiologist must respect: many exposures cannot be randomised for ethical reasons (nobody may be randomised to smoke); trial populations are selected and often unrepresentative of ordinary practice (efficacy versus **effectiveness**); rare and late adverse effects escape trials of limited size and duration — which is why post-marketing surveillance (**pharmacovigilance**) and large observational databases remain indispensable.

8.6. Bias, confounding and interaction

Three distinct threats stand between an observed association and a causal conclusion.

Selection bias arises when the participants included differ systematically from the population of interest, in a way related both to exposure and to outcome. Its classical forms are Berkson's bias in hospital-based studies, the healthy-worker effect in occupational cohorts, and non-response bias in surveys.

Information (measurement) bias arises from errors in classifying exposure or outcome: recall bias, interviewer bias, misclassification. **Non-differential** misclassification (equal in the compared groups) generally dilutes the association towards the null; **differential** misclassification can bias in either direction, and is the more dangerous.

Confounding occurs when a third factor is associated with the exposure and is an independent risk factor for the outcome, without being on the causal pathway between them. The textbook example: the association between coffee drinking and lung cancer, produced by the fact that coffee drinkers smoke more. Confounding is controlled at the **design** stage — by randomisation, restriction, or matching — or at the **analysis** stage — by stratification (Mantel–Haenszel), standardisation, or multivariable regression (logistic, Poisson, Cox proportional hazards).

Interaction (effect modification) is not a bias but a biological or statistical reality: the effect of one factor differs across the strata of another. Smoking and asbestos exposure multiply each other's effect on lung cancer risk; the effect of a vaccine differs between the immunocompetent and the immunosuppressed. Interaction must be described, not eliminated.

To these classical threats, modern texts add **reverse causation**, **immortal time bias** in pharmaco-epidemiological database studies, and **collider stratification bias**, whose recognition has been sharpened by the use of **directed acyclic graphs (DAGs)**, now the standard tool for deciding which variables must — and, crucially, which must *not* — be adjusted for.

8.7. Chance, precision and the interpretation of statistics

The p value expresses the probability of observing a result at least as extreme as the one obtained if the null hypothesis were true; it says nothing about the size or the importance of the effect, and a "statistically significant" result in a huge database may be clinically trivial. The **confidence interval** is more informative, giving both the estimate and its precision: an interval for a relative risk that excludes 1 corresponds to a significant association, but its width tells the reader how much the study actually established.

Two errors must be distinguished: the **type I error (α)**, declaring an effect that does not exist, and the **type II error (β)**, failing to detect an effect that exists. **Statistical power** $(1 - \beta)$ is the probability of detecting a true effect of a given size — the parameter that decides the sample size, and whose neglect is the commonest methodological failure of small studies. Multiple comparisons inflate the type I error, and their control (pre-specification, correction, replication) is the antidote to the "significant" findings that fail to reproduce.

8.8. From association to causation

No single study establishes causality. The classical framework for judging it remains the set of viewpoints proposed by **Austin Bradford Hill** in 1965 [6]: strength of association; consistency across studies, populations and designs; specificity; **temporality** (the only strictly necessary criterion — the cause must precede the effect); biological gradient (dose–response); plausibility; coherence with what is known of the natural history of the disease; experimental evidence; and analogy. Hill himself insisted that these are not a checklist to be scored but aids to judgement.

Contemporary epidemiology complements them with the **counterfactual framework** — the causal effect is the difference between what happened under exposure and what would have happened in its absence — formalised in the potential-outcomes model and in causal diagrams [7]. The practical value of this apparatus is not philosophical but concrete: it tells the analyst which adjustments identify a causal effect and which destroy it.

Finally, the syntheses. The **systematic review** identifies, appraises and summarises all studies addressing a defined question according to a pre-registered protocol (PRISMA reporting standard) [8], and the **meta-analysis** combines their results quantitatively, weighting each by its precision, examining **heterogeneity** (I^2) and **publication bias**. Well conducted, this is the highest level of evidence for questions of effectiveness; poorly conducted, it merely averages the biases of the primary studies — *garbage in, garbage out*. The **GRADE** system, now standard in guideline development, rates the certainty of the resulting evidence from high to very low, taking into account risk of bias, inconsistency, indirectness, imprecision and publication bias [9].

Box 8.2. How the study design shapes what you may conclude. A worked comparison for the same question — "does physical inactivity cause type 2 diabetes?" An *ecological* study finds that countries with more cars per capita have more diabetes; it cannot exclude that the individuals with cars are not those with diabetes. A *cross-sectional* survey finds diabetics are less active; it cannot say whether inactivity preceded the disease. A *case-control* study finds diabetics report less past exercise than controls; it is vulnerable to recall bias. A *cohort* study measures activity in healthy adults and follows them for 15 years, finding an incidence ratio of about 0.7 in the most active quartile; the temporal sequence is right, but the active may differ in diet, weight and education. A *randomised trial* of a lifestyle programme in persons with impaired glucose tolerance shows a reduction of incident diabetes of the order of 50% over three years, and settles the question of effectiveness — for that intervention, in that population. Each design answers a different question, and the epidemiologist's skill is to know which question he is asking.

References

1. Centers for Disease Control and Prevention. Pneumocystis pneumonia — Los Angeles. *MMWR*. 1981;30:250–252.
2. Celentano D.D., Szklo M. *Gordis Epidemiology*. 6th ed. Elsevier; 2019.
3. Doll R, Hill AB. Smoking and carcinoma of the lung: preliminary report. *BMJ*. 1950;2:739–748.
4. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004. doi:10.1136/bmj.38142.554479.AE
5. Rose G. Sick individuals and sick populations. *International Journal of Epidemiology*. 1985;14:32–38.
6. Hill AB. The environment and disease: association or causation? *Proceedings of the Royal Society of Medicine*. 1965;58:295–300.
7. Hernán MA, Robins JM. *Causal Inference: What If*. Boca Raton: Chapman & Hall/CRC; 2020.
8. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021. doi:10.1136/bmj.n71
9. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008. doi:10.1136/bmj.39489.470347.AD

Chapter 9. Screening and Early Detection

9.1. Definition and place among the levels of prevention

Screening is the presumptive identification of unrecognised disease or of a defect, by means of tests, examinations or other procedures that can be applied rapidly to apparently healthy persons. It belongs, as Chapter 1 established, to **secondary prevention**: it does not prevent the disease from occurring, but it advances the moment of diagnosis into the preclinical phase, where treatment is more effective.

A capital distinction must be made at the outset. **Screening is not diagnosis.** A screening test sorts an asymptomatic population into a group at higher probability of disease, who must then undergo diagnostic confirmation, and a group at lower probability. A positive screening test is a request for investigation, never a verdict — a point that must be communicated with care, because the interval between a positive screen and the confirmatory result is a period of genuine anxiety for the person, who was, until that morning, healthy.

Two organisational forms exist, with very different performance: **organised (population) screening**, in which a defined target population is systematically invited, followed up and audited within a quality-assured programme; and **opportunistic screening**, performed when the person happens to consult for another reason. Opportunistic screening reaches disproportionately the worried well and systematically misses the socially disadvantaged, in whom the disease is most frequent — the **inverse care law** applied to prevention.

9.2. The validity of a screening test

The performance of a test is judged against a **gold standard** in a two-by-two table:

	Disease present	**Disease absent**
Test positive	a (true positives)	b (false positives)
Test negative	c (false negatives)	d (true negatives)

- **Sensitivity** = a/(a+c) — the ability to detect those who have the disease. A highly sensitive test, when negative, rules disease out.
- **Specificity** = d/(b+d) — the ability to identify correctly those who do not have the disease. A highly specific test, when positive, rules disease in.
- **Positive predictive value (PPV)** = a/(a+b) — the probability that a person with a positive test truly has the disease.
- **Negative predictive value (NPV)** = d/(c+d) — the probability that a person with a negative test is truly free of it.
- **Likelihood ratios** — LR+ = sensitivity/(1 − specificity), LR− = (1 − sensitivity)/specificity — express how much a result shifts the pre-test probability, and have the advantage of not depending on prevalence [1].

Sensitivity and specificity are (approximately) properties of the test; the **predictive values depend decisively on the prevalence of the disease in the population screened**. This is the single most important — and most often forgotten — fact in the whole field, and it deserves a numerical demonstration.

> **Box 9.1. Why prevalence rules the predictive value.** Consider a test with sensitivity 95% and specificity 95% — excellent by any standard. Applied to 100,000 persons in a population where the disease has a prevalence of 1% (1,000 affected): true positives = 950; false positives = 5% of 99,000 = 4,950. The PPV = 950/5,900 ≈ **16%**: five out of six positive results are false alarms. Now apply the same test in a population where prevalence is 0.1% (100 affected): true positives = 95; false positives = 4,995; PPV ≈ **1.9%** — fifty false alarms for every true case. Nothing changed in the test; everything changed in the population. Three practical consequences follow: screening must be directed at groups in which the disease is sufficiently frequent; a very high specificity matters more than sensitivity when prevalence is low; and no screening programme is complete without an organised, rapid and well-explained pathway for the confirmation of positives.

For tests giving a continuous result (glycaemia, PSA, blood pressure), sensitivity and specificity vary with the **cut-off** chosen, in opposite directions; the **ROC curve** plots this trade-off, and the area under it summarises overall discriminating capacity. The cut-off is not a statistical decision but a clinical and social one: it depends on the relative cost of missing a case and of a false alarm.

9.3. Criteria for instituting a screening programme

The classical criteria formulated for WHO by **Wilson and Jungner** in 1968 [2] remain the framework of every decision, and they concern the disease, the test, the treatment and the programme:

1. the condition sought should be an important health problem;
2. there should be an accepted treatment for patients with recognised disease;
3. facilities for diagnosis and treatment should be available;
4. there should be a recognisable latent or early symptomatic stage;
5. there should be a suitable test or examination;
6. the test should be acceptable to the population;
7. the natural history of the condition should be adequately understood;
8. there should be an agreed policy on whom to treat as patients;
9. the cost of case-finding should be economically balanced in relation to possible expenditure on medical care as a whole;
10. case-finding should be a continuing process and not a "once and for all" project.

Modern reformulations add the requirements of evidence from randomised trials that screening reduces mortality or morbidity, of informed choice for the invited person, of equity of access, and of a quality-assurance system with continuous audit of coverage, of interval cancers and of outcomes.

9.4. The specific biases of screening evaluation

Screening cannot be evaluated by comparing the survival of screen-detected with that of symptom-detected patients: three biases guarantee a flattering but false result.

Lead-time bias. Screening advances the moment of diagnosis. If the date of death is unchanged, the measured survival from diagnosis lengthens by exactly the lead time, without a single day of life being gained.

Length-time bias. Screening at intervals preferentially detects slowly progressing tumours, which spend longer in the detectable preclinical phase; rapidly progressive tumours arise and become symptomatic between two screening rounds (**interval cancers**). Screen-detected cases are therefore, by construction, a prognostically favourable selection.

Overdiagnosis is the extreme of length-time bias: the detection of lesions that would never, in the person's lifetime, have produced symptoms or caused death. Overdiagnosis is not a diagnostic error — the pathology is real — but it converts a healthy person into a patient, with the treatment and the anxiety that follow. Its magnitude is debated for breast and prostate cancer, and it is the demonstrated explanation of the "epidemic" of thyroid cancer in countries that introduced widespread ultrasonography without any change in thyroid cancer mortality.

Healthy-volunteer (self-selection) bias completes the list: those who attend screening are on average healthier, better educated and more compliant than those who do not.

The only valid evaluation is therefore a **randomised comparison of invitation to screening versus usual care, with mortality — ideally all-cause as well as disease-specific — as the endpoint**, analysed by intention to treat.

9.5. Screening programmes of demonstrated value

Cervical cancer. The oldest organised screening, and the most successful. Cytology (Papanicolaou) has been progressively replaced by **primary HPV-DNA testing**, which is more sensitive and permits longer intervals (typically 5 years). Combined with HPV vaccination, it underpins the WHO strategy for the **elimination of cervical cancer**, whose targets — the "90–70–90" — are 90% of girls vaccinated by age 15, 70% of women screened with a high-performance test at 35 and 45, and 90% of women with disease treated [3]. The population effect of vaccination is now measurable: in England, the national programme was followed by a reduction of cervical cancer incidence of the order of 87% in the cohorts vaccinated at ages 12–13 [4], and analyses of mortality data to 2024 have begun to show the corresponding decline in deaths [5].

Breast cancer. Mammography every two years in women aged 50–69 (extended in several countries to 45–74) [6] reduces breast cancer mortality; the debate concerns the magnitude of the benefit relative to overdiagnosis, and modern invitation letters are expected to present both.

Colorectal cancer. The faecal immunochemical test (FIT) every two years, with colonoscopy for positives, or primary screening colonoscopy. The **NordICC trial**, the first randomised trial of screening colonoscopy, showed at 10 years a reduction of colorectal cancer incidence of about 18% and a non-significant effect on mortality in the intention-to-screen (invited) analysis, with substantially larger estimated effects among those who actually attended [7]; its results illustrate precisely the distinction between efficacy and effectiveness, and the decisive role of participation.

Other established programmes include neonatal screening (phenylketonuria, congenital hypothyroidism, cystic fibrosis, congenital hearing loss), screening for abdominal aortic aneurysm in older men, and low-dose CT screening for lung cancer in heavy smokers, which has demonstrated mortality reduction in randomised trials and is being introduced in an increasing number of countries.

Screening for **cardiovascular risk factors** — blood pressure, lipids, glycaemia — differs from cancer screening in that the "case" sought is a risk state rather than a disease, and is best embedded in the periodic global risk assessment performed in primary care.

9.6. Screening in communicable diseases

The logic of screening applies equally to infections, with the important difference that the benefit accrues not only to the individual but to the community, since treatment interrupts transmission:

- **antenatal screening** for HIV, hepatitis B, syphilis and rubella immunity, which underpins the elimination of mother-to-child transmission;
- **blood donor screening** (HBsAg, anti-HCV, anti-HIV, syphilis, with nucleic acid testing where available), discussed in Chapter 14;
- **hepatitis B and C screening** of risk groups and, in high-prevalence settings, of the general adult population — the indispensable first step of the WHO elimination strategy, since the majority of those infected are unaware of it;
- **tuberculosis** contact tracing and screening of high-risk groups (including tests for latent infection);
- **sexually transmitted infection** screening in defined populations, notably *Chlamydia trachomatis* in young women.

9.7. The ethics of screening

Screening differs ethically from clinical medicine in one decisive respect: **the initiative comes from the health system, and it is addressed to a healthy person**. That reversal imposes a higher standard of justification. The person invited has a right to know not only the possible benefit but also the probability of a false positive, the existence of interval cancers, the possibility of overdiagnosis, and the consequences of each result — this is the requirement of **informed choice**, which has progressively replaced the older paternalistic exhortation to attend. Programmes must also monitor equity: a programme that raises the average coverage while widening the gap between social groups has failed in public health terms, however good its aggregate figures.

References

1. Celentano D.D., Szklo M. *Gordis Epidemiology*. 6th ed. Elsevier; 2019.
2. Wilson JMG, Jungner G. *Principles and Practice of Screening for Disease*. Public Health Papers No. 34. Geneva: World Health Organization; 1968.
3. World Health Organization. *Global strategy to accelerate the elimination of cervical cancer as a public health problem*. Geneva: WHO; 2020.
4. Falcaro M, Castañon A, Ndlela B, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. *The Lancet*. 2021. doi:10.1016/S0140-6736(21)02178-4
5. Cervical cancer mortality trends following HPV vaccination in England, 2001–24: an analysis of population-based mortality data. *The Lancet*. 2026. doi:10.1016/S0140-6736(26)00918-9
6. Council of the European Union. Council Recommendation on strengthening prevention through early detection: a new EU approach on cancer screening. 2022/C 473/01.
7. Bretthauer M, Løberg M, Wieszczy P, et al. Effect of colonoscopy screening on risks of colorectal cancer and related death. *New England Journal of Medicine*. 2022. doi:10.1056/NEJMoa2208375

Chapter 10. Surveillance, Outbreak Investigation and International Health Regulations

10.1. Public health surveillance

Surveillance is the continuous, systematic collection, analysis and interpretation of health-related data, closely integrated with the timely dissemination of these data to those responsible for prevention and control. The classical formula of Alexander Langmuir, who founded modern surveillance at the American Communicable Disease Center, remains the best summary: **information for action**. A surveillance system that produces data no one uses is not surveillance but bookkeeping.

Its functions are: to detect outbreaks and unusual events early; to monitor trends and the geographical distribution of diseases; to identify risk groups and evaluate control programmes; to provide the denominator of planning; and to fulfil international reporting obligations.

Types of surveillance.

- **Passive surveillance** — the routine, mandatory notification of diseases by clinicians and laboratories. It is inexpensive and exhaustive in principle, incomplete in practice: under-notification is the rule, and it varies by disease severity and by the interest of the notifier.
- **Active surveillance** — the health authority contacts the reporting sources at regular intervals. Costly, but far more complete; used during outbreaks, in eradication programmes (the active search for acute flaccid paralysis in polio surveillance), and for diseases under elimination.
- **Sentinel surveillance** — a network of selected reporting units (general practices for influenza-like illness, hospitals for severe acute respiratory infection) provides high-quality, timely data on a sample rather than exhaustively.
- **Syndromic surveillance** — monitoring of clinical syndromes rather than confirmed diagnoses (fever with rash, acute watery diarrhoea), and even of proxies such as emergency-department attendance, absenteeism or over-the-counter drug sales; its value is timeliness, in situations where waiting for laboratory confirmation would cost days.
- **Laboratory and genomic surveillance** — the typing of circulating strains, essential for influenza vaccine composition, for tracing chains of transmission, for detecting resistance, and — since the COVID-19 pandemic, on an unprecedented scale — for tracking viral variants.
- **Environmental and wastewater surveillance** — the detection of pathogens in sewage, independent of health-seeking behaviour; used for decades in poliovirus surveillance and generalised during the pandemic to SARS-CoV-2, then extended to influenza, measles and antimicrobial resistance.

- **Serological surveillance (serosurveys)** — the measurement of population immunity, which reveals the submerged part of the iceberg and identifies the accumulation of susceptibles before an epidemic reveals it.

The attributes of a good system, by which any surveillance is evaluated, are: simplicity, flexibility, acceptability, sensitivity, positive predictive value, representativeness, timeliness, stability, and data quality. There is a permanent trade-off between sensitivity and timeliness on one side and specificity and cost on the other.

The case definition is the instrument that makes surveillance data comparable. It normally has three levels — **possible**, **probable** and **confirmed** — combining clinical, epidemiological and laboratory criteria [1]. A broad definition maximises sensitivity (appropriate at the start of an outbreak, when nothing must be missed); a narrow one maximises specificity (appropriate for analytical studies and for final counts). Every change of case definition produces an artefactual break in the time series, and must be recorded and taken into account.

In Romania, the notification of communicable diseases follows the methodologies of the National Institute of Public Health (INSP) through the National Centre for Surveillance and Control of Communicable Diseases (CNSCBT) [2], with the county public health directorates (DSP) as the operational level; data are transmitted to the European Surveillance System (TESSy) of ECDC under the EU case definitions, and, for events of international concern, to WHO under the International Health Regulations.

10.2. The investigation of an outbreak

An **outbreak (epidemic)** is the occurrence of cases of a disease in excess of what is normally expected in a defined community, place and time. The definition is relative to the expected baseline: two cases of botulism constitute an outbreak; two hundred cases of influenza in January may not. A **cluster** is an aggregation of cases in space or time whose number may or may not exceed expectation.

The investigation follows a sequence of steps which, although presented in order, are in practice partly simultaneous — and one principle governs all of them: **control measures must be introduced as soon as they are justified, without waiting for the investigation to be complete** [3].

1. **Prepare for field work** — the team, the materials, the laboratory arrangements, the administrative and legal framework.
2. **Establish the existence of an outbreak** — compare the observed number with the expected, excluding artefacts (a new laboratory test, a new doctor, a change in reporting).
3. **Verify the diagnosis** — clinical review of the cases and laboratory confirmation of a sample of them.

4. **Define and identify cases** — construct a working case definition with the three levels above, and search actively for cases (hospitals, laboratories, general practices, the community).
5. **Describe the outbreak in time, place and person** — the descriptive epidemiology. The **epidemic curve** (histogram of cases by date of onset) is the central instrument: its shape distinguishes a **point-source** outbreak (a single, sharp peak within one incubation period — a contaminated meal), a **continuous common-source** outbreak (a prolonged plateau — a contaminated water supply), and a **propagated** outbreak (successive waves separated by one incubation period — person-to-person transmission). Read backwards from the peak by one mean incubation period, the curve also estimates the probable time of exposure. Mapping (the modern descendant of John Snow's map) and attack-rate tables by age, sex and exposure group complete the description.
6. **Develop hypotheses** on the source, the vehicle and the mode of transmission.
7. **Evaluate the hypotheses analytically** — usually a retrospective **cohort** study when the exposed population is enumerable (a wedding, a school, a ward: compute attack rates and relative risks by food or exposure), or a **case-control** study when it is not (compute odds ratios).
8. **Refine hypotheses and carry out additional studies** — including environmental and laboratory investigation: sampling of food, water and surfaces, and the molecular typing of isolates, which today (whole-genome sequencing) can confirm or refute the epidemiological links with near-certainty.
9. **Implement control and prevention measures** — directed at the source (withdrawal of a food product, treatment or isolation of cases), at the transmission route (chlorination, disinfection, closure of a facility) and at the receptive population (vaccination, chemoprophylaxis).
10. **Communicate the findings** — an oral briefing for immediate action, a written report, and publication where the lessons are generalisable. Risk communication with the public and the press is part of the response, not an afterthought: silence and contradiction are themselves amplifiers of an epidemic.

Box 10.1. Reading an epidemic curve. Three practical rules. (1) The horizontal axis must be in units of about one quarter to one third of the incubation period; a curve drawn in the wrong unit hides its own shape. (2) In a point-source outbreak, the width of the curve corresponds to the range of individual incubation periods, and the interval from the presumed exposure to the peak approximates the median incubation period — which, compared with the known incubation of candidate agents, itself suggests the aetiology (minutes to hours: preformed toxin; 12–72 hours: invasive bacteria; 1–2 days for norovirus; 2–6 weeks for hepatitis A). (3) A "tail" of late cases after a point-source outbreak usually represents secondary person-to-person transmission — and its size measures the efficacy of the control measures introduced.

10.3. Preparedness and the international legal framework

The International Health Regulations (IHR 2005) are the binding instrument of global health security, adopted by 196 States Parties [4]. Their core obligations are: to develop and maintain **core capacities** for surveillance, laboratory diagnosis, risk assessment and response; to **notify WHO within 24 hours** of any event that may constitute a **Public Health Emergency of International Concern (PHEIC)**, using the decision instrument of Annex 2; to designate a **National IHR Focal Point** available at all times; and to apply health measures at points of entry that are no more restrictive of international traffic and trade than necessary. Diseases always notifiable include smallpox, poliomyelitis due to wild-type poliovirus, human influenza caused by a new subtype, and SARS.

A **PHEIC** is declared by the WHO Director-General on the advice of an Emergency Committee. Declarations to date have concerned pandemic influenza A(H1N1) (2009), poliomyelitis (2014, still in force), Ebola in West Africa (2014) and in the Democratic Republic of the Congo (2019), Zika (2016), COVID-19 (2020) and mpox (2022 and again 2024) — a list that shows both the utility of the instrument and the criticism levelled at it, namely that a single binary category cannot express the gradation of global risk.

The COVID-19 pandemic exposed the limits of this architecture — delays in notification and in the sharing of samples and sequences, the collapse of equitable access to countermeasures, the absence of enforcement — and produced two responses:

- the **2024 amendments to the IHR**, which introduce, above the PHEIC, the category of **"pandemic emergency"**, create a National IHR Authority and a States Parties Committee, and insert equity and solidarity among the guiding principles;
- the **WHO Pandemic Agreement**, adopted on 20 May 2025 by the Seventy-eighth World Health Assembly under resolution WHA78.1, after more than three years of negotiation [5]. Legally binding upon the States that ratify it, it addresses prevention and One Health surveillance, the strengthening of health systems, research and development, technology transfer, and above all **equitable access to pandemic-related health products**, through a Pathogen Access and Benefit-Sharing (PABS) system whose annex was entrusted to a further intergovernmental working group. Its practical value will be measured, as with every instrument of international law, by ratification and by implementation.

Preparedness at national level rests on a small number of concrete elements, all of which must exist before the emergency: pandemic and epidemic response plans, exercised and updated; laboratory networks with surge capacity and rapid diagnostic development; stockpiles of vaccines, antivirals and personal protective equipment; trained field epidemiology teams (the network of Field Epidemiology Training Programmes); rules for the ethical allocation of scarce resources decided in advance; and, not least, a strategy of risk communication and of engagement with communities, whose failure was in several countries a greater obstacle to control than any technical deficiency.

Box 10.2. The 2025 measles response in Romania as a case study. Romania experienced from 2023 a national measles epidemic which, in 2024, exceeded 25,000 reported cases — the largest since 1993 — on a background of MMR coverage that had fallen between 2018 and 2024 from about 90% to 78% for the first dose and from 81% to 62% for the second [6]. The response combined the classical steps of this chapter: case-based surveillance and laboratory confirmation; contact tracing with post-exposure prophylaxis; advancing the first MMR dose in outbreak areas; catch-up campaigns; and, decisively, training of primary-care providers, with more than 400 trained in Braşov, Covasna and Timiş counties from November 2025 with EU funding. In the first quarter of 2026, first-dose coverage in children aged 12–24 months had risen by about 20 percentage points on average — and by 25 points in Timiş county [6]. The episode illustrates three lessons of general validity: measles is the sentinel that detects a failing immunisation programme; the determinant of coverage is the functioning of primary care and the confidence it commands, not the availability of vaccine; and a coverage curve can be reversed, quickly, when the system acts deliberately.

References

1. European Centre for Disease Prevention and Control. Case definitions for communicable diseases under EU surveillance (Commission Implementing Decision (EU) 2018/945, as amended). Stockholm: ECDC.
2. Institutul Național de Sănătate Publică — CNSCBT. Metodologii de supraveghere a bolilor transmisibile. Bucharest: INSP.
3. Centers for Disease Control and Prevention. *Principles of Epidemiology in Public Health Practice*. 3rd ed. Atlanta: CDC; 2012 (Lesson 6: Investigating an Outbreak).
4. World Health Organization. *International Health Regulations (2005)*. 3rd ed. Geneva: WHO; 2016, and the amendments adopted by the Seventy-seventh World Health Assembly, 2024.
5. World Health Organization. Pandemic prevention, preparedness and response accord — questions and answers; WHA78.1, 20 May 2025. Geneva: WHO; 2025.
6. World Health Organization Regional Office for Europe. Romania increases vaccination coverage for measles, mumps and rubella. Copenhagen: WHO/Europe; 26 June 2026.

PART III. SPECIAL EPIDEMIOLOGY OF COMMUNICABLE DISEASES

Chapter 11. Influenza and Other Respiratory Viral Infections

11.1. Definition and aetiological agent

Influenza is a viral acute infection with aerogenous transmission and significant general effects on the body. Behind its banal reputation stands one of the most formidable epidemiological adversaries of humankind: the only disease that has repeatedly proven capable of producing, within months, tens of millions of deaths worldwide.

The influenza viruses belong to the family *Orthomyxoviridae*, genus *Influenzavirus*. They are relatively little resistant in the external environment. Influenza viruses of type A are sensitive to amantadine hydrochloride and to rimantadine (see Box 11.2 for the current status of these drugs).

The structure of the virus explains its epidemiology, and must therefore be known in some detail.

The central component of the virus is its soluble antigen. It is made up of ribonucleoprotein (RNP), which contains nucleoprotein and **8 segments of single-chain RNA**, each of which represents a gene. Associated with the ribonucleoprotein is the viral transcriptase. This segmented genome is the decisive feature: it makes theoretically possible 2□ = **256 genetic recombinations** among the RNP fragments when two different viruses meet in the same cell.

The peripheral coating is lipoproteic and double-layered, covered with glycoproteic structures carrying the surface antigens:

- **haemagglutinin (H)** — at least 15 antigenic variants; cane-shaped, with a role in the attachment of the virus to the specific receptors of the host cell and in the onset of the infection;
- **neuraminidase (N)** — at least 9 antigenic variants; mushroom-shaped, with a role in the release of the newly formed virions from the cell.

The nomenclature of the strains records the type, the place, the number and the year of isolation, and the antigenic subtype — for example: **A/Hong-Kong/1/68 (H3N2)**.

11.2. Antigenic variability: drift and shift

The whole epidemiology of influenza revolves around the antigenic instability of the surface glycoproteins.

Antigenic drift (minor variability): once in a few years, the sequence of some antigens in the structure of the haemagglutinin or of the neuraminidase changes through the accumulation of point mutations, and new variants of the same subtype of influenza virus emerge. These variants partially escape the immunity acquired against their predecessors and may cause

moderate epidemics. Drift is the reason why the composition of the influenza vaccine must be re-evaluated every year.

Antigenic shift (major variability): at larger intervals of time, two different influenza virus subtypes simultaneously infect the same host cell and can undergo a **rearrangement (reassortment) of the 8 genic segments**. This generates entirely new subtypes of the influenza virus, against which the population possesses no immunity — new subtypes with **pandemic potential in an immunologically naive population**. Shift is possible only in type A viruses, which alone possess the animal reservoir needed for the meeting of human and animal strains; the pig, susceptible to both avian and human viruses, classically plays the role of "mixing vessel".

11.3. The epidemiological process

The source of infection

The source may be sick humans as well as sick animals, which is why influenza is considered an **anthropozoonosis**.

The human source is represented by:

- the acutely sick person — contagious in the first 3–5 days of the disease;
- the inapparently infected persons — holding the largest share of the source reservoir;
- the persons with latent infection, who maintain the virus among the population between the epidemic seasons.

The animal (extra-human) source: pigs, horses and other wild or domestic animals and birds. These species can display manifest acute infection, persistent infection, vertically transmitted infection, and cross-infection among species. Aquatic wild birds constitute the great natural reservoir of influenza A viruses, from which all known H and N subtypes have been isolated.

Transmission routes and mechanisms

Transmission is direct, aerogenous, through Flügge's droplets, especially in confined spaces. There is also the possibility of transmission of the infection from the animal source to the human species, followed by the inter-human retransmission of viruses of animal origin — the pathway along which pandemics are born.

The receptive population

Receptiveness is general. It is higher among children, who are the most efficient vectors of influenza — they contract the infection first, excrete more virus for longer, and disseminate it in family and school. Post-infectious immunity is strain-specific and permanent; the appearance of illness after reinfection is due not to the loss of immunity but to the antigenic novelty of the successive strains. Post-vaccinal immunity is homologous to the vaccine formula and transitory — no longer than one year.

Favouring factors

The natural factors favour the cold-season character of influenza in the temperate zone; the economic and social factors favour the spreading of the disease among the population, especially through the various types of human agglomeration.

11.4. The manifestations of the epidemiological process

Influenza can manifest itself sporadically (type C), epidemically (types B and A) and pandemically (type A only).

Epidemics occur almost exclusively in the cold season in the temperate zones — October to April in the northern hemisphere, May to September in the southern hemisphere [1] — and in the rainy season in the tropical area. During an epidemic, a single influenza virus strain is usually predominant among the population (with one exception during the past 15 years). In the inter-epidemic periods the influenza virus apparently disappears from the population — but one must not forget the latent infection, which silently bridges the seasons. New influenza virus strains usually appear in the Far East, from where they spread worldwide (with the notable exception of the 2009 H1N1 pandemic, which emerged in North America).

The start of an epidemic is signalled by an increase in school and industrial absenteeism, as well as by an increase in morbidity due to pneumonia and influenza-like illness — indicators that the surveillance systems follow week by week.

In any influenza epidemic wave, the incidence of cases rises rapidly during the first 2–3 weeks and gradually decreases during the following 4–6 weeks. Between epidemics, influenza manifests itself endemo-sporadically, especially among infants, against the background of the collective immunity to the circulating strain. The first epidemic wave of a pandemic affects between 30 and 50% of the population, depending on the age-group distribution; the following waves are smaller and smaller, one wave in each epidemic season, as the pandemic virus settles into seasonal circulation.

Five pandemics have been recorded during the past 100 years, the last one in 2009. The current forecasts envisage the possible emergence of a reassorted virus through the combination of an avian strain of the H5N1 type with a human influenza strain — a permanent concern of global surveillance.

Box 11.1. The influenza pandemics of the past century (supplementary). 1918–1919 — "Spanish influenza", A(H1N1): the most lethal pandemic of the modern era, with an estimated 50 million or more deaths, striking with unusual severity the young adults. 1957–1958 — "Asian influenza", A(H2N2). 1968–1969 — "Hong Kong influenza", A(H3N2). 1977 — the "Russian" re-emergence of H1N1, affecting mainly the young born after the disappearance of the subtype in 1957. 2009 — A(H1N1)pdm09, of swine origin, the first pandemic of the twenty-first century, fortunately of moderate severity. Since 1997, repeated zoonotic outbreaks of avian influenza A(H5N1) — and, since 2013, A(H7N9) — with high case fatality but without sustained inter-human transmission, together with the recent panzootic of clade 2.3.4.4b H5N1 extending to mammals, keep the pandemic alert permanently active and justify the global surveillance network coordinated by WHO (GISRS).

11.5. Prevention and control

Measures regarding sick people: early identification, with home quarantining for one week, or the hospital admission of persons belonging to risk groups and of those with complications. **Measures regarding suspects:** the same as for sick people, pending the possible disproof of the diagnosis.

Measures regarding the transmission routes are those applying to all aerogenous infections: avoiding human agglomerations; the mechanical protection of coughing and sneezing, especially in confined spaces; the hygienic education of the population. The closing and suspension of activity in children's collectivities is generally a consequence of the high absenteeism, not an anti-epidemic measure in itself.

Measures regarding the receptive population:

- measures to increase the non-specific resistance of the body: a balanced diet rich in vitamins, the avoidance of prolonged exposure to cold and of excessive fatigue during epidemics;
- **specific prevention through anti-influenza vaccination**, administered at least 2 weeks before the occurrence of cases — the interval needed for the development of the post-vaccinal antibodies;
- for type A influenza, **chemoprophylaxis** with amantadine or rimantadine, offering approximately 70% protection; it is recommended to unvaccinated people, to those in whom vaccination is not possible, and where the individual risk is high.

Box 11.2. Current vaccines and antivirals (supplementary). The influenza vaccines in current use are trivalent or quadrivalent, produced on embryonated eggs, on cell cultures or by recombinant technology, with a composition recommended twice a year by WHO for each hemisphere. Annual vaccination is recommended in particular for: persons aged 65 and over, patients with chronic cardiovascular, respiratory, renal, hepatic, metabolic or immunological diseases, pregnant women, residents of long-term care institutions, and — as a professional obligation — **healthcare workers**. The adamantanes (amantadine, rimantadine) are no longer recommended in practice, because the circulating A strains have become almost universally resistant to them; the current antivirals are the neuraminidase inhibitors (oseltamivir, zanamivir) and the cap-dependent endonuclease inhibitor baloxavir, effective both in treatment — ideally begun within 48 hours of onset — and in post-exposure prophylaxis.

11.6. Infections with parainfluenza viruses

The parainfluenza viruses (types 1, 2, 3 and 4) are present worldwide and are significant especially in the acute respiratory infection pathology of children under 5 years of age, with a peak of severity under 6 months — laryngotracheobronchitis (croup) and bronchiolitis being their characteristic clinical expressions.

Transmission is aerogenous. Post-infectious immunity is type-specific and incomplete, reinfections being possible throughout life, though milder. The cases show an autumn–winter

seasonal periodicity. There is no specific immunoprophylaxis or chemotherapy; prevention rests on the general measures applicable to all respiratory-entry infections.

11.7. Influenza today: surveillance, the avian threat and the state of the vaccines

Global burden and surveillance. Seasonal influenza is estimated to cause between 3 and 5 million cases of severe illness and of the order of 290,000–650,000 respiratory deaths annually worldwide [2], the burden falling disproportionately on the very young, the elderly and those with chronic disease. The instrument that makes the annual reformulation of the vaccine possible is the **Global Influenza Surveillance and Response System (GISRS)** — a network of national influenza centres and WHO collaborating centres that has been sharing viruses and data since 1952, and that provides the recommendation for the vaccine composition of each hemisphere twice a year. Since the COVID-19 pandemic this network has been reinforced by genomic sequencing and by sentinel surveillance of severe acute respiratory infection, and in several countries by wastewater monitoring.

The avian threat, quantified. Since 2021, the clade 2.3.4.4b of high-pathogenicity avian influenza A(H5N1) has produced the largest panzootic ever recorded in birds, with extension to a very wide range of mammals and, from March 2024, to dairy cattle in the United States — an entirely new epidemiological development, with transmission between herds and virus present in raw milk. Human cases followed the pattern of a zoonosis without human adaptation: of 70 laboratory-confirmed United States cases between March 2024 and May 2025, 41 were exposed to dairy cattle and 24 to poultry; conjunctivitis was the dominant clinical feature (89%), most illnesses were mild, four patients were hospitalised, and one died; **no human-to-human transmission was detected**, and no neuraminidase-inhibitor resistance was found [3]. The public health assessment therefore remains that the risk to the general population is low, and low-to-moderate for occupationally exposed groups [4] — but the situation is monitored continuously, because the acquisition of efficient inter-human transmission by a virus of this kind is the classical pathway to the pandemic described in Section 11.2.

Vaccines: what has changed. Three developments should be known. First, the quadrivalent formulations that dominated the past decade are being simplified, since the B/Yamagata lineage has not been detected in global circulation since March 2020 and WHO has recommended its removal from the vaccine composition — a rare instance of an influenza lineage disappearing. Secondly, **high-dose and adjuvanted vaccines** for adults aged 65 and over have demonstrated superior immunogenicity and, in comparative studies, greater effectiveness than standard-dose vaccines in that age group, and are increasingly preferred in national programmes. Thirdly, **mRNA platforms and "universal" candidates** directed against the conserved stalk of the haemagglutinin are in clinical development, with the objective of ending the annual reformulation altogether; none is yet licensed, and the annual vaccine remains the operative instrument.

Vaccine effectiveness in any given season is variable — typically of the order of 40–60% against medically attended illness when the vaccine is well matched [5], lower when it is not, and lower in the frail elderly — a figure that must be communicated honestly, together with its corollary: even a partially effective vaccine, applied to a large population, prevents a substantial absolute number of hospitalisations and deaths, and protection against severe outcomes exceeds protection against infection.

Antivirals. As Box 11.2 notes, the adamantanes have been abandoned because of near-universal resistance among circulating A strains — an early and instructive example of the antimicrobial resistance discussed in Chapter 20. The neuraminidase inhibitors (oseltamivir, zanamivir) and the cap-dependent endonuclease inhibitor **baloxavir** remain effective; treatment is most beneficial when begun within 48 hours of onset and is indicated in severe disease and in risk groups, while the emergence of baloxavir-resistant variants under treatment is being monitored.

Romania and Europe. Influenza vaccination coverage among persons aged 65 and over reached about 23% in Romania in 2024 — less than half the EU average, and far below the 75% target recommended by the Council of the European Union [6]. Since this is the group in which almost all influenza mortality occurs, the gap represents one of the largest and most easily addressed preventive deficits in the national programme, and one in which the individual clinician's recommendation is the single strongest determinant of uptake.

References

1. European Centre for Disease Prevention and Control. Seasonal influenza — annual epidemiological report. Stockholm: ECDC.
2. World Health Organization. Influenza (seasonal) — fact sheet; and Recommended composition of influenza virus vaccines. Geneva: WHO.
3. Rolfes MA, Kniss K, Kirby MK, et al. Human infections with highly pathogenic avian influenza A(H5N1) viruses in the United States from March 2024 to May 2025. *Nature Medicine*. 2025;31:3889–3898. doi:10.1038/s41591-025-03905-2
4. Food and Agriculture Organization, WOAH, WHO. Updated joint public health assessment of recent influenza A(H5) virus events in animals and people. 2025.
5. Uyeki TM, Hui DS, Zambon M, Wentworth DE, Monto AS. Influenza. *The Lancet*. 2022. doi:10.1016/S0140-6736(22)00982-5
6. OECD/European Observatory on Health Systems and Policies. *România: Profilul de țară din 2025 în ceea ce privește sănătatea*. Paris/Brussels; 2025.

Chapter 12. The HIV/AIDS Infection

12.1. Definition and epidemiological importance

The HIV/AIDS infection is a transmissible disease with a massive and fast spread. It matches perfectly the definition of a pandemic epidemiological process: a new aetiological agent, transmitted fast and efficiently within an immunologically "naive" population.

Since the beginning of the pandemic, some 78 million people have been infected with the human immunodeficiency virus (HIV) and about 39 million people have died of its consequences; at the end of 2020 approximately 42 million people were living with HIV worldwide. Sub-Saharan Africa remains the most severely affected region — nearly 1 in every 20 adults there is living with HIV, the region accounting for around 71% of the people living with HIV worldwide [1].

Box 12.1. The current dimensions of the pandemic (supplementary). According to the UNAIDS estimates for recent years, approximately **40 million people are living with HIV**, about **1.3 million new infections** occur annually — roughly 3,500 every day — and over three quarters of those living with HIV are receiving antiretroviral therapy. Two conceptual changes define the present stage of the fight. First, effective antiretroviral treatment has transformed the infection from a fatal disease into a chronic controllable condition, and a person with a durably undetectable viral load does not transmit the virus sexually (**U = U, "undetectable = untransmittable"**) — treatment has thus itself become a preventive measure. Secondly, **pre-exposure prophylaxis (PrEP)** with antiretrovirals offers high protection to persons at substantial risk. The UNAIDS "95–95–95" targets — 95% of infected persons diagnosed, 95% of the diagnosed treated, 95% of the treated virally suppressed — summarise the current global strategy.

12.2. Features of the aetiological agent

The human immunodeficiency virus is classified within the family *Retroviridae*; its genome of RNA is transcribed into DNA by the reverse transcriptase and integrated into the genome of the host cell — the biological foundation of the lifelong character of the infection.

The virus maintains its virulence at room temperature and in dry material for 3–7 days, and in a water medium for over 2 weeks. Alcohols, hypochlorites and detergents inactivate the virus at lower concentrations than the usual ones (ethanol 25%); in practice, however, the following are used: hydrogen peroxide 6%, ethanol 70°, calcium and sodium hypochlorite 1%, iodophors 2.5%, glutaraldehyde 2%, applied for 1–5 minutes.

The medical instruments must be sterilised by autoclaving or with ethylene oxide; instruments that cannot withstand thermal processing are immersed in glutaraldehyde solutions of 2% concentration for 30 minutes.

12.3. The epidemiological process

The source of infection

The source of infection is represented by the **infected person, who remains contagious throughout life** — symptomatic or not. The groups at risk, which concentrate both the infections and the sources, are:

- homosexual and bisexual men;
- heterosexuals with partners from the risk groups or from areas where heterosexual transmission is dominant;
- children born of HIV-infected mothers;
- people with sexually transmitted diseases, and injecting drug users.

The virus has been isolated from: blood, sperm and vaginal secretion, saliva, milk, tears, urine, and the alveolar and amniotic fluids. A certain (proven) role in transmission, however, belongs to **blood, the genital secretions and human milk** — a distinction of great practical importance for counselling: isolation of the virus from a fluid does not equal transmission through that fluid.

Transmission routes and mechanisms

In practice, transmission occurs through **sexual intercourse, exposure to blood, and perinatally**.

Sexual transmission is the main transmission route worldwide, accounting for about 80% of infections. The transmission risk depends on:

- the sexual practices — the risk being high for unprotected penetrative practices;
- the infectivity of the source — higher towards the final stages of the untreated infection (and, symmetrically, minimal under effective treatment);
- the number of partners;
- the coexistence of venereal diseases, which multiply the risk through mucosal lesions and inflammation;
- vitamin A deficiency;
- the susceptibility of the partner — the receptive partner bearing a risk about 4 times higher;
- possibly the viral strain.

Transmission through blood and blood products. Transmission through contaminated needles and syringes ranks first among consumers of intravenously administered drugs; the risk increases with the duration of drug use, the sharing of needles, the number of injections and residence in areas of high HIV prevalence. The infection risk from a unit of blood coming from an HIV-positive person is practically 100%; the risk following artificial insemination with sperm from an HIV-positive donor is about 3.5%.

The risk of seroconversion after a needlestick injury with needles coming from HIV-positive patients is 0.2–0.5%, but the individual risk is higher if the lesion is deep, if it is produced with contaminated intravenous needles or instruments, or if the source patient is in the final stage of the disease. In the case of such professional (nosocomial) accidents, **chemoprophylaxis should be started with a triple antiretroviral association within 1–2 hours following the exposure**, with serological surveillance at 6 weeks, 3 months and 6 months, and monitoring of adverse reactions.

Perinatal transmission occurs at a rate of 13–30% in the absence of intervention: transplacentally, during birth — through exposure to blood and other contaminated fluids — and postpartum, through breastfeeding. Currently over 80% of HIV-positive women are of reproductive age, and their number is increasing. Although maternal milk contains the virus, in developing countries the risk of infection among breast-fed children has classically been counterbalanced by the protective effects of breastfeeding against diarrhoeal and respiratory illnesses — a genuine public health dilemma, today largely resolved by the antiretroviral treatment of the mother.

Although HIV has been isolated from saliva, the risk of saliva-based transmission is extremely low, and transmission through vectors has not been demonstrated. Ordinary social contact — handshake, shared dishes, bathrooms, swimming pools — carries no risk, a fact that must be stated explicitly in the education of the public, because unfounded fear feeds the stigmatisation of the infected.

The receptive population and the favouring factors

Receptiveness is general and, once contracted, the infection persists for life. Among the favouring factors: ethnic minorities and low-income groups are disproportionately affected, owing to the concentration of risk factors — prostitution, drug consumption, promiscuity — upon a background of reduced access to education and medical services.

The manifestation of the epidemiological process

The manifestation is **pandemic**: on the order of 1.8 million new infections were recorded in 2020 — approximately 16,000 new cases every day at the peak years of the pandemic; the current figures (Box 12.1) remain of the order of thousands of new infections daily. The pandemic is in slow decline, but with profound regional inequalities.

12.4. Prevention and control

The anti-AIDS battle has three major aims:

1. the prevention of HIV infection;
2. reducing the personal and social impact among symptomatic or asymptomatic HIV-positive people;
3. coordinating the national and international efforts.

Prevention is based on interrupting the transmission.

The risk of **sexual transmission** is reduced by: mechanical protection (the condom), reducing the number of partners, and changing sexual behaviour — to which are added today the treatment-as-prevention of the infected partner and the pre-exposure prophylaxis of the exposed partner (Box 12.1).

The prevention of **transmission through blood and blood products** is achieved through: the screening of donors; the thermal and ethanol-based processing of the blood derivatives; and, for drug users, the correct (unshared) use of needles and syringes — the harm-reduction programmes — and, in the second line, the prevention of drug addiction itself.

The prevention of **perinatal infection** involves: counselling HIV-positive persons regarding procreation; the testing of all pregnant women, especially in the areas of average and high prevalence; the possibility of terminating the pregnancy, the decision belonging to the mother; and the monitoring of the pregnancy with the administration of antiretroviral treatment — measures which have reduced maternal–foetal transmission by two thirds, and which today, correctly applied (treatment of the mother, prophylaxis of the newborn, adapted feeding), bring the transmission risk below 1%.

Specific prophylaxis. Most vaccination attempts have been based on the induction of neutralising antibodies against the coating proteins (gp120, gp160), the antigens being obtained through recombinant-molecule technology or chemical synthesis. Other vaccine candidates have included: vaccines with core proteins (p17, p24); live vaccines, less studied; vaccines with recombinant antigens associated with adjuvants; and vaccines with recombinant antigens presented by live vectors, such as the vaccinia virus. Despite four decades of effort, an effective vaccine has not yet been achieved — the extreme mutability of the virus, its integration into the host genome and its direct attack upon the immune system itself remain unsolved obstacles, and prevention continues to rest on the interruption of transmission and on treatment.

12.5. HIV in the present decade: figures, biomedical prevention and the unfinished agenda

The current epidemiology. The most recent UNAIDS estimates, for 2024, give the following picture: **40.8 million people living with HIV** (39.4 million adults and 1.4 million children), of whom women and girls constitute 53%; **1.3 million new infections** in the year; **630,000 AIDS-related deaths**, including about 75,000 children — a death every minute; and **31.6 million people on antiretroviral therapy**, that is 77% of all those living with the virus [2]. Eastern and southern Africa alone account for 21.1 million people living with HIV, more than half the global total, and in that region women and girls represent 63% of new infections, with approximately 4,000 adolescent girls and young women aged 15–24 acquiring HIV every week.

Progress against the **95–95–95 targets** stood, in 2024, at 87% of people living with HIV knowing their status, 77% receiving treatment and 73% virally suppressed [2]. The trend is favourable — new infections and deaths are at their lowest since the peak of the epidemic — but the trajectory is not sufficient to meet the 2030 elimination targets, and the reductions in international financing of recent years have raised the explicit concern of a resurgence.

Treatment as prevention. The demonstration that a person on effective antiretroviral therapy with a durably suppressed viral load does not transmit HIV sexually — the principle known as **U = U, "undetectable = untransmittable"** — was established by prospective studies of serodifferent couples, in which no linked transmission was observed across many thousands of condomless sex acts [3]. Its consequences are simultaneously epidemiological (treatment is prevention, and expanding treatment coverage reduces incidence), clinical (the therapeutic goal is viral suppression, monitored by viral load) and social (it removes the basis for much of the stigma and for several discriminatory practices).

Pre-exposure prophylaxis (PrEP). Oral PrEP with tenofovir-based regimens, recommended by WHO since 2015 for persons at substantial risk [4], is highly effective when taken, and its principal limitation is adherence. The past three years have transformed the field: long-acting injectable **cabotegravir** every two months, and above all **lenacapavir** administered subcutaneously **twice a year**, have shown extraordinary efficacy. In the PURPOSE 1 trial among young women in sub-Saharan Africa, twice-yearly lenacapavir produced **zero incident infections** among the recipients, a result significantly superior to daily oral prophylaxis in the comparison groups [5]; the companion PURPOSE 2 trial in men and gender-diverse persons confirmed a very high level of protection [6]. A twice-yearly injection that prevents HIV infection is, in principle, the closest approach yet achieved to a preventive vaccine — and the decisive question is no longer efficacy but access: price, licensing and delivery in the countries that carry the burden.

Prevention of vertical transmission. With maternal antiretroviral therapy, appropriate obstetric management, infant prophylaxis and adapted feeding, mother-to-child transmission falls below 1%, against the 13–30% quoted in the classical account of Section 12.3. Several countries have received WHO validation of the elimination of mother-to-child transmission of HIV and syphilis — proof that the classical measures of this chapter, fully applied, achieve elimination.

The vaccine. The candidates listed in Section 12.4 have all failed in efficacy trials, most recently the mosaic-vector regimens whose trials were stopped for futility. The obstacles are intrinsic: the extreme variability of the envelope, the integration of proviral DNA into the host genome, the establishment of latent reservoirs within days of infection, and the absence of a natural model of clearance. Research continues on broadly neutralising antibodies and on germline-targeting immunogens; in the meantime, biomedical prevention (PrEP and treatment as prevention) has taken the place that a vaccine was expected to occupy.

Romania. The Romanian HIV epidemic has a unique historical feature — the nosocomial infection of thousands of children in the late 1980s through unsterile injections and untested blood, a cohort that survived into adulthood on antiretroviral therapy and that remains under specialised care. Current transmission is predominantly sexual, with concentrated epidemics in key populations; the national programme provides free treatment, and the priorities are the same as elsewhere: earlier diagnosis (late presentation remains frequent), retention in care, and the introduction of PrEP for those at substantial risk.

References

1. World Health Organization. HIV data and statistics. Geneva: WHO; 2025.
2. UNAIDS. *Global HIV statistics — fact sheet 2025* (data for 2024). Geneva: UNAIDS; 2025; and *Global AIDS Update 2025*.
3. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *The Lancet*. 2019. doi:10.1016/S0140-6736(19)30418-0
4. World Health Organization. *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring*. Geneva: WHO; 2021 and subsequent updates.
5. Bekker LG, Das M, Abdool Karim Q, et al. Twice-yearly lenacapavir or daily F/TAF for HIV prevention in cisgender women. *New England Journal of Medicine*. 2024. doi:10.1056/NEJMoa2407001
6. Kelley CF, Acevedo-Quiñones M, Agwu AL, et al. Twice-yearly lenacapavir for HIV prevention in men and gender-diverse persons. *New England Journal of Medicine*. 2024. doi:10.1056/NEJMoa2411858

Chapter 13. Respiratory-Entry Viral and Bacterial Infections

The infections discussed in this chapter share the respiratory entry and, with it, a common epidemiological physiognomy: transmission through Flügge's droplets, cold-season periodicity, the predilection for children's collectivities, and — for those against which vaccines exist — the decisive dependence of their epidemiology on vaccination coverage. They are presented in the order of the course: measles, rubella, scarlet fever, diphtheria, epidemic parotitis, whooping cough and meningococcal meningitis.

13.1. Measles

Definition and aetiological agent

Measles is a transmissible eruptive viral infection, highly contagious, human-specific, frequent during childhood. The measles virus (a morbillivirus of the family *Paramyxoviridae*) has a low resistance in the external environment, being quickly inactivated by heat, light, ultraviolet radiation, acid pH, common disinfectants and dryness. The entry is the airway mucosa and the conjunctiva.

The epidemiological process

The source of infection is represented by ill people with typical or atypical clinical forms of the disease — there is no carrier state and no animal reservoir, a feature which makes measles, in principle, eradicable. Contagiousness arises at the end of the incubation period, peaks in the catarrhal period and is maintained for 4–6 days after the appearance of the exanthem. The virus is eliminated through the respiratory secretions, the conjunctival secretions and tears, the urine, the blood and the eruptive elements.

Transmission is direct (simple indirect), through Flügge's droplets, with a contagiousness index of **over 95%** — the highest of all common infectious diseases; in exceptional cases the transmission is indirect, the fragility of the virus limiting this route.

The receptive population. Receptivity is general, with a natural peak at the age of 3–5 years and a gradual decrease thereafter. After the introduction of the anti-measles vaccine, the disease more frequently affects persons aged between 5 and 14, adolescents and youth — the classical upward displacement of age produced by any vaccination programme with incomplete coverage. Sucklings possess maternal antibodies during the first 6 months of life, sometimes up to 12 months. Post-infectious immunity is solid and life-long.

The manifestations of the epidemiological process. Morbidity can be sporadic, endemic or epidemic, depending on the immunological state of the population. Before vaccination, the evolution used to be endemic-epidemic, with outbreaks at 3–5-year intervals, especially in the

cold season; after the introduction of vaccination, the periodicity is dictated by the accumulation of a proportion of susceptible persons exceeding about 10% of the population.

Prevention and control

Measures regarding the ill: identification, with isolation at home; isolation in the infectious disease clinic is reserved for the severe and complicated forms. The isolation period is assessed up to the disappearance of the fever and of the exanthem.

Measures regarding contacts: contacts are monitored during the maximum incubation period. They benefit from post-exposure prophylaxis through the administration of standard immunoglobulins during the first 72 hours following the infecting contact. The clinical-epidemiological monitoring of the preschool and school collectivities, as well as of the closed collectivities, completes the picture.

Specific prophylaxis consists in the anti-measles vaccination of children — today administered as the combined measles-mumps-rubella (MMR) live attenuated vaccine.

Box 13.1. Measles — the sentinel of vaccination programmes (supplementary). Because of its extreme contagiousness (R□ ≈ 12–18, herd immunity threshold ≈ 95%), measles is the first vaccine-preventable disease to return whenever coverage declines: it functions as the sentinel of every immunisation programme. Europe has experienced repeated epidemic waves in the past two decades, and Romania has been among the most affected countries — the epidemic begun in 2016 produced tens of thousands of cases and tens of deaths, overwhelmingly among unvaccinated children, and a new national epidemic was declared in December 2023. In the Romanian national immunisation programme the MMR vaccine is administered at the age of 12 months, with a second dose at 5 years; in outbreak conditions the first dose may be advanced. The complications of measles — pneumonia, otitis, encephalitis, and the late subacute sclerosing panencephalitis — together with the recently described "immune amnesia" (the erasure of pre-existing immune memory by the measles virus), are the counterarguments with which the physician must answer vaccine hesitancy.

13.2. Rubella

Definition and aetiological agent

Rubella is a transmissible eruptive viral infection, endemic-epidemic, frequent during childhood, with a benign clinical evolution — benign, that is, with one grave exception: the infection of the pregnant woman, which produces the **congenital rubella syndrome**. The rubella virus has a low resistance in the external environment and to the action of common disinfectants. The entry is the airway mucosa and the conjunctiva.

The epidemiological process

The source of infection is represented by: ill people with typical or atypical clinical forms; people with inapparent infections; and — a category specific to rubella — **children with congenital rubella syndrome**, who eliminate the virus for many months after birth and can contaminate their receptive attendants. The virus is eliminated through the nasopharyngeal

secretions, the urine, the fecal matter and the blood, as well as through the placenta and the organs coming from infants with congenital rubella. The ill person is contagious 4–7 days before the eruption and 6–7 days after its onset — up to 14 days in exceptional cases.

Transmission is direct (simple indirect), through Flügge's droplets; **transplacental**, from the mother to the foetus — the route that gives the disease its whole public health importance; and, in exceptional cases, indirect.

The receptive population. Receptivity is general, with a peak at the age of 4–6 years and a gradual decrease thereafter. Up to the age of 6 months sucklings are protected by the immunity transmitted from the mother. Post-infectious immunity is solid and life-long.

The manifestations of the epidemiological process. Morbidity can be sporadic, endemic or epidemic, depending on the immunological state of the population; epidemic outbreaks are noticed at 5–9-year intervals, among children, adolescents and young adults, especially in the cold season.

Prevention and control

Measures regarding the ill: identification and isolation at home or in hospital, the severe and complicated forms being isolated at the infectious disease clinic; the isolation duration is assessed up to the disappearance of the fever and of the exanthem. Every case of rubella or of contact with rubella in a pregnant woman in the first trimester demands rigorous serological evaluation and specialised counselling.

Measures regarding contacts: monitoring during the maximum incubation period; the clinical-epidemiological monitoring of preschool, school and closed collectivities; quarantine in the closed preschool collectivities for children coming back from the infectious disease clinic.

Specific prophylaxis: the anti-rubella vaccination of children and of fertile-age women — those without a rubella history and who are not in the first trimester of a pregnancy — today with the combined MMR vaccine. The true target of the programme is not the child who would anyway undergo a benign disease, but the future pregnant woman and her foetus: the elimination of congenital rubella is the declared objective of WHO in the European region.

13.3. Scarlet fever

The aetiological agent

Scarlet fever is caused by the **group A β-haemolytic streptococci** (*Streptococcus pyogenes*) — Gram-positive cocci arranged in chains, which on blood-agar media produce within 24–48 hours a complete β-type haemolysis around the colony. The disease is produced by the strains secreting erythrogenic (erythrotoxic) toxin, upon which the eruption depends.

The epidemiological process

The source of infection may be represented by:

- persons with the typical disease, contagious from the end of the incubation period, during the onset phase and the state period;
- convalescent carriers — for up to 10 weeks;
- persons with an inapparent infection;
- apparently healthy carriers.

Formerly ill persons who remain carriers during convalescence can infect other people. The appearance of convalescent carriers is caused by an inoperative penicillin treatment, in cases with cryptic (crypt-bearing) tonsils or with co-infections with *Staphylococcus aureus*, whose penicillinase inactivates the penicillin administered.

Transmission is direct (simple indirect), through Flügge's droplets, or indirect — through contaminated objects, the streptococcus being relatively resistant in the environment.

The receptive population. Receptivity is general, with a peak between 2 and 10 years of age; only the newborns and the sucklings up to 6 months are protected, thanks to the transplacental immunity. Post-disease immunity has two distinct components: **antibacterial immunity**, which is type-specific (against the M protein of the infecting strain), and **antitoxic immunity**, directed against the erythrogenic toxin — those who contract scarlet fever a second time have been infected with a streptococcus possessing a different erythrotoxin. The contagiousness index is about 40%.

The manifestations of the epidemiological process: prolonged endemicity with slight epidemic manifestations, and a multiannual periodicity. The most frequently affected age groups are, in order, 5–9 years, 1–4 years and 10–14 years.

Prevention and control

Measures regarding the ill: early discovery; nominal declaration; isolation in the infectious disease clinic; the epidemiological investigation of the focus; the disinfection of the focus site using formaldehyde, cetrimonium bromide or chloramine.

Measures regarding contacts: discovery; the bacteriological monitoring of the contacts during the maximum incubation period; the treatment with retard penicillin of the contacts with a cardiovascular or renal history — those in whom a streptococcal infection would risk reactivating rheumatic or renal disease.

Measures regarding carriers: the discovery and treatment of the carriers of group A β-haemolytic streptococcus; epidemiological triage in the units and collectivities affected by streptococcal infections.

Measures regarding convalescents: their monitoring, in order to discover in time the non-suppurative complications (poststreptococcal) — acute rheumatic fever and acute

glomerulonephritis — which constitute the real long-term stake of every streptococcal infection.

Other measures: prophylactic epidemiological triages in the preschool and school children's collectivities after the holidays; epidemiological triages in the closed collectivities of children (foster homes), using the nasopharyngeal exudate; prophylactic disinfection; the observance of asepsis and antisepsis in hospital units. There is no vaccine against scarlet fever; the control of the disease rests entirely on these classical measures and on correct antibiotic therapy.

13.4. Diphtheria

Definition and aetiological agent

Diphtheria is an acute transmissible disease of a toxic-infectious type, caused by *Corynebacterium diphtheriae*, currently characterised — thanks to vaccination — by a sporadic evolution.

The diphtheria bacillus is relatively resistant in the external environment, especially when enclosed in albuminous substrates (false membranes, secretions). The most virulent and toxigenic strains belong to the *gravis* type. The sensitivity of the strains to the specific phages makes it possible to establish the origin and filiation of the cases in epidemic foci — a classical instrument of epidemiological typing. The bacillus is sensitive to disinfectants and to some antibiotics.

The entry is represented by tegumental lesions and by the nasopharyngeal, laryngeal, ocular and genital mucosae. At the level of the entry, the pathogen multiplies and releases the **exotoxin**, which then spreads in the body and produces the severe manifestations of the disease — myocarditis, neuritis; diphtheria is the model of the toxin-mediated infectious disease, and everything in its treatment and prevention follows from this fact. Considering the entry and the location, the most frequent clinical form is **diphtheritic angina**; laryngeal diphtheria (diphtheritic croup) is less frequent; other localisations are exceptional, though the incidence of cutaneous forms has recently increased.

The epidemiological process

The source of infection is represented by people suffering from diphtheria with typical or atypical clinical forms, and by germ carriers. The ill person can eliminate the pathogen for 10–30 days following the onset in the absence of antibiotic treatment. The carriers of *C. diphtheriae* may be convalescent — eliminating the pathogen for 2–3 weeks, and up to 2–3 months in the absence of antibiotic treatment — or healthy, with a carriage of about 3 weeks, generally in the entourage of the sources.

Transmission is direct (simple indirect), through the nasopharyngeal secretions expelled as droplets by the ill or the carriers, and indirect — through contaminated objects, especially those soiled with nasopharyngeal secretions or with fragments of false membranes.

The receptive population. Receptivity is general. Morbidity has been decisively influenced by vaccination. Post-infectious immunity is **relative** — the disease itself may not confer solid protection, and convalescents must therefore still be vaccinated. The immunity that matters is the **antitoxic** immunity induced by the toxoid (anatoxin).

The manifestations of the epidemiological process. Currently the sporadic morbidity prevails; the endemic-epidemic aspect is encountered in areas without a functioning vaccination plan. The relaxation of vaccination requirements for adults is currently causing a re-emergence of diphtheria — the massive epidemic of the states of the former Soviet Union in the 1990s, with over 150,000 cases, remains the demonstrative example of what the interruption of a vaccination programme means; diphtheria is the textbook re-emerging disease.

Prevention and control

Measures regarding the ill: the early discovery of the typical and atypical forms; separate isolation at the infectious disease clinic; the titration of the diphtheritic antitoxin in the blood upon admission, and the confirmation of diphtheria clinically, epidemiologically and bacteriologically, by demonstrating *C. diphtheriae* in the pharyngeal and nasal exudates. The duration of isolation extends until clinical healing; the patient ceases to be contagious 2–3 days after the start of the antibiotic treatment, but is released from hospital only after clinical healing, the clearance of the bacillus and a normal ECG examination, being then monitored for 3 months by clinical and ECG examination — the electrocardiogram tracking the toxic myocarditis, the principal cause of death. The declaration is nominal; the epidemiological investigation and the disinfection are compulsory.

Measures regarding contacts: adult contacts are monitored at the workplace for 10 days, with repeated bacteriological examinations of the nasopharyngeal exudate; child contacts are isolated at home until the result of the bacteriological examination is known. The antidiphtheritic vaccine is administered or re-administered according to the vaccinal history and the immunological tests.

Measures regarding carriers: erythromycin, 40 mg/kg body weight/24 h for children and 1 g/24 h for adults, for 7–10 days.

Specific prophylaxis: the antidiphtheritic vaccination — with diphtheria toxoid, invariably combined in the paediatric hexavalent or tetravalent vaccines and in the dT/dTpa boosters of the adolescent and the adult. Because antitoxic immunity wanes, decennial boosters in adults are the condition of maintaining the current sporadic situation.

13.5. Epidemic parotitis (mumps)

Definition and aetiological agent

Epidemic parotitis is an acute transmissible viral infection, endemic-epidemic, clinically characterised by the inflammation and swelling of the salivary glands, as well as of other glands

and tissues — the pancreas, the gonads, the meninges. The mumps virus (family *Paramyxoviridae*) has a low resistance in the external environment, being inactivated by ultraviolet radiation, formaldehyde and phenols. The entry is the rhinopharyngeal and the conjunctival mucosae.

The epidemiological process

The source of infection is represented by people suffering from typical or atypical forms and by persons with inapparent infection — the latter numerous, about a third of all infections. The virus is eliminated through the saliva and the urine. The ill person is contagious from 2–6 days before the onset and remains contagious until the 12th or even the 16th day of the disease; in general, the contagious period is assessed at 21 days.

Transmission is direct (simple indirect), through droplets of saliva, typically after prolonged contact; indirect transmission, through freshly contaminated objects, is very rare.

The receptive population. Receptivity is general, but higher among children, adolescents and young adults; the clinical expression becomes more severe with age (orchitis in the postpubertal male, meningitis). Post-infectious immunity is long-lasting and solid.

The manifestations of the epidemiological process can be sporadic or endemic-epidemic, with frequent cases in winter, and with the classical predilection for collectivities of adolescents and young adults — schools, barracks, universities.

Prevention and control

Measures regarding the ill: early discovery, with isolation — for children, 10 days counting from the onset; for adults, until the clinical phenomena disappear. The declaration is numerical.

Specific prophylaxis: the anti-mumps vaccination, administered today within the combined MMR vaccine. Post-vaccinal immunity being less durable than the post-infectious one, outbreaks in vaccinated young-adult collectivities are still described; they remain, however, incomparably smaller than the epidemics of the pre-vaccinal era, and the severe forms are prevented.

13.6. Whooping cough (pertussis)

Definition and aetiological agent

Whooping cough is an acute bacterial disease with a typically airborne transmission route, affecting mainly children in the absence of active immunisation. *Bordetella pertussis* has a low resistance in the external environment, being sensitive to the action of common disinfectants and to antibiotics. The entry is the mucosa of the upper respiratory tract.

The epidemiological process

The source of infection is represented by ill people with typical or atypical forms, who eliminate *B. pertussis* through the sputum and the nasopharyngeal secretions. The ill are

contagious from the prodromal (catarrhal) period — when the diagnosis is rarely suspected, and the epidemiological efficiency of the source is therefore maximal — up to 3–4 weeks following the onset, in the absence of antibiotic treatment. The role of so-called healthy carriers is debatable; in practice, the mildly ill adolescent and adult, with atypical prolonged cough, plays the true role of reservoir, transmitting the infection to unvaccinated infants.

Transmission is direct (simple indirect), especially during the coughing fits, through the secretions of the bronchial, laryngeal and pharyngeal mucosae in the form of Flügge's droplets.

The receptive population. Receptivity is general, with a peak of morbidity among children in the absence of active immunisation; the disease is most dangerous — sometimes fatal — in the infant of the first months of life, not yet protected by vaccination, in whom apnoea may replace the classical cough. Maternal transplacental protection is weak. Post-infectious immunity is solid, though not absolute in time.

The manifestations of the epidemiological process: currently a sporadic evolution, thanks to the anti-pertussis immunisation plan; the disease is, however, considered **re-emerging** in some regions — the waning of the immunity induced by the acellular vaccines and the reservoir of atypically ill adults explain the epidemic returns recorded even in countries with high coverage.

Prevention and control

Measures regarding the ill: early discovery, with the compulsory isolation at the infectious disease clinic, for 14 days, of the cases treated with antibiotics; the declaration is numerical; final disinfection is not necessary, the germ being fragile.

Measures regarding suspects: separate isolation from the confirmed ill; in closed or half-closed children's collectivities, after the onset of whooping cough, no new members shall be accepted for 3 weeks after the discovery of the last case.

Measures regarding contacts: contacts under 3 years of age and those currently undergoing DTP immunisation receive 0.5 ml of DTP vaccine; children over 3 years of age and those with neurological pathology are given anti-pertussis immunoglobulins, 0.2–0.3 ml/kg body weight, during the first 3–4 days following the suspected infecting contact. Antibiotic prophylaxis can be used, with erythromycin, amoxicillin or ampicillin (100 mg/kg body weight), for 7–10 days — the modern practice preferring the newer macrolides for tolerability.

Specific prophylaxis: the anti-pertussis vaccination — historically with the whole-cell vaccine within DTP, today with acellular components (DTPa) within the combined paediatric vaccines. Because the protection of the infant depends on the immunity of those around him, current strategies add booster doses for adolescents and adults and, in many countries, the **vaccination of the pregnant woman** in the third trimester, which transfers protective antibodies to the newborn for precisely the months of maximum danger.

13.7. Meningococcal meningitis

Definition and aetiological agent

Meningococcal meningitis is an acute bacterial infection with a typically airborne transmission route and sporadic, endemic or epidemic manifestations. *Neisseria meningitidis* is a Gram-negative diplococcus, fragile in the external environment and sensitive to antibiotics. The entry is represented by the rhinopharyngeal mucosa; the meningococcus first colonises the rhinopharynx, and only in a minority of the colonised does it invade the blood and the meninges — the disease is the rare accident of a frequent carriage.

The epidemiological process

The source of infection is represented by: people suffering from meningococcal rhinopharyngitis, from meningococcal meningitis or from other meningococcal infections; and by the rhinopharyngeal carriers of the meningococcus. The ill eliminate the meningococcus through the nasopharyngeal secretions, from the incubation period and continuing through the state period and convalescence in the absence of suitable antibiotic treatment; the meningococci disappear from the rhinopharynx within 24–48 hours from the beginning of an appropriate antibiotic therapy.

The carrier is a debated category, but it is well documented in the literature; theoretically, the following carrier categories can exist: convalescent carriers; long-term carriers (under 3 months); and healthy, contact-type carriers (1–2 weeks). In periods of epidemiological calm, a proportion of the healthy population — maximal among adolescents and young adults — carries meningococci in the rhinopharynx, and this carriage is the true reservoir of the infection.

Transmission is mainly direct (simple indirect), through Flügge's droplets of nasopharyngeal secretion; the fragility of the germ makes indirect transmission negligible. Prolonged, close contact — family, dormitory, barracks — is the characteristic setting.

The receptive population. The receptivity for the clinically manifest disease (meningococcal meningitis) is **reduced**: most of the infected develop either a rhinopharyngitis or an inapparent infection, or remain healthy carriers. Receptivity is higher among children under 4 years of age and decreases with age, owing to the immunising infections accumulated in the personal history. Post-infectious immunity is type-specific (group-specific).

The manifestations of the epidemiological process may be sporadic, endemic or epidemic. Epidemics generally occur in closed collectivities, with a cold-season periodicity and epidemic waves at intervals of 5–10 years. On the global map, the "meningitis belt" of sub-Saharan Africa remains the territory of the great epidemics.

Prevention and control

Measures regarding the ill: early discovery, with compulsory isolation at the infectious disease clinic until clinical healing, the normalisation of the cerebrospinal fluid and the

disappearance of the meningococcus from the rhinopharynx; a bacteriological check-up is performed 7–10 days after the clinical healing. The declaration is nominal; the continuous and final disinfection are compulsory. (Clinically, meningococcal disease is one of the great emergencies of medicine: the interval between the first symptoms and death may be of hours, and the pre-hospital administration of the first antibiotic dose in the suspected purpuric forms is life-saving.)

Measures regarding contacts: clinical monitoring for 10 days after the discovery of the last case. Antibiotic (chemo)prophylaxis is administered according to the sensitivity of the meningococcal strain; for the contacts in the focus, chemoprophylaxis is performed without investigating the carrier state. When an epidemic is imminent, the bacteriological monitoring of the children's and youth collectivities is recommended, together with chemoprophylaxis and the hygienic-sanitary measures generally valid in respiratory infections: avoiding human agglomerations, ventilating the homes, avoiding long-term exposure to cold and excessive fatigue, and measures for boosting the non-specific resistance of the body.

Specific prophylaxis: antimeningococcal vaccination, classically with monovalent or tetravalent polysaccharide vaccines of the Mencevax type.

Box 13.2. Current meningococcal vaccines (supplementary). The polysaccharide vaccines have been superseded by the **conjugate vaccines** — monovalent C and quadrivalent A, C, W, Y — which are immunogenic from infancy, induce immune memory and, crucially, reduce rhinopharyngeal carriage, thus protecting also the unvaccinated. Against serogroup B, responsible for a large share of European cases, protein-based vaccines (4CMenB, MenB-fHbp) have been available since the last decade. The mass campaign with the conjugate A vaccine (MenAfriVac) in the African meningitis belt, which has virtually suppressed the epidemics of serogroup A there, is among the great recent successes of vaccinology; the displacement of cases towards other serogroups (W, X, C) illustrates, at the same time, the permanent capacity of the meningococcus to redistribute itself under vaccine pressure.

13.8. The respiratory-entry infections today: resurgence, new evidence and the Romanian situation

Measles: the global picture. WHO and the US Centers for Disease Control estimated **11 million measles infections and about 95,000 deaths in 2024**, the great majority in children under five; **59 countries** experienced large or disruptive outbreaks, nearly three times the number reported in 2021. First-dose coverage stood at 84% and second-dose coverage at 76%, against the 95% with two doses required to interrupt transmission, leaving **more than 30 million children under-protected**. Between 2019 and 2024, reported cases rose by 86% in the Eastern Mediterranean Region, 47% in the European Region and 42% in South-East Asia, while the African Region recorded a 40% decline. Against this, the long-term achievement remains extraordinary: measles deaths fell by **88% between 2000 and 2024**, and vaccination is estimated to have saved nearly 59 million lives over that period [1].

Measles in Romania. The country has been the epicentre of the European resurgence. The epidemic that began in 2023 produced more than **25,000 reported cases in 2024 — the highest since 1993** — against a background of MMR coverage that had fallen between 2018 and 2024 from about 90% to 78% (first dose) and from 81% to 62% (second dose); vaccination of children under one year stood at 66% in 2024, the lowest in the European Union [2, 3]. The response — surveillance, contact tracing, catch-up campaigns and, decisively, the training of more than 400 primary-care providers in Brașov, Covasna and Timiș counties from November 2025 — raised first-dose coverage in children aged 12–24 months by about **20 percentage points nationally within months, and by 25 points in Timiș county** [2]. The episode confirms the general rule: the limiting factor of an immunisation programme is rarely the vaccine, and almost always the functioning of, and trust in, primary care.

Measles: what recent clinical and immunological research has added. Two findings deserve to be integrated into the classical account. The first is **immune amnesia**: the measles virus destroys a substantial part of the pre-existing repertoire of memory lymphocytes, leaving the convalescent child measurably more susceptible to unrelated infections for two to three years — so that measles vaccination prevents not only measles but a share of the subsequent infectious morbidity. The second concerns the complications: pneumonia and encephalitis remain the principal causes of death, while **subacute sclerosing panencephalitis (SSPE)**, a uniformly fatal late complication, occurs more frequently than the classical figures suggested, particularly after infection in infancy — of the order of 1 in 600 to 1 in 1,400 cases in children infected under five years [4]. There is no antiviral treatment; vitamin A administration reduces mortality in children, and prevention remains entirely vaccinal.

Pertussis: a European resurgence. After years of low incidence, Europe experienced from 2023 a substantial resurgence of whooping cough, with tens of thousands of cases reported and deaths concentrated in unvaccinated infants under three months [5]. Three mechanisms combine: the shorter duration of protection conferred by acellular vaccines compared with the older whole-cell preparations; the accumulation of susceptible adolescents and adults, in whom the disease presents as a prolonged atypical cough and who transmit to infants; and the pandemic-era interruption of both circulation and routine vaccination. The response of most European programmes has been the **vaccination of pregnant women with dTpa in the third trimester**, which transfers protective antibodies to the newborn and has been shown to prevent the great majority of severe infant cases [6] — the single most effective measure currently available against infant pertussis mortality.

Diphtheria remains sporadic where vaccination is maintained, but the European Region has recorded clusters among migrants and in congregate settings since 2022, and the disease retains its capacity for explosive return: the epidemic of the former Soviet states in the 1990s, with over 150,000 cases, remains the reference demonstration of what the interruption of an immunisation programme produces. Decennial adult boosters are the operative preventive measure.

Meningococcal disease has been reshaped by conjugate vaccines (Box 13.2). The near-disappearance of serogroup A epidemics from the African meningitis belt following the MenAfriVac campaigns is among the great successes of public health vaccinology; in Europe, serogroup B predominates, addressed by the protein-based vaccines, while the rise of serogroups W and Y in several countries illustrates the continuing capacity of the meningococcus to redistribute itself under vaccine pressure. The clinical imperative is unchanged and absolute: in suspected invasive meningococcal disease, the first dose of antibiotic must not wait for transfer or for lumbar puncture.

Mumps and rubella. Outbreaks of mumps in vaccinated adolescent and young-adult populations continue to be reported, reflecting the waning of vaccine-induced immunity; a third dose is used in outbreak control in some countries. Congenital rubella syndrome, by contrast, has been eliminated from an increasing number of countries — a success entirely attributable to sustained MMR coverage, and one that the fall in that coverage would be the first to reverse.

13.9. Two further respiratory-entry infections of current importance

The course covers the classical seven diseases; two others are met so frequently in practice, and have changed so much in their preventability, that they belong in a contemporary account of the respiratory-entry infections.

Varicella and herpes zoster

Definition and agent. Varicella (chickenpox) is the primary infection with the varicella-zoster virus (VZV), a herpesvirus which, after the acute illness, establishes lifelong latency in the sensory ganglia and may reactivate decades later as **herpes zoster (shingles)**. The two diseases are therefore two manifestations of one infection — a configuration met nowhere else in this book, and one that governs their epidemiology.

The epidemiological process. The source is the person with varicella (from about two days before the eruption until all lesions are crusted) or with zoster (through the vesicular fluid). Transmission is airborne, by droplet nuclei — varicella is among the most contagious of human infections, with secondary attack rates in susceptible household contacts of the order of 85–90% — and also by direct contact with vesicle fluid; a person with zoster can transmit varicella to a susceptible contact, but not zoster itself. Receptivity is general; in temperate climates without vaccination, the great majority of the population is infected in childhood, with a late-winter and spring seasonality. Post-infectious immunity against varicella is durable, but it does not prevent reactivation as zoster, whose incidence rises steeply after 50 years with the decline of cell-mediated immunity.

Why it matters. Varicella is usually benign in the healthy child, but it is severe in adults, in pregnancy (with congenital varicella syndrome in early pregnancy, and life-threatening neonatal varicella around delivery) and in the immunosuppressed; bacterial superinfection with group A streptococci, pneumonia and cerebellitis are the classical complications. Zoster carries

the burden of **post-herpetic neuralgia**, which may persist for months or years and is one of the most refractory chronic pain syndromes of the elderly.

Prevention. A live attenuated varicella vaccine is included in the childhood schedule of many countries; where coverage has been high and sustained, varicella morbidity and hospitalisation have fallen dramatically [7]. Against zoster, the **recombinant adjuvanted subunit vaccine** has demonstrated efficacy above 90% in adults aged 50 and over [8], including in the very old, with durable protection — a substantial advance over the earlier live vaccine, and one of the more consequential additions to adult immunisation of the past decade. Post-exposure prophylaxis with varicella-zoster immunoglobulin is indicated for exposed susceptible pregnant women, neonates of mothers with peripartum varicella, and immunosuppressed contacts.

Respiratory syncytial virus (RSV)

Importance. RSV is the leading cause of lower respiratory tract infection in infants worldwide [9] — bronchiolitis and pneumonia — and a major cause of severe respiratory illness in adults over 65 and in those with chronic cardiac or pulmonary disease. Practically every child is infected in the first two years of life; reinfection occurs throughout life, since post-infectious immunity is incomplete and transient.

Epidemiology. The source is the infected person; transmission is by droplets and by contaminated hands and surfaces, on which the virus survives for hours — a feature that makes RSV a classical agent of nosocomial transmission in paediatric wards. In temperate zones the epidemics are sharply seasonal, in autumn and winter; the non-pharmaceutical interventions of the COVID-19 pandemic interrupted this pattern almost completely in 2020, and were followed by out-of-season resurgences with older-than-usual first infections — an instructive natural experiment demonstrating both the efficacy of those measures against respiratory transmission and the "immunity debt" that follows their withdrawal.

Prevention: the change of the past three years. Until recently, prevention was limited to hygiene and to monthly palivizumab for a small number of high-risk infants. Three instruments have since become available: **nirsevimab**, a long-acting monoclonal antibody given as a single dose to protect infants through their first RSV season [10], with effectiveness against hospitalisation of the order of 80% in real-world evaluations; **maternal vaccination** in the third trimester, which transfers protective antibodies to the newborn; and **recombinant RSV vaccines for older adults** [11]. Prevention of a disease long considered unpreventable is thus, within a very short period, an operational reality — and an illustration of a general lesson of Chapter 18: that the instruments of prevention are not fixed, and that the physician's duty is to know which ones exist this year.

References

1. World Health Organization. Measles deaths down 88% since 2000, but cases surge. Geneva: WHO; 28 November 2025.
2. World Health Organization Regional Office for Europe. Romania increases vaccination coverage for measles, mumps and rubella. Copenhagen: WHO/Europe; 26 June 2026.
3. OECD/European Observatory on Health Systems and Policies. *România: Profilul de țară din 2025 în ceea ce privește sănătatea*. Paris/Brussels; 2025.
4. Moss WJ, Griffin DE. Measles 2025. *New England Journal of Medicine*. 2025. doi:10.1056/NEJMra2504516
5. European Centre for Disease Prevention and Control. Measles and rubella monthly reports; Pertussis and diphtheria — annual epidemiological reports. Stockholm: ECDC.
6. Orenstein WA, Offit PA, Edwards KM, Plotkin SA (eds.). *Plotkin's Vaccines*. 8th ed. Elsevier; 2023.
7. World Health Organization. Varicella and herpes zoster vaccines: WHO position paper. *Weekly Epidemiological Record*. 2014;89:265–288.
8. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *New England Journal of Medicine*. 2015. doi:10.1056/NEJMoa1501184
9. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years. *The Lancet*. 2022. doi:10.1016/S0140-6736(22)00478-0
10. Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *New England Journal of Medicine*. 2022. doi:10.1056/NEJMoa2110275
11. European Centre for Disease Prevention and Control. RSV and varicella — surveillance and vaccine guidance. Stockholm: ECDC.

Chapter 14. The Viral Hepatitides

14.1. Definition, entities and epidemiological importance

The viral hepatitides are human-specific infectious diseases with an endemic-epidemic evolution, spread over a wide geographical area, and with clinical manifestations in an icteric or an anicteric form. Under this common name are currently united the viral hepatitides caused by the A, B, D, C, E and G viruses — entities profoundly different in their transmission, their evolution and their prevention, whose individualisation is one of the achievements of modern medicine.

A brief history is instructive. The discovery of the **Australia antigen** by Blumberg in 1965 opened the modern era of the field and led, in time, to: the differentiation of hepatitis B from the other types; the more accurate identification of the anicteric forms and of the chronic carriers of the HBs antigen; the demonstration of the transmission of hepatitis B through routes other than the parenteral one; the clarification of important aspects of the pathogenesis of hepatitis B; and the demonstration of the antigenic heterogeneity of the HBs antigens, with their significant geographical variation.

Generally speaking, the viral hepatitides are a serious public health issue due to: their high morbidity; the deaths they generate; their impairing sequelae — chronic hepatitis, cirrhosis, hepatocellular carcinoma; the costs of medical care; and the great share held by hepatitis B and by its non-parenteral transmission routes.

Box 14.1. The global burden today (supplementary). According to the recent WHO estimates, more than **250 million people live with chronic hepatitis B** infection and around **50 million with chronic hepatitis C**; together they cause over a million deaths annually, mainly through cirrhosis and hepatocellular carcinoma — a mortality comparable with that of tuberculosis. Two facts have transformed the perspective of control: the hepatitis B vaccine, and the direct-acting antivirals introduced in the mid-2010s, which cure chronic hepatitis C in over 95% of cases after 8–12 weeks of oral treatment. On these two pillars rests the WHO strategy of **eliminating viral hepatitis as a public health threat by 2030**.

14.2. Features of the pathogens

The hepatitis A virus (HAV) belongs to the family *Picornaviridae*, genus *Hepatovirus*. Seroepidemiological studies have highlighted the presence of anti-HAV antibodies in an average of 70% of the population; in our geographic area most individuals go through an icteric or anicteric form of the disease by the age of 20. The differences among geographic areas are very large, following faithfully the level of sanitation: intensely endemic areas (early, almost universal infection in childhood), medium endemicity areas, and low endemicity areas (where infection is displaced towards adulthood — and where, paradoxically, the clinical forms are more severe, since the severity of hepatitis A grows with age). The virus is sensitive to chlorine in regular doses — 2 mg/l free chlorine in 5 minutes, 0.25 ml/l formaldehyde at 37 °C — is

inactivated within one hour at 60 °C and within one minute at 100 °C, but can last for months in residual waters and in sea water: the profile of a typical water-borne pathogen.

The hepatitis B virus (HBV). In 1965 Blumberg noticed the appearance of a precipitation line between the serum of an Australian Aborigine and the serums of polytransfused patients; the antigen was named the Australia antigen, and subsequent research established its causal relation with hepatitis B, leading to the current name of HBs antigen. In 1970 Dane described the complete, double-contoured viral particle — the hepatitis B virus, member of the family *Hepadnaviridae*. The virus is remarkably resistant: it can last 7 days at room temperature and withstands treatment with 0.2% phenol or ethyl alcohol; it is inactivated by β-propiolactone 4 g/l and by glutaraldehyde in alkaline aqueous solution. The HBs antigen possesses subdeterminants (d/y, w/r), whose geographical distribution — with the "ay" formula predominating in some zones and "ad" in others — has served as an epidemiological marker of the circulation of the virus.

The hepatitis D (delta) virus (HDV). The first observations connected with the delta antigen–antibody system were made by Rizzetto in 1977, who described it as a new antigenic system in B-virus infections; subsequent reconsiderations led to the individualisation of a new hepatitis agent. HDV is a rudimentary, **defective** virus, which cannot multiply on its own but needs HBV as a helper virus, borrowing from it the HBs coat. Two situations must be distinguished, with different prognoses:

- **coinfection** — the D-virus contamination occurs simultaneously with the HBV contamination; the manifestation is generally benign, the replication and survival potential of HDV being limited by the short duration of the HBs antigenaemia;
- **superinfection** — the HDV contamination occurs in a person already infected with HBV; the evolution can be towards fulminant hepatitis or towards aggressive chronic hepatitis, HDV finding at its disposal the large quantities of HBs antigen needed for its synthesis.

The hepatitis C virus (HCV) belongs to the family *Flaviviridae*, genus *Hepacivirus*. From certain epidemiological points of view it resembles HBV, having been responsible — as the retrospective studies showed — for most post-transfusional hepatitides. At least 6 genotypes with several subtypes are known, with distinct geographical distributions.

The hepatitis E virus (HEV) is an RNA virus (genus *Hepevirus*). It is responsible for the hepatitides formerly called "non-A, non-B with epidemic features", with digestive-route transmission, especially under circumstances of deficient hygiene; epidemiologically it resembles HAV. Its most feared feature: in pregnant women it can produce fulminant hepatitis, with death in 20–39% of cases.

The hepatitis G virus (HGV) is an RNA virus of the family *Flaviviridae*, with several genotypes. It is resistant to ambient conditions but destroyed by chlorine-based decontaminants. It generates spontaneously resolutive acute hepatitides, supposed to be able to evolve towards chronicity; the high percentage of chronic co-infections HGV + HBV/HCV suggests the helper role of the two latter viruses.

14.3. Entries, eliminations, sources

The entry differs fundamentally between the two epidemiological families of hepatitis viruses:

- **HAV and HEV** — the digestive tract; in exceptional cases the teguments or the mucosae;
- **HBV, HCV, HDV, HGV** — the teguments and the mucosae (the parenteral and sexual family).

The elimination of the viruses from the source occurs: for HAV through the faeces, the blood and the urine; for HEV through the faeces; for HCV and HDV through the blood; for HBV through the blood, the sperm, the vaginal secretions and possibly other secretions and excretions.

The source of infection:

- **for HAV** — the ill person with an icteric or an anicteric form. The virus is eliminated through the faeces starting with the second half of the incubation period — the patient is thus maximally contagious *before* knowing himself ill — and disappears or is reduced within a few days following the onset of jaundice. The contagious stage lasts in general 10–14 days after the onset, and **there is no chronic carrier state**;
- **for HBV** — the source is multiple: the ill with acute icteric or anicteric forms; the ill with persistent or aggressive chronic hepatitis; the ill with HBV-aetiology cirrhosis; the ill with hepatocarcinoma with positive HBs antigen; and the convalescent or chronic carriers of the HBs antigen — the serological researches having indicated the existence of over 300 million carriers worldwide;
- **for HCV, HDV, HEV and HGV** — the acutely ill and the carriers.

14.4. Transmission routes and mechanisms

HAV has a complex transmission mechanism of the faecal–oral type: the passage of the viral agent eliminated through the faeces occurs through dirty hands, objects, laundry, thermometers, contaminated water and food, and vectors — especially houseflies.

HBV has two transmission ways:

- **parenteral** — through transfusions of contaminated blood, improperly sterilised medical instruments, contaminated shaving machines and scissors, and the instruments used for tattoos, manicure and pedicure — the non-medical percutaneous practices deserving the emphasis they receive in the course;
- **non-parenteral** — through direct sexual contact, and perinatally, from the mother to the baby.

HCV: the transmission is parenteral — through blood (transfusions), coagulation factors, improperly sterilised medical instruments; sexual and vertical transmission are also possible, though less efficient than for HBV.

HDV: similar to HBV — parenteral transmission through blood and medical instruments; transmission through direct contact and possibly vertical transmission.

HEV: transmission through person-to-person contact by the faecal–oral route, or through the consumption of contaminated water.

HGV: similar to HCV — parenteral transmission through blood and contaminated medical instruments; vertical and sexual transmission are also possible.

14.5. The receptive population and the favouring factors

The receptiveness of the population is general for all the forms of viral hepatitis.

For **HAV**, in our geographic area the higher frequency of disease is recorded among preschool and school children and young people. For **HBV**, the incidence of morbidity is higher among adults, both sexes being equally affected; there is a well-defined **professional risk for the medical and healthcare staff**, especially in the haemodialysis, oncology, obstetrics-gynaecology, surgery and stomatology wards, in the medical laboratories, in the transfusion centres, and in the mental institutions. For **HCV**, the spread is universal, the vast majority of the classical cases being post-transfusional, with distinct risk groups — the polytransfused, leukaemia patients, transplantation patients — a similar phenomenon holding for HDV and HGV.

The favouring socio-economic factors are: improper hygiene; human agglomerations; the promiscuity of cohabitation; aberrant sexual practices, promiscuity and drug consumption; residence in areas endemic for the parenterally transmitted hepatitides; frequent contact with blood and blood derivatives; and poor sanitary education.

14.6. The manifestation forms of the epidemiological process

The viral hepatitides evolve endemically-epidemically, with variable densities depending on the geographic area.

HAV evolves sporadically-endemically or endemically-epidemically, with a cyclical tendency after the build-up of a receptive population segment: a 3–10-year periodicity, autumn–spring seasonal features, and higher morbidity in rural areas. The epidemics can be hydric, contact-based or food-based — the foods most frequently incriminated being milk, butter, orange juice, cakes, ice cream, seafood and raw vegetables.

HBV evolves endemically — even hyperendemically in certain geographic areas — with no seasonal variations. Chronic carriage occurs in up to 20% of the cases (the risk being maximal — around 90% — when the infection is acquired perinatally, and minimal in the immunocompetent adult); approximately 40% of the chronically infected will die of the complications of the disease. HBV is **the first human virus clearly involved in the aetiology**

of a malignant process — the primary hepatocellular carcinoma; the hepatitis B vaccine is thus, together with the HPV vaccine, one of the two anticancer vaccines of current medicine.

HCV: in the past, 90% of the cases were post-transfusional; after the introduction of donor screening these have fallen to some 10%, the remainder evolving sporadically, especially among adults and males. Chronic development occurs in over 50% of the cases — the highest chronicisation rate of all hepatitides, aggravated by the fact that the acute infection is most often anicteric and unrecognised.

HDV is endemic in south-eastern Europe, Africa, the Middle East and South America, with epidemic outbreaks in the same areas — its map being necessarily inscribed within the map of HBV.

HEV causes epidemics similar to those of HAV in regions of Asia and the Eastern Mediterranean, the main transmission route being the consumption of contaminated water, with epidemic episodes occurring characteristically after floods.

14.7. Prevention and control

Measures regarding the ill, the carriers and the contacts

For HAV — measures regarding the ill: identification and nominal declaration; the patient is isolated in hospital for 21 days. Similar measures apply to the suspects, with their separation from the other patients until the diagnosis is clarified. Measures regarding contacts: clinical and laboratory check-up for 15–45 days (the incubation limits of the disease).

For HBV — measures regarding the ill: identification and nominal declaration; isolation for 30–40 days, with the segregation of the HBs-positive patients from the other patients with viral hepatitides; the same measures for the suspects, until the clarification of the diagnosis. Measures regarding the carriers: identification and treatment at a medical facility, with check-ups after 1, 3, 6, 9 and 12 months; carriers are considered cured only after 2 successive check-ups with normal results; the **moral isolation** of the carrier state — with recommendations regarding the profession and the attitude towards the persons around — and the mentioning of the carrier state on all hospitalisation and special investigation referral notes. Measures regarding contacts: clinical and laboratory check-up during the maximum incubation of the disease; the epidemiological investigation is compulsory; continuous sanitary education.

Measures regarding the transmission routes

The prevention of the non-percutaneous (digestive) transmission: the disinfection of the discharged matter of the ill (faeces, urine) with 2% chloramine or 20% chlorinated lime; laundry disinfection through a 30-minute contact with 0.5% chloramine; dish disinfection using detergents; terminal disinfection of the rooms with formolisation.

The prevention of the percutaneous transmission: the proper autoclaving and sterilisation of medical instruments — supplemented today by the generalisation of single-use materials

and of the standard (universal) precautions, which treat every patient as potentially infected; the disinfection of shared objects; the avoidance of accidental professional exposure to blood and to other infected biological fluids; and the sterilisation of the instruments used for manicure, pedicure, tattooing and piercing.

Measures regarding the receptive population

For HAV:

- **passive immunoprophylaxis** — the administration of total immunoglobulins, 0.02–0.05 ml/kg body weight, during the first 72 hours following the infecting contact; it is applied in children's collectivities where cases have occurred, and in collectivities where the epidemiological investigation forecasts the possibility of epidemic outbreaks; mass prophylactic administration is not recommended;
- **active immunoprophylaxis** — the administration of inactivated vaccine (Havrix), in the paediatric presentation of 0.5 ml/dose up to the age of 15 and the adult presentation of 1 ml/dose, intramuscularly; another commercially available product is Avaxim. The administration comprises 2 doses at an interval of 6–12 months; the adverse reactions are minor — pain, erythema, local induration, subfebrile state, headache, asthenia, gastro-intestinal disorders.

For HBV:

- **passive immunoprophylaxis** — the administration of anti-HBV specific immunoglobulins: pre-exposure, in haemodialysis patients and before an organ transplant; post-exposure, in the newborns of HBs-positive mothers (0.5 ml) and in the sexual partners of an HBs carrier or after exposure to blood and potentially contaminated biological fluids (5 ml for adults);
- **active immunoprophylaxis** — with the anti-HBV vaccines obtained through genetic recombination: the HBs antigen is produced on yeast (*Saccharomyces cerevisiae*) or on *E. coli* cells in which the S gene — the HBs antigen synthesis gene — has been introduced as a plasmid; the commercial products include Engerix B, Euvax and Recombivax, in paediatric vials of 10 µg/0.5 ml and adult vials of 20 µg/1 ml. The vaccine is administered to the newborns in maternities — the first dose ideally within the first 24 hours of life, together with specific immunoglobulins when the mother is HBs-positive — to previously unvaccinated children and teenagers, and to the adults in the risk groups: the medical staff, the prison staff and inmates, the personnel and residents of mental institutions, children in closed collectivities, homosexual men, drug users, and patients with haematological or renal pathology.

The prevention of post-transfusion hepatitides

Measures regarding the donors: the lifelong exclusion from donation of the ex-hepatitis patients; screening, with the exclusion of the HBs-positive persons; the exclusion for 6 months

of the contacts of HBs carriers and of transfused persons; the preference for honorary (voluntary, unpaid) donors rather than remunerated ones — the economic interest in donation being a classical amplifier of transfusional risk.

Measures regarding the product: treatment with ultraviolet radiation and β-propiolactone; storage for 6 months (quarantine of the products); the checking of the doses.

Measures regarding the population: limiting the transfusions to the strictly necessary indications and replacing them, wherever possible, with substitutes.

Box 14.2. From screening to elimination (supplementary). The screening of donations has been progressively extended — HBs antigen, anti-HCV antibodies (from the early 1990s), anti-HIV, and in many countries nucleic acid testing (NAT), which shortens the diagnostic window to days — reducing the residual transfusional risk of hepatitis to the order of one per million units. To the classical arsenal of prevention have since been added: the universal vaccination of newborns against hepatitis B (in Romania since 1995), which is projected to make the disease exceptional in the vaccinated cohorts; the antiviral treatment of chronic hepatitis B (nucleos(t)ide analogues) and the antiviral prophylaxis of the highly viraemic pregnant woman in the third trimester, which completes the blocking of vertical transmission; and the direct-acting antivirals for hepatitis C which, by curing the sources, act simultaneously as treatment and as prevention. For hepatitis E, a recombinant vaccine (Hecolin) is licensed in China. The elimination of viral hepatitis as a public health problem — WHO's declared objective for 2030 — has thus become, for the first time, technically conceivable; what remains decisive is the screening of the undiagnosed, in whom the infection silently progresses towards cirrhosis and carcinoma.

14.8. Viral hepatitis today: the elimination agenda and its arithmetic

The current burden, precisely stated. The WHO global hepatitis report gives, for 2022, the figures that should replace the older estimates used in the classical account: **254 million people living with chronic hepatitis B** and **50 million with chronic hepatitis C**; **1.3 million deaths a year** — 83% from hepatitis B and 17% from hepatitis C — which is about **3,500 deaths every day**, a mortality comparable to that of tuberculosis; and **2.2 million new infections annually** (1.2 million hepatitis B, nearly 1 million hepatitis C) [1]. Ten countries — Bangladesh, China, Ethiopia, India, Indonesia, Nigeria, Pakistan, the Philippines, the Russian Federation and Viet Nam — carry nearly two thirds of the global burden; the African Region accounts for 63% of new hepatitis B infections, and the Western Pacific for 47% of hepatitis B deaths.

The diagnostic gap is the central problem. At the end of 2022, only **13% of persons with chronic hepatitis B had been diagnosed and 3% were receiving treatment**; for hepatitis C the figures were **36% diagnosed and 20% having received curative treatment** [1]. This is the arithmetic that governs everything else: an infection that is silent for decades, that is transmitted from persons unaware of carrying it, and that presents clinically only at the stage of cirrhosis or hepatocellular carcinoma, cannot be controlled by treating those who present. **Screening is therefore the rate-limiting step of elimination**, and the practical

recommendation for the clinician is to test — at least once in adult life for hepatitis B and C, and repeatedly in defined risk groups [2] — rather than to wait for a clinical indication.

Hepatitis C: cure as prevention. The direct-acting antivirals introduced in the mid-2010s cure over 95% of chronic infections with 8–12 weeks of well-tolerated oral treatment, without interferon. The epidemiological consequence is that treatment is simultaneously prevention: each cured patient is a source of infection removed. Where treatment has been scaled up together with harm reduction for people who inject drugs, incidence has fallen; Egypt, which conducted the largest screening and treatment campaign ever undertaken for any disease, became in 2023 the first country to achieve WHO "gold tier" status on the path to elimination [3] — a demonstration that elimination is an organisational, not a scientific, problem.

Hepatitis B: vaccination and the interruption of vertical transmission. Universal infant vaccination, with the **birth dose within 24 hours of life**, is the decisive intervention, since perinatally acquired infection carries a risk of chronicity approaching 90%. Where it has been sustained for a generation — Taiwan being the classical example, with a documented fall in childhood hepatocellular carcinoma [4] — the effect is measurable in cancer incidence, which makes the hepatitis B vaccine, with the HPV vaccine, one of the two anticancer vaccines of current medicine. To vaccination is added, for highly viraemic pregnant women, antiviral prophylaxis in the third trimester, which reduces residual transmission further [5]. Romania has provided universal newborn hepatitis B vaccination since 1995; the cohorts vaccinated then are now adults, and the epidemiological benefit will continue to accumulate for decades.

Hepatitis D and E. Hepatitis D, dependent on HBV, affects a subset of hepatitis B carriers and causes the most rapidly progressive form of viral liver disease; bulevirtide, an entry inhibitor licensed in Europe, has provided a first specific therapy. Hepatitis E remains a major cause of water-borne epidemic hepatitis in Asia and Africa, with the case fatality of 20–39% in pregnancy noted in Section 14.2; a recombinant vaccine (Hecolin) is licensed in China and has been used in outbreak settings, and WHO has supported its use in emergencies.

The elimination target and where it stands. WHO's goal — a 90% reduction in new infections and a 65% reduction in deaths by 2030, relative to 2015 [6] — remains formally in force, but the trajectory is not on track: deaths have risen rather than fallen, because the treatment of the infections acquired decades ago has not kept pace with the progression to cirrhosis and cancer. The instruments exist; the deficit is in screening, in linkage to care, and in financing.

A note on hepatitis A. The classical epidemiology of Section 14.6 — the paradox that improved sanitation, by delaying first infection to adulthood, increases the severity of the disease — has a direct practical corollary in countries in epidemiological transition, Romania included: outbreaks now occur in adolescents and adults rather than in small children, and vaccination is indicated for travellers, for men who have sex with men, for persons with chronic liver disease and in outbreak control.

References

1. World Health Organization. *Global hepatitis report 2024: action for access in low- and middle-income countries*. Geneva: WHO; 2024 (data for 2022); and WHO news release, 9 April 2024.
2. European Centre for Disease Prevention and Control. Hepatitis B and C — annual epidemiological reports. Stockholm: ECDC.
3. World Health Organization. Egypt is first country to achieve WHO validation on the path to elimination of hepatitis C. Geneva: WHO; 2023.
4. Chang MH, You SL, Chen CJ, et al. Long-term effects of hepatitis B immunization of infants in preventing liver cancer. *Gastroenterology*. 2016. doi:10.1053/j.gastro.2016.06.048
5. World Health Organization. *Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection*. Geneva: WHO; 2024.
6. World Health Organization. *Global health sector strategies on HIV, viral hepatitis and sexually transmitted infections, 2022–2030*. Geneva: WHO; 2022.

Chapter 15. Infections with a Digestive Entry

The diseases of this chapter — cholera, typhoid fever, the paratyphoid fevers, bacterial dysentery, poliomyelitis and food poisoning — share the digestive entry and the **complex indirect transmission by the faecal–oral mechanism**: the pathogen eliminated through the faeces of the source reaches the mouth of the receiver through the relay of water, food, dirty hands, objects and vectors. Their epidemiology is therefore, before all, the epidemiology of sanitation: of drinking water, of sewerage, of food hygiene and of washed hands; and their seasonal signature is the warm season.

15.1. Cholera

Definition and aetiological agent

Cholera is the most serious acute infectious diarrhoeic disease: sudden onset, watery diarrhoeic stools, sometimes vomiting, followed by rapid dehydration with acidosis and hypovolaemic shock. The prognosis depends dramatically on how early the correct therapy is begun: fatality is **over 50% in the absence of therapy and under 1% with optimal therapy** — few diseases illustrate more brutally the value of simple treatment (rehydration) applied in time. With all the apparent progress made in cholera control, the specific mortality worldwide is rising.

The disease is caused by *Vibrio cholerae* O1 and O139 — a Gram-negative, aerobic, comma-shaped, mobile germ, pathogenic only to humans. There are two biotypes: **classic** and **El Tor**, the latter more widespread, more resistant in the external environment and more resistant to antibiotics (co-trimoxazole, ampicillin). Clinically, the incubation is short — several hours up to 5 days (which is why cholera is the quarantinable disease with the shortest quarantine) — and the classical severe picture occurs more frequently in the classic biotype and less frequently in El Tor infections.

The epidemiological process

The source of infection is represented by the ill, by the subclinically infected and by carriers. The ill person is contagious from the onset, through the faeces and the vomited fluid; the vibrio is eliminated massively but over a short duration, even in the absence of anti-infectious treatment. The carrier state, lasting a few days, occurs rarely; chronic carriers are exceptional and occur on the background of cholecystopathy. The El Tor biotype, with its higher ratio of subclinical infections, travels hidden in apparently healthy travellers — the modern vehicle of the pandemic waves.

Transmission is complex indirect, by the faecal–oral mechanism. Cholera is **the prototype of the infectious diarrhoeic disease with water-based transmission**; the infecting dose is high — 10□–10□ germs for the classic biotype, 10^3–10□ for El Tor — which explains why massive contamination of water is its natural setting. It is also transmitted through contaminated food (especially seafood fished in contaminated waters), dirty hands, objects and vectors.

The receptive population. Receptivity to the infection is general. Receptivity to the *disease* differs by biotype: average in classic cholera — about 50% disease and 50% subclinical forms — and lower in El Tor — about 25% disease, 25% atypical diarrhoea, 50% subclinical forms. Receptivity is maximal among children in the endemic areas, and among adults in the areas of imported cholera. Post-infectious immunity is serotype-specific and long-term, consolidated through subsequent reinfections.

The favouring factors: the scarcity of drinking water in the endemic areas; faulty hygiene; a low economic and cultural level; unsatisfactory medical assistance. Wherever war, disaster or mass displacement destroy sanitation, cholera follows — the great epidemics accompanying humanitarian crises are its contemporary form of manifestation.

Prevention and control

Measures regarding the ill: discovery, with urgent, "contact"-type isolation in the infectious disease clinic; the nominal announcement of the confirmed cases — cholera being on the list of **quarantinable diseases** established by WHO under the International Health Regulations; the disinfection of the faeces, the vomited fluids, the linen and the objects used by the ill person, either by heat or chemically; compulsory final disinfection.

Measures regarding contacts: monitoring for 5 days after the last known infecting contact; chemoprophylaxis for the family contacts with tetracycline (1 g/day for adults; 50 mg/kg for children over 9 years, 5 days), doxycycline (200 mg single dose for adults; 4–6 mg/kg/day for children) or furazolidone (4 × 100 mg/day for adults; 5 mg/kg/day for children, 3 days). The vaccination of contacts is not recommended — post-exposure vaccination cannot outrun the short incubation.

Measures regarding the transmission routes: hand washing; the hygienic storage and disposal of the discharged matter; the provision of drinking water; rigorous food hygiene; promoting the natural (breast) feeding of sucklings — the most effective protection of the infant against all infectious diarrhoeas; disinsection and preventing vectors from reaching food; the moral isolation of carriers; laboratory checks of the water and of the population in the focus.

Specific prophylaxis: anti-cholera vaccination.

Box 15.1. The seventh pandemic and the modern vaccines (supplementary). Cholera has swept the world in seven pandemics since 1817; the current, seventh pandemic, caused by the El Tor biotype, began in 1961 and continues, with major recent epidemics in Haiti (2010, following the earthquake), Yemen (from 2016, among the largest ever recorded) and a global upsurge since 2021 that has forced the rationing of vaccine stocks. The old injectable inactivated vaccine, of modest and short-lived efficacy, has been abandoned; the current instruments are the **oral cholera vaccines** (Dukoral; Shanchol/Euvichol), administered in two doses, used both preventively in endemic zones and reactively, in ring or mass campaigns, during epidemics — always as a complement to, never a substitute for, water and sanitation. For the individual traveller to affected areas, the essential advice remains behavioural: "boil it, cook it, peel it — or forget it."

15.2. Typhoid fever

Definition and aetiological agent

Typhoid fever is a major, systemic salmonellosis with an insidious onset, characterised by high fever, headache, anorexia, bradycardia, splenomegaly, rose-coloured spots on the trunk, irritative coughing and constipation — a systemic, bacteraemic disease, and not a banal diarrhoea.

Salmonella typhi is a Gram-negative, unsporulated bacillus of group D of the genus *Salmonella*; 106 major epidemiological lysotypes are known — phage typing having long served to trace the filiation of cases. Its resistance in the external environment is average; it is sensitive to chloramphenicol, ampicillin, third-generation cephalosporins and quinolones (with the reservation of the modern multiresistance — see Box 15.2). The entry is oral; the disease starts at infecting doses of 10□–10□ germs, while asymptomatic infection can be triggered by doses 100 times smaller.

The epidemiological process

The source of infection is exclusively human: the ill and the carriers. The ill person not receiving antibiotic treatment is contagious in the last 2 days of incubation, throughout the state period and for 2–6 weeks during convalescence; about 10% of untreated patients excrete typhoid bacilli for over 3 months, and 2–5% become **chronic carriers** — formerly ill or inapparently infected persons, usually with cholelithiasis, in whose gallbladder the bacillus persists for years or for life (the reader will recognise the biography of Typhoid Mary, Box 2.1). Family contacts can be temporary carriers. The elimination occurs mainly through the faeces and less frequently through the urine.

Transmission is complex indirect, by the faecal–oral mechanism, through water and through faecally or urinarily contaminated food, with the participation of dirty hands and of vectors. The disease requires a high infecting dose, which explains its relatively reduced contagiousness in conditions of decent hygiene.

The receptive population. Receptivity is general; the risk is higher among people with gastric hypoacidity — the gastric acid barrier being the first, non-specific defence against all digestive infections. Post-infectious immunity is variable and consolidated through subsequent infecting contacts, but it does not always protect. Receptivity is maximal among children and youth in the endemic areas, but homogeneous among all age groups in the areas of reduced incidence.

The favouring factors: heavy rain, sudden snow-melting and floods — all of which carry faecal contamination into the water sources; and the abundance of vectors.

The manifestations of the epidemiological process: in most areas typhoid fever currently has an endemic-sporadic manifestation, with a spring–summer seasonality in the temperate zone; in regions of Asia and South America epidemics with multiresistant strains have emerged.

Prevention and control

Measures regarding the ill: discovery, with compulsory isolation at the infectious disease clinic; nominal declaration of the confirmed cases; the disinfection of the faeces, the vomited fluid, the linen and the objects used by the ill; compulsory final disinfection and epidemiological investigation of the focus. The patient is released from hospital only when the typhoid bacillus is no longer excreted, and former patients receive dispensary care (follow-up) for one year — the instrument through which chronic carriers are detected.

Measures regarding contacts: monitoring for the maximum incubation period (3 weeks); the protection of the family contacts of the ill and of the carriers with the anti-typhoid vaccine, whose protective effect lasts at most 5 years; chemoprophylaxis is not recommended for contacts.

Measures regarding carriers: their active discovery and systematic vaccination in the risk sectors — the garbage-disposal staff, the workers of the food sector and of the drinking water supply sector; the moral isolation of carriers, with their exclusion from the epidemiologically critical workplaces.

Measures regarding the transmission routes: hand washing; the hygienic storage of the discharged matter; the provision of drinking water with compulsory chlorination; rigorous food hygiene; disinsection and the protection of food from vectors; laboratory checks of the water and of the population in the focus.

The paratyphoid fevers (caused by *Salmonella paratyphi* A, B and C) resemble typhoid fever epidemiologically; there is no efficient vaccine against them, and their prevention and control are based on the same general rules.

Box 15.2. Typhoid today: resistance and conjugate vaccines (supplementary). Typhoid fever remains a disease of millions of cases annually in southern Asia and sub-Saharan Africa. Its modern history is dominated by antimicrobial resistance: chloramphenicol resistance from the 1970s, multidrug resistance in the 1990s, fluoroquinolone non-susceptibility thereafter, and — since 2016, in Pakistan — the **extensively drug-resistant (XDR)** clone, sensitive practically only to azithromycin and carbapenems. This escalation has given new weight to vaccination: alongside the classical injectable Vi polysaccharide vaccine and the oral live attenuated Ty21a vaccine, the **typhoid conjugate vaccines (TCV)**, immunogenic from infancy and with durable protection, have been WHO-prequalified since 2018 and introduced into the national programmes of the most affected countries.

15.3. Bacterial dysentery (shigellosis)

Definition and aetiological agent

Bacterial dysentery is an acute, bacterial, febrile diarrhoea characterised by a generally degraded condition, colicky pains, tenesmus and diarrhoeic stools containing mucus, blood and pus — the classical invasive, inflammatory diarrhoea of the distal colon.

It is caused by germs of the genus *Shigella*. The most severe forms are produced by *Shigella dysenteriae* type 1 (the producer of Shiga toxin), and the most benign by *S. sonnei*; between them stand *S. flexneri* and *S. boydii*. The resistance in the external environment is average, resembling that of the salmonellae. Clinically: incubation of at most 7 days; invasive-type diarrhoea.

The epidemiological process

The source of infection is exclusively human: the ill with typical forms, contagious from the end of the incubation period and sometimes during convalescence; the ill with *formes frustes* and atypical forms — more frequent, harder to discover and to neutralise, mostly children; convalescent carriers, excreting germs up to 3 months after the acute episode; chronic carriers, excreting for several months — rare; and the subclinically infected — unknown, un-neutralised, and therefore of maximal epidemiological efficiency. Elimination occurs through the faeces.

Transmission is complex indirect, by the faecal–oral mechanism: dirty hands and vectors, contaminated food and water. The feature that dominates the whole epidemiology of shigellosis is the **very low infecting dose — 10 to 100 germs** — which makes direct hand-borne, person-to-person transmission fully efficient: dysentery is *par excellence* the "disease of dirty hands", capable of circulating even in communities with piped water. The favouring factor is low personal hygiene.

The receptive population. Receptivity is higher among children between 6 months and 10 years; the disease is more severe among old people and the malnourished. The contagiousness is highest among preschool children — up to 40%. Post-infectious immunity is type-specific and reflects the spectrum of the strains circulating in the given area.

The manifestations of the epidemiological process. The disease is spread worldwide, with an estival (summer) seasonality in the temperate zones. *S. flexneri* prevails among the paediatric population and in hospitals and closed institutions, while *S. sonnei* is frequent among adults and in the general population. **Underreporting is constant and very significant** — the mild and atypical forms never reach the laboratory, and the surveillance figures are only the emerged tip of the real morbidity.

Prevention and control

Measures regarding the ill: discovery, with isolation at the infectious disease clinic; treatment using intestinal disinfectants or eubiotics, the antibiotics being reserved for the severe cases and for the sterilisation of carriers — a restraint doubly justified today by the antimicrobial resistance of shigellae; compulsory current and final disinfection and epidemiological investigation of the focus. The patient is released only after 3 negative coprocultures, the first performed 24 hours after the completion of the anti-infectious treatment. The education regarding personal hygiene and proper hand washing accompanies every case.

Measures regarding contacts: immunoprophylaxis and chemoprophylaxis are not indicated; the persons working in the epidemiological risk sectors can resume their activity only after 3 negative coprocultures; hygiene education.

Measures regarding the transmission routes: identical with those for all acute infectious diarrhoeic diseases — water, food, hands, vectors.

Specific prophylaxis: antidysentery vaccination has been recommended in collectivities of children above 1 year of age with a high annual dysentery morbidity maintained by functional deficiencies difficult to influence. (No modern licensed vaccine of general use exists; candidate vaccines — conjugate and others — are in clinical development under WHO priority, precisely because of the growing resistance of shigellae.)

15.4. Poliomyelitis

Definition and aetiological agent

Poliomyelitis is an acute systemic infectious disease with widely varying degrees of severity — from inapparent forms to non-specific minor disease, aseptic (clear-fluid) meningitis, paralytic disease and death. Its historical weight and its current interest are concentrated in one word: **eradication**.

All three polioviruses — types 1, 2 and 3 — can produce the paralytic disease. Type 1 is the most frequently isolated from paralytic cases produced by wild viruses; types 2 and 3 have been more frequently involved in the post-vaccinal paralytic accidents. Clinically, the incubation is average (7–14 days as an order of magnitude), and the fatality of the paralytic cases varies between 2 and 10%, increasing with the age at which the disease occurs.

The epidemiological process

The source of infection is exclusively human: the polio-infected ill; the persons inapparently infected with wild or with vaccinal viruses; and the healthy carriers, excreting the virus for a short period. Contagiousness begins 36 hours after the infecting moment through the pharyngeal excretion, and 72 hours after it through the faecal excretion; the pharyngeal excretion lasts about one week, the faecal excretion 3–6 weeks or even longer. Contagiousness is maximal during the few days before and after the onset of the disease.

Transmission is complex indirect:

- mostly through the **faecal–oral mechanism** — dirty hands, objects, possibly vectors, and more rarely contaminated food (dairy) and water — dominant under circumstances of poor hygiene;
- through the **airborne route**, by Flügge's droplets — dominant among populations with a high sanitary standard, where the faecal–oral road has been closed by sanitation.

The receptive population. The receptivity to the infection is general, but the clinical expression follows the iceberg model in its purest form: the major (paralytic) disease occurs in 1–2% of the infected, the minor disease in 4–8%, while 90–95% undergo only inapparent infection. The tip of the iceberg — the rare paralytic cases — signals an enormous invisible base of infected persons; one paralytic case in a community means, epidemiologically, a hundred or more contagious infections. The paralytic form is more frequent among male subjects up to 15 years of age, and thereafter among females — through pregnancy and the intimate contact with the virus-excreting child.

Post-infectious immunity is type-specific and permanent, with humoral and enteral (intestinal, secretory) components; there is no cross-immunity among the polioviruses, except weak reactions between types 1 and 2. Maternal immunity, transmitted transplacentally and through milk, is transient. The infection risk is maximal among sucklings and decreases with age. The collective receptivity depends on the immune background of the population and ultimately reflects the accuracy of the immunoprophylaxis programme.

The favouring factors. The natural factors give the disease its summer–autumn seasonality in the temperate zone. The economic and social factors condition the epidemiological physiognomy: in populations with mediocre sanitation, the faecal–oral transmission produces primary infection at an early age — when maternal antibodies still attenuate it — building early specific immunity, consolidated by frequent reinfections, with a low risk of major disease; the improvement of sanitation, by postponing the first infection to later ages, paradoxically *increased* the paralytic epidemics of the twentieth century — the classical demonstration that the age at infection can matter as much as the infection itself.

The manifestation of the epidemiological process. Polio is pending global eradication through intensive generalised vaccination. Currently, polio cases may still occur: with **wild (non-vaccinal) virus**, in unvaccinated persons; and with **vaccinal virus** — in vaccinated persons or their contacts (vaccine-associated paralytic poliomyelitis and circulating vaccine-derived polioviruses). A country is declared polio-free only 3 years after the last declared case.

Prevention and control

Measures regarding the ill: discovery, with compulsory isolation at the infectious disease clinic; nominal declaration; compulsory current and final disinfection and epidemiological investigation; the disinfection of the patient's faeces for 3–6 months following the acute episode — as long as the excretion may last.

Measures regarding contacts: monitoring for at least 21 days after the discovery of the last case in the focus; isolation at home, at relative physical rest — intense effort during the incubation favouring the paralytic localisation; their vaccination or revaccination with anti-polio vaccine.

Measures regarding the transmission routes: identical with those recommended for all the digestive-transmission infectious diseases.

Specific prophylaxis is the main preventive measure and the one that renders polio susceptible to eradication: anti-polio vaccination at an age as young as possible. Proper vaccinal coverage reduces morbidity to sporadic occurrences and eliminates the seasonal and periodic features of the cases. Vaccination is maintained even in the countries where polio has been declared eradicated, because of the risk of the transmission of the virus from one geographical area to another, even at very long distances.

Two types of vaccine are used:

- **the inactivated polio vaccine (IPV)** — containing formaldehyde-inactivated strains of the three serotypes; its main advantage is the absence of any risk of post-vaccinal poliomyelitis;
- **the trivalent live attenuated oral vaccine (OPV/TOPV)** — with the advantages of easy oral administration, low cost and the induction of enteral immunity, but with the risk of paralytic accidents in vaccinees or their contacts.

Post-vaccinal poliomyelitis may occur 3–30 days after vaccination in the vaccinated person, and 3–75 days after the vaccination in the contacts; the risk is higher at the primary vaccination and lower after the boosters — which is why the combination of IPV followed by OPV has been used in the countries still employing OPV. (Romania, like the whole WHO European region — certified polio-free in 2002 — currently uses exclusively IPV; globally, the withdrawal of the type 2 component from OPV in 2016 and the introduction of the genetically stabilised nOPV2 vaccine mark the final stage of the eradication endgame, in which the last wild type 1 chains of transmission persist only in Afghanistan and Pakistan.)

15.5. Food poisoning

Definition and aetiological agents

The term **food poisoning (FP)** covers the acute disorders of various causes — toxic or infectious — occurring no longer than 72 hours after the consumption of food contaminated with microorganisms, with microbial toxins or with toxic chemical substances. Epidemiologically, its signature is the **collective outbreak with a common meal**: several persons, one food, one short interval.

Among the germs most frequently involved are:

- the enterotoxigenic cocci, especially the staphylococci;
- the enterobacteria — the minor (non-typhoid) salmonellae, the shigellae, *Escherichia coli*, *Proteus* spp.;
- the aerobic sporulated bacilli (*Bacillus cereus*) and the anaerobic ones (*Clostridium botulinum*, *C. perfringens*);
- other aetiologies: *Campylobacter* spp., *Vibrio cholerae* O1 and non-O1, *Yersinia enterocolitica*.

Clinically, two categories of manifestations can occur:

- **toxic food poisoning** — produced by the preformed toxin: short incubation, from 15–30 minutes to 6–12 hours; degradation of the general condition, toxic phenomena (nausea, vomiting, vertigo, shock), fever and, less frequently, diarrhoea; examples — staphylococcal food poisoning, botulism;
- **infectious food poisoning** — produced by the multiplication of the germ in the host: incubation of 12–72 hours; the picture of an acute febrile gastroenterocolitis; example — the minor salmonelloses.

The epidemiological process

The source of infection is very heterogeneous: humans (carriers or ill — the staphylococcal panaritium or angina of a cook is the classical origin of staphylococcal FP); animals, birds and insects, which can disseminate the infection over long distances. The contamination of the food can occur at any stage, from the source (the animal of origin) to the consumption.

Transmission: complex indirect — the food is the last runner of the relay race that carries the pathogen from the source to the consumer. The foods most frequently involved are: eggs and meat; dairy products; creams, mayonnaise and salads — the reader will recognise the "mixed foods" of Chapter 3, good culture media handled much and heated little.

The receptive population. Receptiveness is conditioned by the intake of an infecting dose — of germs or of toxin — high enough to trigger the symptom complex; the size of this dose varies with the cause. Post-infectious immunity generally does not occur, reinfections being possible indefinitely.

The favouring factors. The warm season favours both the contamination of food, through the biological activity of the extra-human factors, and the multiplication of the microorganisms in food kept at improper temperatures. The social and economic factors act through low sanitary education, faulty hygiene and insalubrity.

The manifestation of the epidemiological process: diseases with a net estival seasonality, manifested as isolated sporadic cases — much more frequent in summer — or as collective outbreaks (epidemics); the clinical severity depends on the aetiology and on the dose ingested.

Prevention and control

Measures regarding the ill: discovery and, depending on the clinical-epidemiological context, isolation at the infectious disease clinic — hospitalisation being **compulsory whenever botulism is suspected**; the numerical declaration of the cases. The epidemiological investigation of the focus aims to identify the contaminated food, its origin, the method of contamination and the complete list of consumers; the incriminated food is withdrawn from human consumption; pathological samples are taken from the ill (faeces, vomited fluid, haemocultures), together with food and environmental samples, in order to determine the aetiology.

The measures regarding the transmission route are condensed in the **ten golden rules for proper food preparation** (WHO):

1. choosing properly processed foods;
2. the complete (thorough) cooking of the food;
3. the consumption of the food immediately after preparation;
4. the proper storage of prepared food;
5. the full reheating of prepared food;
6. avoiding any contact between raw foods and prepared food;
7. repeated hand washing;
8. maintaining meticulous cleanliness in the kitchen;
9. protecting food against the access of insects, rodents and other animals;
10. using only drinking water for the preparation of food.

15.6. The digestive-entry infections today

Cholera: a global upsurge. After a decade of relative decline, cholera returned from 2021 as one of the principal emergencies of international public health. More than **600,000 cases of cholera or acute watery diarrhoea and nearly 7,600 deaths were reported to WHO from 33 countries in 2024**, figures that the organisation itself describes as substantial underestimates; reported cases began to decline in 2025, but **deaths continued to rise** over the same period [1] — the signature of epidemics occurring where treatment cannot be reached, since a disease whose fatality falls below 1% with rehydration alone should not kill.

The vaccine supply, which collapsed in 2022–2023 to the point where the global stockpile was emptied and the standard two-dose schedule had to be reduced to a single dose, has since recovered: annual production of oral cholera vaccine doubled from about 35 million doses in 2022 to nearly 70 million in 2025, permitting the resumption of **preventive** campaigns alongside reactive ones, with an initial allocation of 20 million doses to Mozambique, the Democratic Republic of the Congo and Bangladesh. The one-dose strategy remains standard for outbreak response — one dose protecting for at least six months, two doses for about three years — with two doses considered case by case [1]. The doctrine of Section 15.1 is unaltered: vaccination is a complement to water, sanitation and case management, never a substitute for them.

Typhoid fever and the conjugate vaccines. The escalation of antimicrobial resistance described in Box 15.2 — culminating in the extensively drug-resistant clone reported from Pakistan since 2016 — has changed the balance of prevention decisively in favour of vaccination. The **typhoid conjugate vaccines (TCV)**, WHO-prequalified since 2018, are immunogenic from six months of age, provide durable protection [2], and have been introduced through routine programmes and campaigns in several of the highest-burden countries, with

cluster-randomised trials in Nepal, Malawi and Bangladesh demonstrating efficacy of the order of 80%. The classical measures of Section 15.2 — water, food hygiene, the detection and management of chronic carriers — remain the foundation.

Bacterial dysentery. *Shigella* has moved onto the WHO priority pathogen list: multidrug-resistant and extensively drug-resistant strains, including azithromycin- and ciprofloxacin-resistant *S. sonnei*, have spread internationally, notably in outbreaks among men who have sex with men in high-income countries — an epidemiologically instructive reminder that a classical faecal–oral pathogen can find new transmission networks in populations with excellent sanitation. No vaccine is yet licensed; several conjugate candidates are in clinical development under WHO priority.

Poliomyelitis: the last mile. The eradication programme has approached, without yet reaching, its objective [3]. Wild poliovirus type 1 caused **99 cases in 2024 and 40 cases in 2025** (31 in Pakistan, 9 in Afghanistan), with no cases reported in the first months of 2026; environmental surveillance detected 673 wild-virus-positive samples in 2025, indicating that transmission continues even where paralytic cases are not detected [4]. The other half of the problem is vaccine-derived: **202 cases of circulating vaccine-derived poliovirus in 27 countries in 2025** (192 of them type 2), with Nigeria, Ethiopia and Yemen most affected, and new outbreaks in Lao PDR and Namibia. The novel oral poliovirus vaccine type 2 (**nOPV2**), of which more than two billion doses have been administered since 2021, has demonstrated substantially greater genetic stability and a lower risk of reversion than Sabin OPV2 [4]. Poliomyelitis has remained a Public Health Emergency of International Concern since 2014; the Director-General determined in March 2026 that it continues to constitute one [4]. For a country such as Romania, certified polio-free and using IPV exclusively, the operative obligations are the maintenance of high coverage, sensitive surveillance for acute flaccid paralysis, and environmental surveillance — because importation remains possible for as long as any transmission persists anywhere.

Food-borne disease. WHO's global estimates attribute some 600 million illnesses and 420,000 deaths a year to unsafe food, with 30% of the deaths in children under five [5]. In the European Union, the annual "One Health" zoonoses report of EFSA and ECDC consistently identifies campylobacteriosis as the most frequently reported zoonosis and salmonellosis as the most frequent cause of food-borne outbreaks [6], with *Listeria monocytogenes* — rare but with a case fatality of the order of 13–20% — responsible for the most severe outcomes, particularly in pregnancy, the elderly and the immunosuppressed. The investigative method has been transformed by **whole-genome sequencing**, which allows the recognition of geographically dispersed outbreaks caused by a single contaminated ingredient — outbreaks invisible to the classical investigation of a common meal, and detectable only by international comparison of sequences.

15.7. The viral and bacterial gastroenteritides of everyday practice

The classical chapter is built around the great historical diseases of the faecal–oral route. In daily European practice, however, the digestive-entry infections that the physician actually meets are four, and their epidemiology deserves to be stated explicitly.

Rotavirus was, before vaccination, the leading cause of severe dehydrating gastroenteritis in children under five worldwide, responsible for a very large share of paediatric hospitalisations and, in low-income settings, for a substantial number of deaths. The source is the infected child, who excretes enormous quantities of virus; transmission is faecal–oral with a very low infecting dose, and the virus is resistant on surfaces, which makes nosocomial and day-care transmission characteristic. Two **live attenuated oral vaccines**, administered in the first months of life, have reduced hospitalisations for rotavirus gastroenteritis by 70–90% in the countries that introduced them, with demonstrable herd protection of unvaccinated older children; a small excess risk of intussusception (of the order of one to six cases per 100,000 vaccinees) is accepted as far outweighed by the benefit. Rotavirus vaccination is recommended by WHO for all national programmes [7].

Norovirus has, in countries with rotavirus vaccination, become the leading cause of epidemic gastroenteritis at all ages [8]. Its epidemiological properties are extreme and worth memorising: an infecting dose of a few tens of viral particles; excretion in vomit as well as in faeces, with **airborne dispersion of aerosolised vomit**; environmental persistence and resistance to alcohol-based hand rub; and short-lived, strain-specific immunity. Together these explain the explosive outbreaks in hospitals, care homes, schools and cruise ships, and they dictate the control measures: exclusion of ill staff until 48 hours after symptoms cease, hand **washing** with soap and water rather than alcohol rub, cleaning with hypochlorite, and cohorting or ward closure. No vaccine is licensed.

Campylobacter is the most frequently reported zoonotic gastrointestinal infection in the European Union [6]. The reservoir is poultry above all; transmission occurs through undercooked meat and, importantly, through cross-contamination in the kitchen — raw chicken to work surface to salad. The infecting dose is low. Beyond the acute enteritis, its importance lies in the sequelae: reactive arthritis and **Guillain–Barré syndrome**, of which *C. jejuni* infection is the most frequently identified antecedent [9]. Prevention is a food-chain problem — reduction of colonisation in flocks, hygiene at slaughter, and the domestic rules of Section 15.5.

Listeria monocytogenes is rare but carries a case fatality of the order of 13–20%, the highest of the common food-borne pathogens [10]. It multiplies at refrigeration temperatures — the property that distinguishes it from all the others in this chapter — and is associated with ready-to-eat foods with long shelf lives: soft cheeses, smoked fish, pâté, pre-packed salads. The groups at risk are pregnant women (in whom infection is often mild but may cause fetal loss, stillbirth or neonatal sepsis), the elderly and the immunosuppressed, and the specific preventive

advice given to them is one of the few instances in which food restriction is genuinely evidence-based. Because the incubation may extend to several weeks, outbreak investigation depends entirely on molecular typing of isolates.

A note on the practical management of acute diarrhoea, which unites all of these: the decisive intervention is **oral rehydration**, the single measure that has saved the greatest number of children's lives in the history of public health; antibiotics are unnecessary in the great majority of cases, contribute to resistance, and in Shiga-toxin-producing *E. coli* infection may increase the risk of haemolytic-uraemic syndrome. Zinc supplementation reduces duration and severity in children in low-resource settings. The epidemiological duty accompanying the clinical one is to consider, in every case, whether the patient belongs to a risk occupation (food handling, childcare, health care, water supply), whether other cases exist, and whether the case must be notified.

References

1. World Health Organization. Preventive cholera vaccination resumes as global supply reaches critical milestone. Geneva: WHO; 4 February 2026; and Multi-country outbreak of cholera, external situation reports, 2025.
2. World Health Organization. Typhoid vaccines: WHO position paper. *Weekly Epidemiological Record*. 2018;93:153–172.
3. Global Polio Eradication Initiative. Polio this week; strategy 2022–2029. Geneva: GPEI.
4. World Health Organization. Statement of the forty-fourth meeting of the Polio IHR Emergency Committee. Geneva: WHO; 4 March 2026.
5. World Health Organization. *WHO estimates of the global burden of foodborne diseases*. Geneva: WHO; 2015.
6. European Food Safety Authority and European Centre for Disease Prevention and Control. The European Union One Health Zoonoses Report. *EFSA Journal* (annual).
7. World Health Organization. Rotavirus vaccines: WHO position paper. *Weekly Epidemiological Record*. 2021;96:301–320.
8. Ahmed SM, Hall AJ, Robinson AE, et al. Global prevalence of norovirus in cases of gastroenteritis: a systematic review and meta-analysis. *The Lancet Infectious Diseases*. 2014. doi:10.1016/S1473-3099(14)70767-4
9. Kaakoush NO, Castaño-Rodríguez N, Mitchell HM, Man SM. Global epidemiology of *Campylobacter* infection. *Clinical Microbiology Reviews*. 2015. doi:10.1128/CMR.00006-15
10. World Health Organization. *Listeriosis* — fact sheet; and *WHO estimates of the global burden of foodborne diseases*. Geneva: WHO.

Chapter 16. Infections with a Tegumentary Entry: Tetanus

16.1. Definition and importance

Tetanus is an acute infectious disease with a severe evolution, determined by the exotoxin produced in anaerobiosis by *Clostridium tetani*, and manifested clinically by the tonic spasm of the skeletal muscles, paroxysmal spasm fits and neurovegetative disorders [1]. In the architecture of this course it stands as the model of the **tegumentary-entry infection**: no source in the classical sense, no interhuman transmission, no herd immunity — everything in its epidemiology is individual: the wound and the vaccination status.

The prognosis of the disease is reserved. Fatality is high — 30–40% — and is influenced by age, by the duration of incubation, by the severity of the symptoms and by the earliness of the therapeutic intervention. **Neonatal tetanus** is a particularly severe clinical form, with a fatality of 50–90%, having the infected umbilical wound as its entry; it occurs in the absence of asepsis at birth, in newborns whose mothers have not received ATPA (adsorbed purified tetanus toxoid) prophylaxis during pregnancy — and it remains, in the poorest regions of the world, one of the preventable tragedies that the WHO maternal and neonatal tetanus elimination programme has come close to abolishing.

16.2. The aetiological agent

Clostridium tetani in its **vegetative form** is sensitive to heat and cannot survive in the presence of oxygen. Its **spores**, by contrast, have a high resistance in the external environment — dust, soil, animal faeces, surfaces — under conditions of dryness and temperature variation and sheltered from light they can survive for years. The spores resist the common antiseptics, alcohol and boiling, and are destroyed by autoclaving for 15–20 minutes and by the oxidising disinfectants — hydrogen peroxide, potassium permanganate — within a few minutes. The germ is sensitive to penicillin, tetracycline and erythromycin, and resistant to the aminoglycosides.

Clinically, the diagnosis is made on clinical grounds and by the exclusion of other causes; the incubation is of 3–30 days, the short incubations being associated with intensely contaminated wounds, severe forms and a serious prognosis.

16.3. The epidemiological process

The natural reservoir of infection is represented by the herbivores — horses, sheep, cattle — and by other domestic animals and birds, which host the tetanus bacilli in their intestine and eliminate them in large quantities into the external environment through their faeces. Through the surface waters, the bacilli reach again the digestive tract of the animals, completing the

natural circulation of the germ; the soil thus remains permanently seeded with spores, and tetanus permanently non-eradicable.

Transmission occurs through the contact of tegumentary or mucosal wounds with the soil, the dust or the objects contaminated with tetanus bacilli or spores. The tetanic risk is real when **two conditions** are cumulatively fulfilled: the contamination of the wound, and the existence of anaerobiosis conditions at the level of the wound. The disease is **not transmitted from human to human**.

The **tetanigenic (tetanic-potential) wounds** must be known by every physician, because their recognition triggers the prophylactic conduct:

- wounds pierced with splinters, thorns or nails — even after the apparent closing of the wound;
- animal-bite wounds;
- wounds with retained foreign bodies;
- wounds with deep, irregular margins and devitalised tissue;
- the wounds of traffic accidents;
- open fractures;
- empirical abortion;
- second- and third-degree burns;
- chronically infected varicose ulcers;
- wounds soiled with soil or street dust;
- the puncture wounds of parenteral drug administration;
- umbilical wounds produced in the absence of asepsis;
- very rarely — surgical sutures and contaminated hospital instruments.

The receptive population. Receptivity is general, but it is decisively modelled by the anti-tetanus vaccination, which induces a solid and durable humoral immune response. The individual risk depends on the coexistence of the tetanigenic wound with the absence of specific immunity. A feature of capital importance: **the immunity after the disease is weak or absent** — the quantity of toxin sufficient to kill is smaller than the quantity needed to immunise — which is why the convalescent must be actively immunised with ATPA, and relapses are possible. Transplacental immunity exists if the pregnant woman is immunised; the newborns of non-immunised mothers are receptive from the first day of life — the whole rationale of the antenatal ATPA prophylaxis.

The favouring factors. The warm season favours injuries, especially in rural areas. The economic and social factors intervene through: deficiencies in the vaccination programme; the neglect of tetanigenic wounds; late presentation to the doctor; empirical abortive practices; unqualified birth assistance in precarious hygiene conditions, with the faulty bandaging of the umbilical stump; the use of injectable drugs without asepsis; and the lack of sanitary education.

The manifestation of the epidemiological process. The disease is spread universally, with great differences depending on the application of the prophylactic measures. It is more frequent in the areas with a warm and moist climate and a soil rich in organic matter; in the temperate areas it is more frequent in the warm months. In the developed countries most cases occur in persons over 60 — the generations with remote or absent vaccination, in whom immunity has waned. In Romania, the annual incidence over the past decade has been of 0.1–0.2 per 100,000 inhabitants, more frequent among children and old people, following wounds of the lower limbs. The current manifestation is **sporadic** — the exemplary illustration of the sporadic form discussed in Chapter 6.

16.4. Prevention and control

Measures regarding the ill: discovery, with isolation at the infectious disease clinic and the application of the specific therapy; the nominal declaration of the confirmed cases, with operative information on the day of discovery. The epidemiological investigation aims to identify the vaccinal history and to perform serological tests regarding the level of anti-tetanus immunity in the territory where the case occurred, with the re-evaluation of the immune potential of the population and differentiated measures of mass vaccination — every case of tetanus being, by definition, a failure of the vaccination system, which must be audited.

Specific prophylaxis. Tetanus is the typical example of a disease that **cannot be eradicated but can be controlled up to elimination** through vaccination and through the proper care of the tetanigenic wound. The instrument is the vaccination with ATPA — today administered within the combined vaccines of the national programme (the paediatric hexavalent, followed by the dT/dTpa boosters), with periodic boosters in the adult, and with the antenatal doses that protect the newborn.

The preventive conduct in the case of a tetanigenic wound comprises, in obligatory sequence:

1. **the surgical sterilisation of the wound** — large debridement, the elimination of foreign bodies, the excision of the devitalised tissue, haemostasis; the wound is **not to be sutured** (suture would recreate the anaerobiosis that the toilet has just abolished);
2. **the antisepsis of the wound** — hydrogen peroxide 3%, cetrimonium bromide 1% — the oxidising antiseptics being chosen precisely against an anaerobe;
3. **antibiotic therapy** — penicillin 1,200,000 U/day or erythromycin 2 g/day, for 10 days;
4. **post-exposure anti-tetanus immunoprophylaxis**, differentiated by the vaccinal history:
   - **persons with a proper vaccination history**: one dose of 0.5 ml ATPA, intramuscularly, in the deltoid; in the case of severe multiple trauma with massive blood loss, passive immunoprophylaxis is added — 3,000–15,000 IU of anti-tetanus serum, or 200–500 IU of specific anti-tetanus immunoglobulins;

- **non-vaccinated persons or persons with an unknown vaccinal history**: anti-tetanus serum 3,000–15,000 IU (after desensitisation) or specific anti-tetanus immunoglobulins 200–500 IU, **plus** accelerated active vaccination with 3 doses of 0.5 ml ATPA, intramuscularly, at 14-day intervals — the passive component covering the immediate danger, the active one building the durable protection;
- in the case of superficial, clean wounds, the anti-tetanus vaccination alone is administered.

The association, on the same occasion but at different sites, of the passive and the active immunisation is the model — already met in hepatitis B and rabies — of the modern post-exposure prophylaxis; and the systematic verification of the tetanus vaccination status at *every* medical contact for a wound remains one of the simplest and most efficient reflexes of preventive medicine.

16.5. Tetanus and the other tegumentary-entry infections today

Tetanus: global situation. Tetanus remains the model of a disease that cannot be eradicated but can be reduced to sporadic occurrence, and the global figures show how far that reduction has gone. **Maternal and neonatal tetanus elimination** — defined as fewer than one case of neonatal tetanus per 1,000 live births in every district — has been validated in the great majority of the countries that had not achieved it in 1999, when the initiative began; the deaths from neonatal tetanus, once numbered in the hundreds of thousands annually, have fallen by more than 90% [2]. The instruments were exactly those set out in Section 16.4: maternal immunisation with tetanus toxoid during pregnancy, clean delivery and clean cord care, and supplementary immunisation in high-risk districts.

In the countries with mature immunisation programmes, tetanus has become a disease of the **elderly and of the incompletely immunised** [3], because antitoxic immunity wanes and because the cohorts vaccinated before the programmes were universal are now old. The Romanian incidence quoted in the classical text — 0.1–0.2 per 100,000 — corresponds to this pattern, and the practical consequence for the clinician is unchanged and worth repeating: **the vaccination status must be verified at every consultation for a wound**, and the decennial adult booster is the measure that keeps the disease sporadic [4].

Rabies: the tegumentary-entry infection with the highest case fatality. Although not developed in the original course, rabies belongs in this chapter as the other classical infection acquired through the skin. It kills an estimated 59,000 people a year, almost all in Asia and Africa, and about 40% of them children under 15; dog-mediated rabies is the source of over 99% of human cases [5]. The disease is, once symptomatic, essentially always fatal — and entirely preventable. The **post-exposure prophylaxis** is the exact analogue of the tetanus protocol taught in Section 16.4: immediate and thorough washing of the wound with soap and water for 15 minutes, infiltration of rabies immunoglobulin into and around the wound in category III exposures, and a course of modern cell-culture vaccine. The "Zero by 30" strategy

of WHO, FAO and WOAH — the elimination of dog-mediated human rabies by 2030 — rests on mass canine vaccination, which is the One Health intervention that removes the source rather than treating the exposed.

Gas gangrene and the other clostridial infections share with tetanus the ecology described in Section 16.3: sporulated anaerobes ubiquitous in soil and in animal faeces, requiring devitalised tissue and anaerobiosis. Their prevention is the same surgical doctrine — debridement, removal of foreign bodies, no primary closure of contaminated wounds — and the reason why that doctrine is taught in a course of epidemiology is that it is prevention, not treatment.

Injecting drug use as a modern tegumentary route. The classical list of tetanigenic wounds includes "wounds pierced for the parenteral administration of drugs", and this route has acquired renewed importance: outbreaks of wound botulism, tetanus and severe soft-tissue infection among people who inject drugs have been reported repeatedly in Europe, alongside the blood-borne viruses of Chapters 12 and 14. Harm-reduction services — sterile equipment, wound care, vaccination against tetanus and hepatitis A and B — are the epidemiologically effective response, and they illustrate a general principle of this book: the transmission route is interrupted where people actually are, not where the health system would prefer them to be.

References

1. Heymann DL (ed.). *Control of Communicable Diseases Manual*. 21st ed. APHA; 2022.
2. World Health Organization/UNICEF. Maternal and neonatal tetanus elimination (MNTE) — progress reports. Geneva; 2024.
3. European Centre for Disease Prevention and Control. Tetanus — annual epidemiological report. Stockholm: ECDC.
4. World Health Organization. Tetanus vaccines: WHO position paper. *Weekly Epidemiological Record*. 2017;92:53–76.
5. World Health Organization. Rabies vaccines: WHO position paper. *Weekly Epidemiological Record*. 2018;93:201–220; and *Zero by 30: the global strategic plan to end human deaths from dog-mediated rabies by 2030*. Geneva: WHO/FAO/WOAH/GARC; 2018.

Chapter 17. COVID-19 and the Lessons of the Pandemic

17.1. Why COVID-19 belongs in a textbook of epidemiology

No event of the past century has illustrated the concepts of general epidemiology as completely, or as publicly, as the COVID-19 pandemic. Within three years, terms that had been the private vocabulary of this discipline — incubation period, basic reproduction number, herd immunity, excess mortality, case-fatality, non-pharmaceutical interventions — became the daily language of governments and of the press. For the student, the pandemic is therefore not merely one more disease to learn, but the most extensive natural demonstration available of everything contained in Parts I and II of this book.

17.2. The aetiological agent and its variability

SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is an enveloped, positive-sense single-stranded RNA virus of the family *Coronaviridae*, subgenus *Sarbecovirus*, closely related to bat coronaviruses and to SARS-CoV of 2003. Entry into the host cell occurs through the binding of the **spike (S) protein** to the ACE2 receptor, with priming by the cellular protease TMPRSS2 — the molecular reason for the tropism of the virus for the respiratory epithelium and the vascular endothelium.

Being an RNA virus, SARS-CoV-2 evolves continuously; unlike influenza, it does not possess a segmented genome and cannot undergo reassortment, so its variability proceeds by the accumulation of mutations and by recombination. WHO designated successive **variants of concern** — Alpha, Beta, Gamma, Delta and, from November 2021, **Omicron**, whose descendant lineages have dominated global circulation ever since [1]. Three properties changed measurably across this succession: transmissibility (the effective reproduction number rose from an ancestral R□ of about 2.5–3 to substantially higher values for Omicron sublineages), immune escape (progressive, and the reason for vaccine reformulation), and intrinsic severity (lower for Omicron, on a background of accumulated population immunity). The evolution of the virus is now followed by genomic surveillance networks that share sequences in near-real time — the largest exercise of pathogen genomics in history, and one of the durable methodological legacies of the pandemic.

17.3. The epidemiological process

The source of infection is the infected person, whether symptomatic, presymptomatic or asymptomatic. Two features determined the epidemiological behaviour of the disease and defeated the classical containment strategies: **substantial presymptomatic transmission**, with infectiousness beginning about two days before symptom onset and peaking around the onset, and a large share of **asymptomatic infections**. Together, these mean that isolating only the symptomatic can never interrupt transmission — the reason for testing of contacts, for mass testing strategies, and for population-wide measures. No animal reservoir maintains human

transmission, although the virus infects a wide range of mammals (mink, deer, hamsters, cats), with documented back-transmission from mink farms and a permanent theoretical risk of the establishment of animal reservoirs.

Transmission is airborne, through the whole spectrum of respiratory particles described in Chapter 3: at short range by droplets projected onto the mucosae, and at longer range by aerosols accumulating in closed, crowded and poorly ventilated spaces. Contact transmission via contaminated surfaces, feared in the first months and responsible for a vast expenditure on surface disinfection, proved to be of minor importance. The recognition of aerosol transmission — resisted for a considerable time by official guidance — was one of the principal scientific controversies of the pandemic, and it changed the hierarchy of protective measures towards ventilation, air filtration and well-fitting respirators.

A defining epidemiological feature was **overdispersion**: transmission was highly heterogeneous, with a minority of infected persons (of the order of 10–20%) producing the majority of secondary cases in **superspreading events**, typically in indoor gatherings. Overdispersion has a practical corollary of general value: where transmission is concentrated in events rather than distributed evenly, backward contact tracing (searching for the source that infected the case, and thus for the cluster) is more efficient than forward tracing alone.

The receptive population was, at the outset, the whole of humanity — the textbook situation of a new agent in an immunologically naive population, and therefore of a pandemic. Susceptibility to infection was general; susceptibility to *severe* disease was strongly graded by **age**, rising steeply after 60, and by comorbidity: obesity, diabetes, hypertension and cardiovascular disease, chronic respiratory and renal disease, immunosuppression, and pregnancy. The interaction between the pandemic and the epidemic of chronic non-communicable diseases (Part IV) was one of its cruellest features: the populations with the highest burden of chronic disease paid the highest price, and social deprivation multiplied every risk — through exposure at work, crowded housing and reduced access to care.

17.4. The manifestation of the epidemiological process

Declared a Public Health Emergency of International Concern on 30 January 2020 and characterised as a pandemic on 11 March 2020, COVID-19 evolved in successive waves shaped by the interplay of variants, immunity and control measures, until the emergency was declared over on 5 May 2023 [2] — the disease passing, as pandemic agents do, into endemic circulation with seasonal recrudescence. WHO surveillance continues: in the four weeks to 26 July 2026, 55 countries reported some 34,000 new cases and 33 countries 164 deaths, with a test positivity of 3.4% — figures which the organisation itself cautions are a large underestimate, since testing and reporting have contracted worldwide [3].

The true toll must be measured by **excess mortality**, for the reasons given in Chapter 7. WHO estimated **14.9 million excess deaths** associated with the pandemic in 2020 and 2021 [4]; the

independent GBD analysis produced a still higher estimate for the same period [5]. Against about 7 million deaths officially reported as due to COVID-19 in that interval, the comparison is the most eloquent single argument for excess mortality as the reference indicator of a crisis.

Post-COVID-19 condition (long COVID) is the durable morbidity left by the pandemic: persistent symptoms — fatigue, dyspnoea, cognitive impairment ("brain fog"), autonomic dysfunction — lasting beyond three months and not explained by an alternative diagnosis. Prevalence estimates vary enormously with the definition, the population and the design; an updated systematic review and meta-analysis of 144 contributing studies and over two million infected individuals estimated a pooled prevalence of about 36%, with respiratory, fatigue, psychological, neurological and dermatological subtypes, and identified as the principal risk factors being unvaccinated (OR 2.09), infection in the pre-Omicron period (OR 1.74) and female sex (OR 1.56) [6]. Whatever the exact figure — and the heterogeneity is a caution in itself — the burden is large enough to constitute a chronic disease problem generated by an infectious agent, and to justify dedicated services.

17.5. Prevention and control: what the pandemic taught

Non-pharmaceutical interventions. In the absence of vaccines and treatment, the classical measures of Part I were deployed on an unprecedented scale: case isolation and quarantine of contacts, testing and tracing, masks, distancing, restrictions on gatherings, school and workplace closure, travel measures and, at the extreme, general confinement. Their effectiveness was real but unequal, and their costs — educational, economic, psychological, and in delayed care for other diseases — were themselves public health harms. The mature judgement, now widely shared, is that the early, layered and time-limited use of the less costly measures (ventilation, masks in high-risk settings, rapid testing, protection of institutions for the elderly) achieves most of the benefit, whereas prolonged general closures have decreasing returns and increasing harms. This is not a retrospective condemnation of decisions taken under uncertainty; it is the epidemiological lesson to be applied next time.

Vaccines. The development of effective vaccines within a year of the identification of the agent — building on two decades of research into mRNA platforms and viral vectors — was the greatest single scientific achievement of the response. The mRNA vaccines showed efficacies of about 95% against symptomatic disease in their pivotal trials, and the vaccines as a whole retained substantial and durable effectiveness against severe disease and death even as immune escape eroded protection against infection. Modelling studies estimate that vaccination averted millions of deaths in the first year alone. The pandemic also demonstrated the counterpart: **vaccine inequity** between rich and poor countries, which the COVAX facility mitigated but did not solve, and which is the principal reason for the equity provisions of the Pandemic Agreement discussed in Chapter 10.

Treatment. The great therapeutic lesson was methodological. In a field flooded with observational claims and enthusiasm for repurposed drugs, only the large randomised platform

trials produced reliable answers: dexamethasone reduced mortality in patients requiring oxygen or ventilation, while hydroxychloroquine and several other candidates were shown to be useless. That contrast — between rapid, pragmatic randomisation and the accumulation of uncontrolled series — is the applied form of Chapter 8, and the single most transferable lesson of the pandemic for clinical practice.

Infodemic and trust. WHO gave currency to the term **infodemic** for the overabundance of information, accurate and inaccurate, that accompanied the pandemic. Misinformation about the origin of the virus, about treatments and about vaccines measurably reduced adherence to protective measures and vaccine uptake, and it has left a durable deposit of vaccine hesitancy that is now visible in the measles epidemics of Europe. Communication, transparency about uncertainty, and the maintenance of public trust are therefore not adjuncts to epidemic control but core components of it.

References

1. World Health Organization. WHO COVID-19 epidemiological updates and variant risk evaluations. Geneva: WHO; 2024–2026.
2. World Health Organization. Statement on the fifteenth meeting of the IHR (2005) Emergency Committee regarding the COVID-19 pandemic. Geneva: WHO; 5 May 2023.
3. World Health Organization. COVID-19 dashboard: global situation summary, data to 26 July 2026. Geneva: WHO; 2026.
4. World Health Organization. 14.9 million excess deaths associated with the COVID-19 pandemic in 2020 and 2021. Geneva: WHO; 5 May 2022.
5. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21. *The Lancet*. 2022. doi:10.1016/S0140-6736(21)02796-3
6. Hou Y, Gu T, Ni Z, Shi X, Ranney ML, Mukherjee B. Global prevalence of long COVID, its subtypes, and risk factors: an updated systematic review and meta-analysis. *Open Forum Infectious Diseases*. 2025;12(9):ofaf533. doi:10.1093/ofid/ofaf533

Chapter 18. Vaccinology and Immunisation Programmes

18.1. The place of vaccination in preventive medicine

Vaccination is the specific active immunoprophylaxis defined in Chapter 1, and it is, after the provision of clean water, the intervention that has saved the greatest number of human lives. A systematic analysis conducted for the fiftieth anniversary of the Expanded Programme on Immunization estimated that vaccination has averted of the order of 150 million deaths over five decades, the great majority of them in children under five, and that measles vaccine alone accounts for a large share of that total [1]. The eradication of smallpox, the near-eradication of poliomyelitis and the disappearance of diphtheria from most of Europe are the visible monuments of this work; its paradox is that success renders it invisible, and that the diseases it prevents are forgotten faster than the fear of the vaccines themselves.

18.2. Types of vaccine

Live attenuated vaccines contain organisms whose virulence has been reduced by passage or by genetic manipulation: MMR, varicella, BCG, oral poliovirus vaccine, yellow fever, rotavirus, live attenuated influenza vaccine. They reproduce the natural infection in miniature, inducing strong humoral and cellular immunity, often after a single dose and for a long duration; they may induce mucosal immunity, and — in the case of OPV — protect contacts by secondary spread. Their disadvantages follow from the same property: they are contraindicated in significant immunosuppression and, as a rule, in pregnancy; they require a strict cold chain; and, exceptionally, they may revert (the vaccine-derived polioviruses of Chapter 15).

Inactivated (killed) vaccines contain whole organisms killed by heat or chemicals: inactivated poliovirus vaccine, hepatitis A, rabies, most influenza vaccines. They are safe in the immunosuppressed, but induce weaker, mainly humoral immunity and require several doses and boosters, usually with an adjuvant.

Subunit, toxoid and polysaccharide vaccines contain purified components: the tetanus and diphtheria **toxoids** (formaldehyde-inactivated exotoxins, which induce antitoxic immunity); acellular pertussis components; the recombinant **hepatitis B surface antigen**; the **HPV** virus-like particles; and the capsular **polysaccharides** of pneumococcus, meningococcus and *Haemophilus influenzae* type b.

Conjugate vaccines solved the great limitation of pure polysaccharides — their T-cell independence, and hence their poor immunogenicity under two years of age and their inability to induce memory — by covalently linking the polysaccharide to a carrier protein. The result was one of the most consequential advances of modern vaccinology: conjugate vaccines against *Haemophilus influenzae* type b, pneumococcus and meningococcus are immunogenic

in infants, induce durable memory and, decisively, **reduce nasopharyngeal carriage**, thereby protecting the unvaccinated through herd protection [2].

Viral vector and nucleic acid vaccines are the newest platforms. Replication-deficient adenoviral vectors (used for Ebola and for some COVID-19 vaccines) and **mRNA vaccines** encapsulated in lipid nanoparticles moved from experimental status to global deployment during the COVID-19 pandemic. Their significance for the future lies in the speed of design — a new sequence can be inserted within weeks — which makes them the most promising platform for responding to a novel pandemic agent, and which is being explored for influenza, RSV and oncological applications.

Passive immunisation — normal and specific immunoglobulins, and now monoclonal antibodies (nirsevimab against RSV in infants being the outstanding recent example) — provides immediate but transient protection, and is used for post-exposure prophylaxis and for the protection of persons who cannot be vaccinated.

18.3. Immunisation schedules and the Romanian National Immunisation Programme

An immunisation schedule is a compromise between three constraints: administering the vaccine **before** the age of maximum risk; **after** the interference of maternal antibodies has sufficiently declined; and at moments when the child is in any case in contact with the health services. The **primary series** in infancy is followed by **boosters** that consolidate and prolong immunity.

The Romanian National Immunisation Programme provides, free of charge, vaccination against tuberculosis (BCG, in the maternity), hepatitis B (first dose in the first 24 hours of life), diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenzae* type b (hexavalent vaccine at 2, 4 and 11 months), pneumococcal conjugate vaccine, measles–mumps–rubella (at 12 months and 5 years), with boosters of DTPa-IPV at 6 years and dTpa at 14 years; HPV vaccination is offered to girls and boys in the target age groups, and influenza vaccination to risk groups. The schedule is periodically updated by order of the Ministry of Health, and the practitioner must always verify the version in force [3].

Practical rules that every clinician should know: (a) simultaneous administration of several vaccines at different sites is safe and does not diminish the response; (b) an interrupted schedule is resumed, never restarted from the beginning — "the dose counts, whenever it was given"; (c) the genuine contraindications are few — anaphylaxis to a previous dose or to a component, and significant immunosuppression or pregnancy for live vaccines; (d) a mild intercurrent illness, with or without low fever, antibiotic treatment, prematurity, breastfeeding and a family history of adverse events are **false contraindications**, and each missed opportunity to vaccinate is an epidemiological loss.

The cold chain — the maintenance of the vaccine between +2 °C and +8 °C from manufacture to administration — is the invisible infrastructure on which the whole programme rests. Freezing damages adsorbed vaccines (DTP, hepatitis B) as surely as heat damages live ones; vaccine vial monitors, continuous temperature recording and documented procedures for cold-chain breaks are therefore integral parts of quality assurance.

18.4. Vaccine safety and adverse events

Public confidence depends on the rigour with which safety is monitored and communicated. **Adverse events following immunisation (AEFI)** are classified by cause into: reactions to the vaccine product; reactions to a defect in quality; **immunisation error-related** reactions (wrong dose, wrong route, contaminated multidose vial) — historically the largest preventable category; immunisation **anxiety-related** reactions (vasovagal syncope in adolescents); and **coincidental** events, which occur after vaccination but are caused by something else. The distinction between the last category and true adverse reactions is the central task of causality assessment, and the reason why surveillance requires background incidence rates for comparison.

Common reactions — local pain and erythema, fever, malaise — are frequent and self-limited. Serious adverse reactions are rare and quantified: anaphylaxis of the order of one per million doses; intussusception after rotavirus vaccine at an excess of a few cases per 100,000 vaccinees; myocarditis after mRNA COVID-19 vaccines, predominantly in young males after the second dose, of the order of tens of cases per million and generally mild. In every case, the epidemiological judgement is a comparison: the risk of the vaccine against the risk of the disease it prevents — myocarditis, for instance, being substantially more frequent after SARS-CoV-2 infection than after vaccination.

Two historical episodes deserve to be known, because they shaped public perception permanently. The **1955 Cutter incident**, in which incompletely inactivated poliovirus vaccine caused paralytic poliomyelitis, created modern vaccine regulation. The **1998 publication in *The Lancet*** alleging a link between MMR and autism was based on twelve children, was shown to be fraudulent, was retracted in 2010, and its author was struck off the medical register; the association has since been refuted by cohort studies including millions of children — among them a Danish nationwide cohort of more than 650,000 children [4]. Yet the fall in MMR coverage that followed cost lives across Europe for two decades, which is the most complete demonstration available of the epidemiological weight of misinformation.

18.5. Vaccine hesitancy and confidence

Vaccine hesitancy — the delay in acceptance or the refusal of vaccines despite availability of services — was listed by WHO among the ten threats to global health, and it operates through the "three C" model: **complacency** (the disease is not perceived as a risk), **convenience** (access, cost, time, quality of the service), and **confidence** (in the vaccine, in the provider, in the

system). The determinants are context-specific, and the interventions that work are correspondingly specific: reminder and recall systems, reduction of practical barriers, presumptive rather than participatory announcement of vaccination by the clinician, dialogue-based interventions with the hesitant (never confrontation), engagement of community and religious leaders, and prompt, transparent correction of misinformation [5].

Romania offers a demonstration of the whole cycle. Falling coverage (Section 10.2 and Box 10.2) produced the largest measles epidemic since 1993; a response combining primary-care strengthening, training and local promotion raised first-dose coverage in children aged 12–24 months by about 20 percentage points nationally, and by 25 points in Timiș county, within months [6]. The determinant of coverage, in other words, was not the availability of vaccine but the functioning of, and the trust invested in, the primary-care service — a conclusion of general validity for every immunisation programme.

18.6. New and forthcoming vaccines

The past decade has been unusually productive, and the practitioner should be aware of the principal additions:

- **RSV**: maternal vaccination and the long-acting monoclonal antibody nirsevimab for infants, and recombinant vaccines for older adults, have transformed the prevention of a disease long considered unpreventable;
- **malaria**: the RTS,S/AS01 and R21/Matrix-M vaccines, recommended by WHO and being introduced across endemic Africa, are the first vaccines against a human parasitic disease;
- **dengue**, **Ebola** (rVSV-ZEBOV, used in ring vaccination) and **mpox** vaccines for outbreak response;
- **tuberculosis**: the candidate **M72/AS01E**, which showed about 50% efficacy against progression to pulmonary disease in a phase 2b trial [7], has entered phase 3 — the first realistic prospect of a vaccine superior to BCG in adults in a century;
- **HIV**: despite four decades of effort and repeated failures of efficacy trials, research continues, while long-acting pre-exposure prophylaxis (Chapter 12) provides in the meantime a biomedical prevention of high efficacy;
- **influenza**: broadly protective ("universal") vaccine candidates and mRNA platforms aim at ending the annual reformulation described in Chapter 11.

References

1. Shattock AJ, Johnson HC, Sim SY, et al. Contribution of vaccination to improved survival and health: modelling 50 years of the Expanded Programme on Immunization. *The Lancet*. 2024. doi:10.1016/S0140-6736(24)00850-X

2. Orenstein WA, Offit PA, Edwards KM, Plotkin SA (eds.). *Plotkin's Vaccines*. 8th ed. Elsevier; 2023.
3. Ministerul Sănătății, România. Programul Național de Vaccinare — calendarul național de vaccinare (versiunea în vigoare). Bucharest.
4. Hviid A, Hansen JV, Frisch M, Melbye M. Measles, mumps, rubella vaccination and autism: a nationwide cohort study. *Annals of Internal Medicine*. 2019. doi:10.7326/M18-2101
5. World Health Organization. Immunization Agenda 2030: a global strategy to leave no one behind. Geneva: WHO; 2020.
6. World Health Organization Regional Office for Europe. Romania increases vaccination coverage for measles, mumps and rubella. Copenhagen: WHO/Europe; 26 June 2026.
7. Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. *New England Journal of Medicine*. 2019. doi:10.1056/NEJMoa1909953

Chapter 19. Healthcare-Associated Infections

19.1. Definition and importance

A **healthcare-associated infection (HAI)**, formerly called nosocomial infection, is an infection acquired in connection with the provision of health care, absent and not incubating at the time of admission; conventionally, an infection appearing more than 48 hours after admission, more than 3 days after discharge, or within 30 days of a surgical procedure (one year in the case of an implant). The change of name is not cosmetic: it recognises that such infections are acquired not only in hospitals but also in long-term care facilities, in ambulatory surgery, in dialysis units and in home care.

HAI is the paradigmatic epidemiological problem of modern medicine, for three reasons. It is **frequent**: the European point prevalence survey conducted by ECDC in 2022–2023 estimated that **4.3 million patients acquire at least one healthcare-associated infection each year in EU/EEA hospitals** [1]. It is **serious**: HAIs prolong hospital stay, generate substantial costs, and cause a burden of disease in the European Union comparable to that of all the other communicable diseases under surveillance combined. And it is **partly preventable**: ECDC estimates that at least 20% — and for some infection types considerably more — could be prevented by sustained, multimodal infection prevention and control programmes [1].

Historically, HAI is where epidemiology began as an applied science: Semmelweis's demonstration of the transmission of puerperal fever on the hands of doctors (Chapter 1) is the founding act of both hospital hygiene and outbreak investigation.

19.2. The epidemiological process in the hospital

The general schema of Part I applies, with characteristic peculiarities.

Sources of infection. Two categories must be distinguished, with different implications. **Endogenous** infections — the majority — arise from the patient's own flora, translocated to a normally sterile site by a device or a procedure: the skin flora carried into the blood by a catheter, the intestinal flora reaching the urinary tract or the surgical wound. **Exogenous** infections come from other patients, from staff (hands, carriage), from the inanimate environment (water systems for *Legionella* and *Pseudomonas*, air for *Aspergillus* during building works) or from contaminated devices and solutions.

Transmission routes. The hands of healthcare workers are the principal vehicle, as they were in 1847. Contact transmission — direct and indirect via equipment and surfaces — dominates; droplet and airborne transmission matter for respiratory viruses, tuberculosis, measles and varicella; the common vehicle route (contaminated infusions, endoscopes, water) produces the most explosive outbreaks; and vector-borne transmission is negligible in modern hospitals.

The receptive population is the feature that distinguishes hospital epidemiology from all the rest: the hospital concentrates, by definition, the most susceptible individuals — the extremes of age, the immunosuppressed, the critically ill, the surgical, the burned — and then subjects them to procedures that breach every natural barrier described in Chapter 1. Every intravascular catheter, every urinary catheter, every endotracheal tube is an artificial transmission route created by medicine itself. This is why the **device-associated infection rate** (infections per 1,000 device-days) is the correct measure of hospital performance, rather than a crude rate per patient.

19.3. The main types and their prevention

The European survey found respiratory tract infections (including pneumonia and healthcare-associated COVID-19) to be the most frequent group — nearly one third of all HAIs — followed by urinary tract infections, surgical site infections, bloodstream infections and gastrointestinal infections, the last dominated by *Clostridioides difficile* [1].

Ventilator-associated and hospital-acquired pneumonia. Prevention: semi-recumbent positioning, sedation interruption and daily assessment of readiness to extubate, oral care with attention to oral hygiene, avoidance of unnecessary intubation (non-invasive ventilation where possible), and subglottic secretion drainage.

Catheter-associated urinary tract infection, the most common and the most preventable. The decisive measure is not a technique but a decision: **do not insert the catheter unless it is necessary, and remove it as soon as it is not** — supplemented by aseptic insertion, a closed drainage system kept below bladder level, and the avoidance of routine irrigation or antibiotic prophylaxis.

Surgical site infection. Prevention rests on a well-defined bundle: antibiotic prophylaxis administered within 60 minutes before incision and not prolonged after operation; hair removal with clippers, not razors, or not at all; skin preparation with alcoholic chlorhexidine; maintenance of normothermia and glycaemic control; and appropriate ventilation and discipline in the operating theatre [2]. The WHO Surgical Safety Checklist, whose introduction was associated with substantial reductions in complications and mortality in a multi-country study [3], embodies these steps in a form that survives the pressures of daily practice.

Central line-associated bloodstream infection (CLABSI). The demonstration that a simple five-element bundle — hand hygiene, full-barrier precautions at insertion, chlorhexidine skin antisepsis, avoidance of the femoral site, and daily review with prompt removal of unnecessary lines — could reduce infection rates to near zero and sustain the reduction, first shown in the Michigan Keystone ICU project [4], changed the way patient safety is understood: not as exhortation, but as the reliable implementation of a small number of evidence-based steps, measured continuously.

Infection with *Clostridioides difficile* is the archetype of the collateral damage of antibiotics: the disturbance of the intestinal microbiota permits the multiplication of a spore-forming anaerobe transmitted by the faecal–oral route in the hospital. Its control requires both antimicrobial stewardship (Chapter 20) and specific measures — contact precautions, **hand washing with soap and water rather than alcohol rub** (spores resist alcohol), and sporicidal environmental disinfection.

19.4. Prevention and control programmes

The infrastructure of infection prevention and control (IPC) is defined by the WHO core components [5]: an organised IPC programme with trained personnel; evidence-based guidelines and their implementation; education and training of all staff; **surveillance** of infections with feedback of the data to the clinical teams; multimodal implementation strategies; monitoring, audit and feedback of practice; adequate workload, staffing and bed occupancy; and a built environment with the materials and equipment that make correct practice possible.

Hand hygiene remains the central measure, and the "five moments" formalised by WHO — before touching a patient, before a clean/aseptic procedure, after body fluid exposure risk, after touching a patient, after touching patient surroundings — are the operational form of Semmelweis's discovery [6]. Alcohol-based hand rub, placed at the point of care, made compliance feasible for the first time; the persistent gap between observed and expected compliance remains one of the most studied problems in implementation science.

Standard precautions apply to every patient, whatever the diagnosis: hand hygiene, gloves, gown, mask and eye protection according to the anticipated exposure, safe injection practice, safe handling of sharps and of waste, and cleaning and disinfection of equipment and surfaces. **Transmission-based precautions** — contact, droplet, airborne — are added according to the pathogen. The invisible foundation of all of this is the correct **sterilisation** of instruments (autoclaving, with validation and documentation) and the correct classification of devices as critical, semi-critical or non-critical, which determines whether they must be sterilised, high-level disinfected, or cleaned.

Occupational protection closes the circle: immunisation of staff (hepatitis B, influenza, MMR, varicella, and COVID-19 where indicated), post-exposure prophylaxis protocols for HIV, hepatitis B and tuberculosis, and the reporting and analysis of every sharps injury.

Box 19.1. What the European survey shows about antibiotics in hospitals. In the 2022–2023 ECDC point prevalence survey, **35.5% of hospitalised patients were receiving at least one antimicrobial** on the survey day, up from 32.9% in 2016–2017 — approximately 390,000 patients on any given day in the EU/EEA — and **one in three microorganisms isolated from healthcare-associated infections was resistant** to the antibiotics that would normally be used against it [1]. The two figures belong together: antibiotic use in the hospital selects the resistant flora that then causes the next infections, and the control of healthcare-associated infection and the control of resistance (Chapter 20) are, in practice, one programme with two names.

References

1. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals, 2022–2023. Stockholm: ECDC; 2024. (Press release: "Each year, 4.3 million patients in hospitals in the EU/EEA are affected by healthcare-associated infections.")
2. World Health Organization. *Global guidelines for the prevention of surgical site infection*. 2nd ed. Geneva: WHO; 2018.
3. Haynes AB, Weiser TG, Berry WR, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. *New England Journal of Medicine*. 2009. doi:10.1056/NEJMsa0810119
4. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *New England Journal of Medicine*. 2006. doi:10.1056/NEJMoa061115
5. World Health Organization. *Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level*. Geneva: WHO; 2016.
6. World Health Organization. *WHO Guidelines on Hand Hygiene in Health Care*. Geneva: WHO; 2009.

Chapter 20. Antimicrobial Resistance

20.1. A slow pandemic

Antimicrobial resistance (AMR) is the capacity of microorganisms to survive exposure to antimicrobial agents that would previously have killed or inhibited them. It has been described as a "slow pandemic", and the description is apt: it advances without epidemic curves or emergency declarations, and yet its cumulative toll already exceeds that of the great communicable diseases.

The first global assessment produced by the **Global Research on Antimicrobial Resistance (GRAM) project**, published in *The Lancet* in 2024, estimated that in 2021 bacterial AMR was **directly attributable to more than 1.1 million deaths and associated with 4.71 million deaths** worldwide, and forecast, on current trends, **1.91 million attributable and 8.22 million associated deaths in 2050** — a cumulative **169 million AMR-associated deaths between 2025 and 2050** [1]. The same analysis revealed a striking divergence by age: between 1990 and 2021, AMR deaths in children under five **fell by more than half** — a success attributable largely to vaccination (notably conjugate pneumococcal vaccine, which reduced deaths from drug-resistant *Streptococcus pneumoniae* from about 158,000 to 35,100) and to improved child survival — while AMR-attributable deaths in adults over 70 **rose by 89%**. Resistance is thus increasingly a problem of ageing populations and of intensive health care. The leading resistant pathogens in 2021 were methicillin-resistant *Staphylococcus aureus* (about 130,000 attributable deaths) and the carbapenem-resistant Gram-negative bacteria (about 216,000 deaths) [1].

20.2. Mechanisms and epidemiology of resistance

Resistance may be **intrinsic** (a natural property of the species) or **acquired**, by chromosomal mutation or — epidemiologically far more important — by the **horizontal transfer** of mobile genetic elements: plasmids, transposons and integrons, carried by conjugation, transformation or transduction. Horizontal transfer explains why resistance can spread between species and genera, and why a resistance gene selected in animal husbandry can appear in a human pathogen.

The biochemical mechanisms are four: enzymatic inactivation of the drug (β-lactamases, including the extended-spectrum β-lactamases and the carbapenemases); modification of the target (altered penicillin-binding proteins in MRSA, ribosomal methylation, mutated DNA gyrase); reduced permeability and active efflux; and the bypass of the inhibited pathway.

The epidemiological driver is **selection pressure**. Every use of an antimicrobial — appropriate or not, in human medicine, in veterinary medicine, or as a growth promoter in animal production — confers an advantage on the resistant subpopulation. Three consequences follow, and they define the whole strategy of control: resistance is generated wherever antimicrobials

are used; it is transmitted like any other infectious trait, by the routes of Chapter 3, in hospitals, in the community, in food and in the environment; and it can therefore be contained only by acting simultaneously on use and on transmission, in human, animal and environmental settings — the **One Health** approach.

The WHO **priority pathogens list** focuses research and development on the organisms that matter most [2], headed by the carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacterales, and third-generation cephalosporin-resistant Enterobacterales; alongside them stand MRSA, vancomycin-resistant enterococci, drug-resistant *Salmonella*, *Shigella*, *Neisseria gonorrhoeae* (for which few therapeutic options remain), *Helicobacter pylori*, and multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis*.

The picture in Europe is monitored by the EARS-Net network of ECDC [3] and by the WHO **GLASS** system globally [4]. Two features of the European map are constant and instructive: a strong **north–south and west–east gradient**, with the lowest resistance in the Nordic and Baltic countries and the highest in the south-east — Romania among the most affected, particularly for carbapenem-resistant *Klebsiella pneumoniae* and *Acinetobacter* — and a close correlation of that gradient with national antibiotic consumption and with the intensity of infection prevention and control.

20.3. Resistance in the classical diseases of this book

Several chapters of Part III have already met the phenomenon, and the recapitulation makes the point better than any general statement:

- **Tuberculosis**: an estimated 390,000 people developed multidrug-resistant or rifampicin-resistant TB in 2024, of whom only about 42% were enrolled on treatment; treatment success for RR-TB has nevertheless improved to 71% with the newer all-oral regimens [5].
- **Typhoid fever**: the successive loss of chloramphenicol, then of the multidrug-resistance-era drugs, then of the fluoroquinolones, culminating in the **extensively drug-resistant (XDR)** clone described in Pakistan since 2016 — the reason for the introduction of typhoid conjugate vaccines (Chapter 15).
- **Influenza**: the adamantanes have been abandoned because of near-universal resistance of circulating A strains (Chapter 11).
- ***Neisseria gonorrhoeae***, ***Shigella***, ***Salmonella***, ***Helicobacter pylori***: progressive erosion of first-line options.
- **Hospital pathogens**: the carbapenem-resistant Gram-negatives of Chapter 19, for which treatment may require colistin or the newest β-lactam/β-lactamase inhibitor combinations.

20.4. Containment: what actually works

Antimicrobial stewardship is the organised effort to optimise antimicrobial use: prescribing only when a bacterial infection is probable; obtaining cultures before starting therapy; choosing the narrowest effective spectrum; using the correct dose and the shortest effective duration — the evidence of the past decade has consistently shown that shorter courses are equivalent to longer ones in most common infections; de-escalating on the basis of culture results; and switching from intravenous to oral therapy as soon as possible. Institutionally, stewardship requires a multidisciplinary team, local guidelines based on local resistance data, restriction or pre-authorisation of reserve agents, prospective audit with feedback, and measurement of consumption in defined daily doses. The WHO **AWaRe** classification — **Access, Watch, Reserve** — provides the practical framework, with the target that at least 70% of national antibiotic consumption should come from the Access group.

Infection prevention and control is the other half of the strategy: every infection prevented is an antibiotic course avoided and a transmission chain broken (Chapter 19).

Vaccination is an underappreciated instrument against resistance, and the GRAM data quantify it: conjugate pneumococcal vaccine reduced deaths from drug-resistant pneumococcus by a factor of four in children [1]; typhoid conjugate vaccine prevents infections that would otherwise require increasingly scarce antibiotics; influenza vaccination reduces the antibiotic prescriptions generated by viral illness and by secondary bacterial infection.

Diagnostics shorten the period of empirical therapy: rapid molecular tests, C-reactive protein and procalcitonin-guided decisions in primary care and intensive care, and rapid identification with susceptibility testing directly from blood cultures.

Action outside human medicine is indispensable: the European Union banned antibiotics as growth promoters in animal feed in 2006, and Regulation (EU) 2019/6 further restricted prophylactic and metaphylactic use and reserved certain critically important antimicrobials for human medicine [6]; environmental control of pharmaceutical manufacturing effluent and of wastewater completes the One Health picture.

Research and development must replenish a pipeline that market forces do not sustain — a new antibiotic, correctly used, is a drug held in reserve and therefore not sold — which is why "push" and "pull" incentives (subscription models, prizes, non-profit development partnerships such as GARDP) have become part of the policy discussion, alongside alternatives to antibiotics: bacteriophages, monoclonal antibodies, microbiome-based therapies and anti-virulence agents.

Governance. The Global Action Plan on AMR (2015) requires national action plans [2]; the United Nations General Assembly held high-level meetings on AMR in 2016 and 2024, the latter adopting a political declaration with quantified targets, including the reduction of the 4.95 million annual AMR-associated deaths by 10% by 2030 and the commitment that at least 70% of human antibiotic consumption should be from the Access group [7].

Box 20.1. What the clinician can do tomorrow morning. The great strategies above are made of small daily decisions, and the medical student should leave this chapter with a short list: do not prescribe an antibiotic for an upper respiratory infection that is almost certainly viral, and explain rather than prescribe; take the culture before the first dose; check the local antibiogram rather than habit; write the intended duration in the notes at the moment of prescription; review at 48–72 hours and de-escalate; remove the catheter and the line that are no longer needed; wash your hands; and vaccinate the patient in front of you. Nothing in the containment of resistance is more powerful than the aggregate of these decisions, and nothing else is available to the individual physician.

References

1. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050. *The Lancet*. 2024. doi:10.1016/S0140-6736(24)01867-1
2. World Health Organization. *Global action plan on antimicrobial resistance*. Geneva: WHO; 2015; and *WHO bacterial priority pathogens list, 2024*.
3. European Centre for Disease Prevention and Control. *Antimicrobial resistance in the EU/EEA (EARS-Net) — annual epidemiological report*. Stockholm: ECDC.
4. World Health Organization. *GLASS report: global antimicrobial resistance and use surveillance system*. Geneva: WHO.
5. World Health Organization. *Global tuberculosis report 2025*. Geneva: WHO; 2025.
6. Regulation (EU) 2019/6 of the European Parliament and of the Council on veterinary medicinal products.
7. United Nations General Assembly. Political declaration of the high-level meeting on antimicrobial resistance. New York: UN; 2024.

Chapter 21. Tuberculosis

21.1. Definition and importance

Tuberculosis is a chronic, granulomatous infectious disease caused by the *Mycobacterium tuberculosis* complex, transmitted by the airborne route, whose principal localisation is pulmonary but which may affect any organ. It occupies a special place in this book for three reasons: it is the infectious disease that has killed the greatest number of human beings in history; it is, after a brief interruption by COVID-19, again the leading single infectious cause of death worldwide; and its epidemiology illustrates, better than any other disease, the dependence of an infection upon social conditions.

The current figures, from the WHO global report, are these: **an estimated 10.7 million people fell ill with tuberculosis in 2024**, of whom 8.3 million were newly diagnosed and notified — the highest number ever recorded, reflecting improved case-finding as well as real burden; **1.23 million people died**, including 150,000 among people living with HIV; **1.2 million of those who fell ill were children and young adolescents**; and an estimated **390,000 developed multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB)**, of whom only about 42% were enrolled on treatment, although treatment success for RR-TB has risen to 71%. Funding remains the binding constraint: **US$ 5.9 billion was available in 2024 against the US$ 22 billion a year required**, a shortfall of some US$ 16 billion [1].

21.2. The aetiological agent

The *M. tuberculosis* complex comprises *M. tuberculosis* proper (the overwhelming majority of human disease), *M. bovis* (the source of the bovine tuberculosis that pasteurisation has largely eliminated from Europe, and from which BCG derives), *M. africanum* and others. The bacillus is:

- **acid-alcohol fast**, owing to the mycolic acids of a lipid-rich wall — the property on which the Ziehl–Neelsen and auramine stains depend;
- **strictly aerobic**, which explains its predilection for the well-ventilated apices of the lungs;
- **slow-growing**, with a generation time of 15–20 hours, which accounts for the long incubation, the chronic evolution, the six months of treatment, and the weeks required for culture;
- **resistant to desiccation and to many disinfectants**, surviving for long periods in dust and in the dark, but **rapidly killed by ultraviolet light and by direct sunlight** — the biological basis of the sanatorium era and of the modern emphasis on ventilation and natural light in waiting rooms and wards.

21.3. The epidemiological process

The source of infection is the person with **pulmonary or laryngeal tuberculosis whose sputum contains bacilli**, and above all the **smear-positive** patient, who is far more contagious than the smear-negative, culture-positive one. Extrapulmonary tuberculosis is, with rare exceptions (open abscesses, genitourinary disease), not contagious. Contagiousness falls rapidly — within about two weeks — after the start of effective treatment, which is the epidemiological argument for treating early and for treating well. *M. bovis* provides a residual animal source through unpasteurised milk in countries without bovine control.

The transmission is airborne, by droplet nuclei generated in coughing, sneezing, speaking and singing, which remain suspended for hours in unventilated rooms. It follows the physics of Section 3.4 exactly: the determinants of risk are the concentration of bacilli in the air, the ventilation, and the duration of exposure — which is why transmission occurs predominantly among **household contacts and in congregate settings** (prisons, shelters, mines, hospitals) rather than through casual contact.

The receptive population and the natural history. Here tuberculosis differs from every disease so far discussed, and the distinction must be exact:

- of those exposed, a proportion become **infected** — the bacillus is contained by cell-mediated immunity within granulomas, and the person is asymptomatic, non-contagious and detectable only by immunological tests (tuberculin skin test, interferon-gamma release assays). This is **tuberculosis infection (latent tuberculosis)**, and about a quarter of the world's population is estimated to carry it;
- of those infected, approximately **5–10% develop disease during their lifetime** in the absence of immunosuppression, half of them within the first two years after infection [2];
- the risk of progression is multiplied by **HIV infection** (the single strongest risk factor, raising annual risk from about 0.1% to 5–10%), and increased by diabetes, silicosis, malnutrition, tobacco and alcohol, renal failure, treatment with corticosteroids or TNF-alpha inhibitors, gastrectomy, and the extremes of age.

The "iceberg" of Chapter 4 thus takes a particular form in tuberculosis: a very large reservoir of latent infection, a small fraction of which becomes contagious disease, and from which the cases of the coming decades will arise.

Favouring factors. Tuberculosis is the classical social disease: overcrowding, poor ventilation, malnutrition, poverty, migration, imprisonment, homelessness, alcohol and drug dependence. Its historic decline in western Europe began before any effective therapy existed, driven by improvements in housing and nutrition — the single most instructive demonstration in the history of epidemiology that the determinants of an infection may lie outside medicine.

Manifestation of the epidemiological process. Tuberculosis evolves endemically, with enormous geographical variation: about two thirds of cases occur in eight countries, led by India, Indonesia, China, the Philippines and Pakistan. In the European Union incidence is low

but concentrated in vulnerable groups; in the countries of eastern Europe, Romania included, incidence has fallen substantially over two decades but remains among the highest in the Union, with drug resistance a particular problem [3].

21.4. Diagnosis in the epidemiological perspective

The instruments have changed decisively in the past decade, and the change matters for control, not only for the patient:

- **rapid molecular tests** (Xpert MTB/RIF Ultra and equivalents) detect the bacillus and rifampicin resistance within two hours, and are recommended by WHO as the **initial** diagnostic test rather than smear microscopy [4];
- **culture** with drug-susceptibility testing remains the reference, and **whole-genome sequencing** increasingly provides both a full resistance profile and the epidemiological typing that distinguishes recent transmission from reactivation;
- **smear microscopy**, cheap and still widely used, identifies the most contagious patients but misses a large share of cases;
- **chest radiography with computer-aided detection** has been endorsed for systematic screening in high-risk groups;
- **tests for infection** — tuberculin skin test and interferon-gamma release assays — diagnose infection, not disease, and their role is to identify candidates for preventive treatment.

21.5. Prevention and control

Treatment as the principal preventive measure. The cardinal principle of tuberculosis control is that **the treatment of the patient is the prevention of the next case**. A cured patient stops transmitting; an inadequately treated one continues, and may generate resistance. Hence the insistence on complete, supervised, correctly combined regimens — the historical DOTS strategy, now delivered increasingly through patient-centred support, digital adherence technologies and, where appropriate, shorter regimens. Drug-susceptible pulmonary tuberculosis is treated for six months; WHO has since recommended four-month regimens for selected patients, and all-oral regimens of six months (BPaLM) for MDR/RR-TB, which have replaced the injectable-containing regimens of two years that were the standard within living memory [4].

Contact investigation is the classical epidemiological operation: identification and evaluation of household and close contacts, with chest radiography and symptom screening for disease and testing for infection.

Preventive treatment of tuberculosis infection (isoniazid alone for 6–9 months, or the shorter rifapentine-based regimens of 1–3 months) is offered to those at highest risk of progression: people living with HIV, child contacts under five, and other immunosuppressed contacts. This

is the intervention that acts on the reservoir rather than on the cases, and its scale-up is one of the pillars of the End TB Strategy.

BCG vaccination, given at birth in countries of high incidence — Romania included — protects children against the disseminated forms, miliary tuberculosis and tuberculous meningitis, but offers unreliable protection against pulmonary tuberculosis in adults. It is therefore a measure for the protection of infants, not for the interruption of transmission. The prospect of a better vaccine is, for the first time in a century, realistic: the candidate **M72/AS01E** showed about 50% efficacy against progression to pulmonary disease in a phase 2b trial and has entered phase 3 (Chapter 18) [5].

Infection prevention and control in health facilities applies the hierarchy of Chapter 19: administrative measures first (rapid identification, separation and prompt treatment of coughing patients — the measures that prevent most transmission), then environmental (ventilation, upper-room ultraviolet germicidal irradiation), and only then respiratory protection (fit-tested respirators for staff).

The strategic framework. The **End TB Strategy** targets a 90% reduction in deaths and an 80% reduction in incidence by 2030 relative to 2015, together with the elimination of catastrophic costs for affected households [6] — the last target being a recognition that a disease of poverty cannot be controlled by clinical means alone.

Box 21.1. Tuberculosis and antimicrobial resistance. MDR/RR-TB — resistance to at least rifampicin, with or without isoniazid — is the largest single component of the global burden of drug-resistant infection discussed in Chapter 20, and the one for which treatment is longest and costliest. Of the estimated 390,000 people who developed it in 2024, fewer than half were diagnosed and started on treatment [1] — the gap being the classic sequence of failures: no access to rapid molecular testing, no drug-susceptibility testing, and no continuity of care. Two conclusions follow, and they apply to resistance in general: resistance is generated by incomplete and incorrect treatment, so the first defence against it is the quality of the treatment given to the ordinary patient; and it is detected only where the diagnostic capacity exists to look for it.

References

1. World Health Organization. *Global tuberculosis report 2025*. Geneva: WHO; 2025 (data for 2024).
2. Furin J, Cox H, Pai M. Tuberculosis. *The Lancet*. 2019. doi:10.1016/S0140-6736(19)30308-3
3. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. *Tuberculosis surveillance and monitoring in Europe* (annual report). Stockholm/Copenhagen.
4. World Health Organization. *WHO consolidated guidelines on tuberculosis*: Module 2 (screening and diagnosis), Module 4 (treatment of drug-susceptible and drug-resistant TB), Module 1 (prevention: tuberculosis preventive treatment). Geneva: WHO.

5. Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of a trial of M72/AS01E vaccine to prevent tuberculosis. *New England Journal of Medicine*. 2019. doi:10.1056/NEJMoa1909953
6. World Health Organization. *The End TB Strategy*. Geneva: WHO; 2015.

Chapter 22. Zoonoses, Vector-Borne Diseases and Sexually Transmitted Infections

This chapter gathers three groups of diseases which the preceding chapters have repeatedly invoked as examples but not treated systematically: the zoonoses, whose source is the animal reservoir of Chapter 2; the vector-borne diseases, whose transmission route was described in Section 3.10; and the sexually transmitted infections, of which HIV (Chapter 12) is only the most studied member. They are grouped here because each is defined by its *epidemiological mechanism* rather than by its aetiological agent, and because each illustrates a general principle of prevention.

22.1. Zoonoses: the general framework

A **zoonosis** is a disease transmissible under natural conditions from vertebrate animals to humans [1]. Some 60% of known human infectious diseases and about three quarters of emerging infections are zoonotic, which makes this the largest single category of human infection and the principal frontier of emergence.

The prevention of zoonoses follows a rule with few exceptions: **the decisive intervention is applied to the animal reservoir, not to the human host**. Vaccinating dogs prevents human rabies; controlling brucellosis in small ruminants prevents human brucellosis; pasteurising milk prevents bovine tuberculosis and brucellosis; controlling rodents prevents leptospirosis and hantavirus disease. Measures applied to humans — post-exposure prophylaxis, protective equipment, occupational surveillance — are necessary but always secondary, because they do not diminish the reservoir. This is the practical content of the **One Health** approach [2].

Rabies is the model. Virtually 100% fatal once symptomatic, it causes an estimated **59,000 human deaths a year**, almost all in Asia and Africa, about 40% of them in children under 15; **dog-mediated rabies accounts for over 99% of human cases**. The chain of prevention has three links: mass canine vaccination (the only measure that eliminates the source — 70% coverage interrupts transmission); responsible dog population management; and human **post-exposure prophylaxis**, which is fully effective when correctly applied — immediate washing of the wound with soap and running water for 15 minutes, infiltration of rabies immunoglobulin into and around the wound in category III exposures, and a course of modern cell-culture vaccine. The global strategy "Zero by 30" aims at eliminating dog-mediated human rabies by 2030 [3]. In Romania and in the European Union, canine and sylvatic rabies have been brought under control by oral vaccination of foxes, and human cases are exceptional — but the clinical rule stands: **every bite from a suspect animal is a medical emergency**, and prophylaxis is never withheld while awaiting laboratory confirmation.

The other classical zoonoses met in earlier chapters may be summarised by their source and route:

- **Brucellosis** — small ruminants and cattle; unpasteurised milk and cheese, and occupational contact with parturition products. Prevention: animal vaccination and test-and-slaughter, pasteurisation.
- **Anthrax** — herbivores; contact with skins, wool and carcasses (cutaneous form), inhalation of spores, ingestion of infected meat. The spores persist in soil for decades; prevention is veterinary, with occupational vaccination where indicated.
- **Leptospirosis** — rodents and domestic animals; contact of skin and mucosae with water or soil contaminated by animal urine — hence its epidemic behaviour after floods, and its occupational and recreational risk.
- **Toxoplasmosis** — the cat as definitive host; ingestion of oocysts or of tissue cysts in undercooked meat. Its public health importance lies in congenital infection, and its prevention in the counselling of seronegative pregnant women.
- **Echinococcosis (hydatid disease)** — the dog–sheep cycle; ingestion of eggs. It remains endemic in Romania's sheep-rearing regions, and its control is veterinary and educational.
- **Q fever, tularaemia, hantavirus infections, avian influenza** (Chapter 11) complete the picture of occupational and environmental zoonoses.

22.2. Vector-borne diseases in Europe

Vector-borne diseases account for a large share of the global infectious burden — malaria alone caused an estimated 610,000 deaths in 2024, among some 282 million cases, most of them young children in the WHO African Region [4] — and their European map has been redrawn in the past two decades by the expansion of vectors described in Section 3.11.

West Nile virus is the most instructive European example, and one that concerns Romania directly. The virus circulates between birds and *Culex* mosquitoes; humans and horses are dead-end hosts. About 80% of human infections are inapparent, some 20% produce a febrile illness, and fewer than 1% produce neuroinvasive disease — a classical iceberg, whose visible tip is meningoencephalitis in older adults. In the 2026 European season to early August, **245 locally acquired human cases and 12 deaths** were reported from seven countries, Italy and Greece accounting for most cases and Romania reporting 6 cases and one death, with the seasonal peak expected in August and September [5]. Romania experienced a major epidemic in 1996 and has recorded transmission every summer since; surveillance combines human case notification, veterinary surveillance in horses and birds, and entomological monitoring, and prevention is vector control together with personal protection. There is no human vaccine.

Tick-borne diseases have become the most frequent vector-borne infections of temperate Europe. **Lyme borreliosis**, transmitted by *Ixodes ricinus*, is estimated at hundreds of thousands of cases a year in Europe [6]; prevention is personal (clothing, repellents, prompt and correct

tick removal — the risk of transmission being low in the first 24 hours of attachment), and no vaccine is currently licensed for human use. **Tick-borne encephalitis**, by contrast, is preventable by an effective inactivated vaccine, recommended for residents of and travellers to endemic areas, and its range has extended northwards and to higher altitudes with warming.

Imported vector-borne disease — malaria, dengue, chikungunya — must be considered in every febrile traveller returning from an endemic area; malaria is a medical emergency in which the delay in thinking of the diagnosis is the principal determinant of death. To imported cases has been added, in the past decade, **autochthonous transmission** of dengue and chikungunya in southern Europe wherever *Aedes albopictus* is established and an imported case introduces the virus in the transmission season.

22.3. Sexually transmitted infections

The sexually transmitted infections illustrate a transmission route (direct, Section 3.2) whose control depends less on technology than on behaviour, services and the removal of stigma.

The magnitude. WHO estimates that the four curable STIs — syphilis, gonorrhoea, chlamydia and trichomoniasis — account for **more than one million new infections every day** among adults. Syphilis has risen sharply: **8 million new adult infections in 2022** among people aged 15–49, with congenital syphilis at 523 cases per 100,000 live births and about 230,000 syphilis-related deaths a year [7]. Antimicrobial resistance is eroding treatment: among 87 countries with gonococcal surveillance, nine reported ceftriaxone resistance at levels between 5% and 40% [7] — a trajectory that points towards untreatable gonorrhoea, and one more instance of the argument of Chapter 20.

The epidemiological peculiarities of this group are four, and they explain why classical measures work imperfectly:

1. **asymptomatic infection is the rule**, particularly in women (chlamydia, gonorrhoea) — the source is therefore usually unaware;
2. transmission occurs within **sexual networks** whose structure, more than the average number of partners, determines the epidemic potential — which is why interventions targeted at highly connected groups have disproportionate effect;
3. **stigma** delays presentation, discourages testing and obstructs partner notification;
4. the infections **facilitate one another**: ulcerative and inflammatory STIs increase the transmission of HIV several-fold.

Prevention accordingly combines: comprehensive sexuality education; condom promotion; **screening** of defined populations (antenatal screening for syphilis, HIV and hepatitis B is the intervention with the greatest yield per test performed anywhere in medicine); prompt diagnosis and treatment with **partner notification and treatment**, without which the patient is re-infected by an untreated partner; **vaccination** where it exists — HPV (Chapter 28) and hepatitis B (Chapter 14), the two vaccines that prevent sexually transmissible cancers and

chronic disease; and, for HIV, the biomedical prevention described in Chapter 12. Doxycycline post-exposure prophylaxis has been introduced in several countries for bacterial STIs in defined high-incidence populations, with a documented reduction in syphilis and chlamydia but an unresolved question about its effect on antimicrobial resistance.

Congenital syphilis deserves a final word, because it is the sentinel indicator of an antenatal care system. It is entirely preventable by a test that costs a few euros and a treatment — benzathine penicillin — that has been available since the 1940s. Every case represents a woman who was not tested, or who was tested and not treated. In a book of epidemiology, no single figure states more clearly that the determinants of infectious disease outcomes are organisational.

References

1. Heymann DL (ed.). *Control of Communicable Diseases Manual*. 21st ed. APHA; 2022.
2. World Health Organization, FAO, WOAH, UNEP. *One Health Joint Plan of Action (2022–2026)*. Geneva; 2022.
3. World Health Organization. Rabies vaccines: WHO position paper. *Weekly Epidemiological Record*. 2018;93:201–220; and *Zero by 30: the global strategic plan to end human deaths from dog-mediated rabies by 2030*. Geneva: WHO/FAO/WOAH/GARC; 2018.
4. World Health Organization. *World malaria report 2025*. Geneva: WHO; 2025.
5. European Centre for Disease Prevention and Control/EFSA. Surveillance of West Nile virus infections in humans and animals in Europe — monthly report, data to 5 August 2026. Stockholm/Parma; 2026.
6. European Centre for Disease Prevention and Control. Vector-borne diseases — annual epidemiological reports; Tick-borne encephalitis and Lyme neuroborreliosis surveillance. Stockholm: ECDC.
7. World Health Organization. New report flags major increase in sexually transmitted infections, amidst challenges in HIV and hepatitis. Geneva: WHO; 21 May 2024 (data for 2022); and Sexually transmitted infections — fact sheet.

PART IV. SPECIAL EPIDEMIOLOGY OF NON-COMMUNICABLE DISEASES

Chapter 23. General Characteristics of Chronic Non-Communicable Diseases

23.1. Definition

The **chronic non-communicable disease** is defined as "an impairment in body function or structure that necessitates a modification in the person's life-style, or has persisted for a long length of time". The definition captures the two constitutive notes of chronicity: duration, and the remodelling of life that the disease imposes.

The principal chronic diseases with which this part is concerned are: diabetes mellitus, asthma, congestive heart failure, hypertension, hyperlipidaemia and cancer — to which are added obesity, as both disease and risk factor, and the chronic respiratory diseases.

23.2. The global burden

The dimensions of the phenomenon justify the term of **epidemic** applied to chronic diseases. In the WHO projections used in the course, of a total of about 58 million deaths worldwide in one year, the distribution by broad cause groups is the following: cardiovascular diseases — heart disease and stroke — about 30%; communicable diseases, maternal and perinatal conditions and nutritional deficiencies — about 30%; cancer — 13%; chronic respiratory diseases; injuries — 9%; diabetes — 2%; other chronic diseases — 9%. In total, **about 60% of all deaths are due to chronic diseases** — some 35 million people in a single year — and the distribution by World Bank income groups shows that the majority of these deaths occur, contrary to the widespread perception, in the low- and middle-income countries.

Box 23.1. The current figures (supplementary). The WHO estimates for the present decade confirm and amplify the projections above: non-communicable diseases now cause about **41 million deaths per year, i.e. roughly three quarters (74%) of all deaths worldwide** — cardiovascular diseases about 18 million, cancers about 10 million, chronic respiratory diseases about 4 million and diabetes (with its renal component) over 2 million. More than three quarters of these deaths occur in low- and middle-income countries, and some 17 million NCD deaths annually are "premature" — before the age of 70. The COVID-19 pandemic added a further demonstration: the persons with chronic diseases were precisely those who paid the heaviest tribute to the new infection, the two epidemics — infectious and non-infectious — potentiating one another.

23.3. The epidemiological peculiarities of chronic diseases

Six peculiarities distinguish the epidemiology of chronic diseases from that of the infectious diseases studied in Parts I and III, and they command the entire methodology of the field:

1. **Multifactorial causation.** There is no single "pathogen"; the disease results from the interplay of numerous risk factors — genetic, behavioural, environmental, social. The epidemiological instrument is therefore no longer the isolation of an agent, but the measurement of **risk** — relative risk, attributable risk — in cohort and case-control studies.

2. **The latent period.** Between the action of the risk factors and the clinical disease stretch years or decades — the silent interval in which atherosclerosis progresses, the transformed cell clone expands, glucose tolerance degrades. This latency hides the causal connection from common perception (the smoker of today does not see the cancer of thirty years hence), but it is also the great opportunity of prevention: a long window in which intervention is possible.
3. **The insidious onset.** The disease does not announce itself; it is discovered — at a check-up, at a screening, or through its first complication, which may be an infarction or a stroke.
4. **Non-reversible changes.** Once constituted, the lesions — the scarred myocardium, the destroyed nephron, the invaded tissue — do not return to normal; therapy limits, compensates, but rarely restores. Hence the strategic priority of prevention over treatment.
5. **The modification of life-style.** The chronic disease, by definition, obliges the patient to reorganise his or her existence — diet, effort, medication, controls — for the rest of life; compliance (adherence) becomes a central epidemiological variable.
6. **The multi-directional approach.** No single intervention suffices: the control of chronic diseases requires the simultaneous action upon several risk factors, at several levels (individual, community, legislative), by several sectors — health, education, agriculture, finance, urbanism.

23.4. Common risk factors and the strategy of prevention

The apparent diversity of the chronic diseases hides a remarkable convergence: a small set of common, modifiable risk factors — **tobacco smoking, the unhealthy diet, physical inactivity, the harmful use of alcohol** — expressed through the intermediate biological factors — hypertension, hyperglycaemia, hyperlipidaemia, overweight and obesity — generates the greater part of the burden of cardiovascular disease, diabetes, chronic respiratory disease and a substantial share of cancers. This convergence is the scientific foundation of the integrated strategy of prevention: acting upon four behaviours prevents simultaneously the four great groups of diseases.

The levels of prevention defined in Chapter 1 apply integrally: primordial and primary prevention address the risk factors in the whole population and in the high-risk groups; secondary prevention rests on **screening** — the active search for the disease in its preclinical stage; tertiary prevention limits complications and disability. The chapters that follow apply this framework to the principal chronic diseases of the course: obesity, coronary heart disease, hypertension, diabetes mellitus and cancer.

23.5. The current global figures and the framework of action

The projections cited in the classical text have been overtaken by measurement, and the figures that follow are those the student should carry.

The burden. Non-communicable diseases caused **at least 43 million deaths in 2021 — 75% of all non-pandemic-related deaths worldwide**. The distribution is dominated by cardiovascular disease (at least 19 million deaths), followed by cancers (10 million), chronic respiratory diseases (4 million) and diabetes with the kidney disease attributable to it (over 2 million). **Eighteen million people died from an NCD before the age of 70**, and **82% of these premature deaths occurred in low- and middle-income countries**, which also account for 73% of all NCD deaths [1]. Elevated blood pressure is the single leading metabolic risk factor, to which about 25% of global NCD deaths are attributed; air pollution accounts for 6.7 million deaths a year, of which some 5.6 million are due to NCDs [1].

The risk factors, quantified. Tobacco use has fallen — from 1.38 billion users in 2000 to **1.2 billion in 2024**, a relative reduction of 27% since 2010 — but still involves **one adult in five**, with the European Region carrying the world's highest prevalence at 24.1%; and a new phenomenon has appeared, with **more than 100 million people now using e-cigarettes**, including at least 15 million adolescents aged 13–15, who are on average nine times more likely to vape than adults [2]. Obesity affected **more than one billion people in 2022** — 879 million adults and 159 million children and adolescents — with adult obesity having more than doubled in women and nearly tripled in men since 1990, and childhood obesity having quadrupled [3]. Diabetes affects **589 million adults**, projected to reach 853 million by 2050, with 43% undiagnosed [4]. Hypertension affects **1.3 billion adults**, half of them unaware [5].

The interaction with communicable disease. The classical separation of the two epidemiologies, preserved for didactic reasons in the structure of this book, is contradicted by the facts: chronic diseases multiplied the lethality of COVID-19; the pandemic disrupted the detection and treatment of chronic disease for two years, with consequences that are still being counted in later-stage cancer diagnoses; infections cause cancers (Chapter 28); and diabetes increases the risk of tuberculosis. The physician meets these interactions in single patients, and the "multi-directional approach" of Section 23.3 is their practical answer.

23.6. The strategy: from declarations to "best buys"

The international framework has three levels, and the student should be able to name them.

The political level. The United Nations High-Level Meetings on NCDs (2011, 2014, 2018, 2025) and **Sustainable Development Goal target 3.4** — a one-third reduction in premature NCD mortality by 2030 — provide the commitments; the WHO Global Action Plan and its extension to 2030, with its nine voluntary global targets, provide the metrics; and the WHO NCD Progress Monitor documents, country by country, how far implementation has actually gone.

The technical level. The **"best buys"** are the interventions that WHO has costed and shown to be highly cost-effective in all settings [6]: increased taxation of tobacco, alcohol and sugar-sweetened beverages; smoke-free environments and comprehensive advertising bans, with

graphic health warnings; reduction of population salt intake through reformulation and labelling; elimination of industrial **trans-fats** from the food supply — a measure that now covers a majority of the world's population and is the clearest recent example of a regulatory intervention with a documented mortality benefit; promotion of physical activity; drug therapy and counselling for those at high cardiovascular risk; hepatitis B and HPV vaccination; and cervical, breast and colorectal cancer screening.

The clinical level. The **WHO PEN package** (Package of Essential Noncommunicable Disease Interventions) and the HEARTS technical package define what a primary-care service must be able to do: measure blood pressure and cardiovascular risk correctly, treat with a limited formulary of essential medicines, follow up, and refer. This is where the great majority of the achievable benefit lies, and where the deficits of most systems — including the Romanian, whose treatable mortality of 215 deaths per 100,000 is the highest in the European Union [7] — are concentrated.

A note on method. Two ideas from Part II govern the whole of this Part. Geoffrey Rose's distinction between the **population strategy** and the **high-risk strategy**, and his "prevention paradox" (a large number of people at small risk generate more cases than a small number at high risk) [8], explain why fiscal and regulatory measures achieve what clinical prevention alone cannot. And the **population attributable fraction** (Chapter 8) is the arithmetic that ranks the risk factors of this Part in the order in which they should be attacked.

References

1. World Health Organization. Noncommunicable diseases — key facts. Geneva: WHO; 2025 (data for 2021).
2. World Health Organization. WHO tobacco trends report: 1 in 5 adults still addicted to tobacco. Geneva: WHO; 6 October 2025.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. *The Lancet*. 2024. doi:10.1016/S0140-6736(23)02750-2
4. International Diabetes Federation. *IDF Diabetes Atlas*, 11th edition. Brussels: IDF; 2025.
5. World Health Organization. *Global report on hypertension: the race against a silent killer*. Geneva: WHO; 2023.
6. World Health Organization. *Tackling NCDs: best buys and other recommended interventions*. Geneva: WHO; updated edition.
7. OECD/European Observatory on Health Systems and Policies. *România: Profilul de țară din 2025 în ceea ce privește sănătatea*. Paris/Brussels; 2025.
8. Rose G. *The Strategy of Preventive Medicine*. Oxford University Press; 1992.

Chapter 24. Obesity

24.1. Definitions

Obesity is a type of malnutrition characterised by the abnormal growth of the adipose tissue. This growth can occur through the increase in size (hypertrophy) and/or in the number (hyperplasia) of the fat cells. A body mass index above 30 in males and above 28.6 in females is indicative of obesity.

Overweight is the term used for a weight greater than that expected for the given age, sex and occupation.

Obesity deserves its place at the head of the chronic diseases for a double reason: it is a disease in itself, and it is at the same time a major risk factor for the diseases of the following chapters — coronary disease, hypertension, diabetes, several cancers.

24.2. Aetiology

The aetiology of obesity is multifactorial, uniting:

1. **Age** — the frequency increases with age; overweight infants are more likely to become obese adults, a continuity which founds the paediatric prevention of adult obesity;
2. **Sex** — post-menopausal women are more likely to gain weight; in men, obesity occurs about a decade earlier than in women;
3. **The sedentary life-style** — the reduction of energy expenditure in modern work, transport and leisure;
4. **Genetic factors** — the familial aggregation of obesity, confirmed by twin studies;
5. **Diet** — the caloric excess, particularly of fats and refined carbohydrates;
6. **Psychosocial factors** — eating as compensation for tension, anxiety, frustration;
7. **Endocrine factors** — hypothyroidism, Cushing's syndrome and other endocrinopathies, responsible for a small minority of cases.

24.3. The measurement of obesity

Body weight. The actual body weight (ABW) is compared with the expected body weight (EBW), calculated by:

- **Broca's method:** EBW = height in cm − 100;
- **Lorenz's method:** EBW (males) = height in cm − 100 − (height in cm − 150)/4; EBW (females) = height in cm – 100 – (height in cm – 150)/2.

The ratio ABW/EBW is called the **corpulence index**; a value above 1.2 is considered overweight.

The body mass index (BMI) — weight in kilograms divided by the square of the height in metres. The desirable range is 20.1–25 for males and 18.7–23.8 for females; a person is considered obese at a BMI above 30.0 (males) or 28.6 (females).

Skin fold thickness — measured at mid-triceps, biceps, the subscapular and the supra-iliac regions; the method is little used in practice, owing to the lack of standardisation, its poor repeatability and the technical problems of measurement.

Box 24.1. The current WHO classification (supplementary). The international classification in current use applies the same BMI thresholds to both sexes: normal weight 18.5–24.9 kg/m²; overweight 25–29.9; obesity grade I 30–34.9; grade II 35–39.9; grade III (severe) ≥ 40. To the BMI — which does not distinguish fat from muscle, nor the distribution of fat — practice adds the **waist circumference** and the waist/hip ratio, markers of the abdominal (visceral) obesity that carries the metabolic and cardiovascular risk: values above 94 cm in men and 80 cm in women signal increased risk in the European populations, and above 102/88 cm a substantially increased risk. Worldwide, according to WHO, more than one billion people now live with obesity [1], and the prevalence of childhood obesity is rising fastest — the ground on which the primordial prevention of the next generation of chronic diseases is being lost or won.

24.4. The hazards of obesity

Mortality: obesity is a known risk factor for mortality in ischaemic heart disease, hypertension and renal diseases. **Morbidity:** obesity is a risk factor for numerous conditions — hypertension, ischaemic heart disease, gallstones, osteoarthritis; in addition, obese persons carry a higher risk of post-operative complications and of accidents. To these the current literature adds type 2 diabetes — for which obesity is the dominant modifiable risk factor — obstructive sleep apnoea, hepatic steatosis and an increased risk of several cancers (endometrium, breast, colon).

24.5. Prevention and control

1. **Diet** — the reduction of fats and carbohydrates in the diet, especially refined foods, sweets and oils, is recommended both for treatment and for prevention; the increase in the consumption of dietary fibre from unrefined foods is the other side of the coin.
2. **Physical exercise** — regular physical exercise, such as fast walking, outdoor games such as tennis, and swimming, is the necessary adjuvant of the diet.
3. **Other measures** — drugs, the surgical removal of excess fat, gastric bypass and related procedures have been tried, but have a limited value at the population scale; they remain reserved for selected severe cases.

The epidemiological lesson of obesity is that it cannot be treated one patient at a time: being the product of an "obesogenic" environment — cheap caloric food, motorised transport, sedentary work and leisure — its control belongs to primordial prevention: food policies, urban planning that favours movement, the protection of children from the marketing of unhealthy food, and health education begun in childhood.

24.6. Obesity today: magnitude, mechanisms and the new pharmacology

The magnitude, measured. The pooled analysis of 3,663 population-representative studies including 222 million people, conducted by the NCD Risk Factor Collaboration with WHO, established that **more than one billion people were living with obesity in 2022** — 879 million adults and 159 million children and adolescents. Between 1990 and 2022, adult obesity **more than doubled in women** (from 8.8% to 18.5%) and **nearly tripled in men** (from 4.8% to 14.0%), while in children and adolescents it **quadrupled** (girls 1.7% to 6.9%; boys 2.1% to 9.3%). Over the same period underweight more than halved, so that in most countries obesity now affects more people than undernutrition — the "double burden of malnutrition" having tipped decisively [2].

Romania in this picture. Self-reported adult obesity is comparatively low (about 10%), but **26% of adolescents are overweight or obese**, and fewer than one adult in five exercises more than three times a week [3] — the classical configuration of a country in the ascending phase of the epidemic, in which the burden of the next decades is being assembled in the present generation of children.

What has changed in the understanding of causation. The classical aetiology of Section 24.2 remains valid, but three emphases have shifted. First, obesity is now understood as a **chronic, relapsing disease with strong physiological defence of the elevated body weight** — the adaptive fall in energy expenditure and the hormonal drive to eat that follow weight loss explain the near-universal regain after dietary interventions alone, and they remove the moral framing that long attached to the condition. Secondly, the **obesogenic environment** — the ubiquity, palatability, price and marketing of energy-dense food, together with the engineering of sedentarism into transport, work and leisure — is regarded as the principal driver of the population shift, since the human genome has not changed in three decades. Thirdly, **ultra-processed foods** have emerged as a distinct exposure of interest: a controlled feeding trial in which participants ate ad libitum from ultra-processed or unprocessed diets matched for macronutrients found an excess intake of about 500 kcal/day and consequent weight gain on the ultra-processed diet [4], and large cohort studies associate high consumption with cardiometabolic outcomes.

Measurement: beyond the BMI. The critique of the body mass index, sketched in Box 24.1, has been formalised. A Lancet Commission on clinical obesity has proposed distinguishing **preclinical obesity** — excess adiposity with preserved organ function — from **clinical obesity**, in which adiposity has produced demonstrable organ dysfunction or limitation of daily activities, and has recommended that the diagnosis rest on adiposity confirmed by anthropometry beyond BMI alone (waist circumference, waist-to-height ratio, or direct measurement) together with clinical assessment [5]. The practical implication for the student: the BMI remains an excellent *population* indicator and a poor *individual* one, and the waist circumference thresholds given earlier — 94/80 cm signalling increased and 102/88 cm substantially increased risk in European populations — carry the metabolic information that the BMI misses.

The consequences, quantified. Obesity is a cause of type 2 diabetes (the dominant modifiable risk factor), of hypertension, ischaemic heart disease and stroke, of osteoarthritis, of obstructive sleep apnoea and of metabolic dysfunction-associated steatotic liver disease, and it is causally implicated in at least thirteen cancers, including postmenopausal breast, endometrial, colorectal, oesophageal adenocarcinoma, pancreatic, renal and hepatic. It shortens life expectancy by several years at grade II and above, and it accounted for a substantial and rising share of global disability-adjusted life-years in the GBD analyses.

The new pharmacology, and what it does not solve. The incretin-based agents have altered the therapeutic landscape: semaglutide produced mean weight reductions of about 15% at 68 weeks in the STEP programme, and tirzepatide of about 20% in SURMOUNT-1; more importantly for a book of epidemiology, the **SELECT trial** demonstrated in patients with overweight or obesity and established cardiovascular disease, but without diabetes, a **20% reduction in major adverse cardiovascular events** with semaglutide — the first demonstration that treating obesity itself reduces cardiovascular outcomes [6]. This is a genuine advance in tertiary and secondary prevention. It is not, however, a solution to the epidemic: the drugs are expensive, must be taken indefinitely (weight is largely regained on discontinuation), and cannot be scaled to a billion people. The population problem remains a population problem, addressed by the fiscal, regulatory and environmental measures of Chapter 23 — taxation of sugar-sweetened beverages, marketing restrictions directed at children, front-of-pack labelling, reformulation, school food standards, and urban design that makes movement the default [7].

References

1. World Health Organization. Obesity and overweight — fact sheet. Geneva: WHO; 2025.
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022. *The Lancet*. 2024. doi:10.1016/S0140-6736(23)02750-2
3. OECD/European Observatory on Health Systems and Policies. *România: Profilul de țară din 2025 în ceea ce privește sănătatea*. Paris/Brussels; 2025.
4. Hall KD, Ayuketah A, Brychta R, et al. Ultra-processed diets cause excess calorie intake and weight gain: an inpatient randomized controlled trial of ad libitum food intake. *Cell Metabolism*. 2019. doi:10.1016/j.cmet.2019.05.008
5. Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. *The Lancet Diabetes & Endocrinology*. 2025. doi:10.1016/S2213-8587(24)00316-4
6. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes (SELECT). *New England Journal of Medicine*. 2023. doi:10.1056/NEJMoa2307563
7. World Health Organization. *WHO acceleration plan to stop obesity*. Geneva: WHO; 2023.

Chapter 25. Coronary (Ischaemic) Heart Disease

25.1. Definition and clinical presentations

Coronary heart disease (CHD) — ischaemic heart disease — has been described by WHO as the modern epidemic of the world. It can be defined as **the impairment of the heart function due to the inadequate blood flow to the heart, compared to its needs, caused by obstructive changes in the coronary circulation** — in the overwhelming majority of cases, atherosclerosis of the coronary arteries.

CHD may manifest itself in several presentations: angina pectoris on effort; myocardial infarction; irregular heart rhythms (arrhythmias); cardiac failure; and sudden death — this last presentation giving the disease its particular epidemiological gravity: for a substantial share of patients, the first symptom is the fatal one.

25.2. Magnitude and burden

CHD causes about one quarter of all deaths in the industrialised countries, where it is the first leading cause of death. Of those suffering a heart attack, 25–28% die suddenly — instantly or within 24 hours; and 55% of all cardiac deaths occur within the first hours, before the hospital can intervene — the strongest possible argument that the real battle against CHD is fought in prevention, not in the coronary care unit.

In the developing countries, the reported CHD mortality has classically been lower than in the developed ones — partly a real difference, partly the effect of masking by other causes of death and of problems in diagnosis and reporting. The trend, however, is unambiguous: CHD death rates in those countries are increasing — in Singapore, for instance, the death rate doubled within 20 years — while the countries where the epidemic started earliest have passed their peak.

25.3. Descriptive epidemiology: person, time, place

Person. CHD is more frequent among middle-aged and older men, through the accumulation of hazards with age; men have higher CHD death rates than women (the female protection up to menopause pointing to the role of hormones). The disease aggregates in families with a CHD history; hypertensive and diabetic persons are particularly prone; life-styles and habits — smoking, diet, inactivity — shape the individual risk; type A personalities (competitive, hurried, hostile) have been described as more prone to CHD. Socially, CHD was a disease of the high social classes in the 1950s; since the 1970s, however, it has become more frequent among the lower classes — the classical "crossover" that accompanies the maturation of the epidemic, as the educated classes adopt prevention first.

Time. The epidemics of CHD began at different times in different countries: in the USA in the early 1920s, in Britain in the 1930s, later in the other European countries. The epidemics that started earlier are now declining — in the USA the decline began in 1968, with a 25% fall in mortality by 1980, and similar declines have been seen in New Zealand, Canada and Australia — while the developing countries are catching up. The decline demonstrates, better than any single study, that CHD is preventable: it preceded and accompanied the fall of smoking, the control of blood pressure and cholesterol, and the improvement of treatment.

Place. Mortality is highest in northern Europe; the rates of southern Europe are much lower (the "Mediterranean" gradient, classically attributed in part to diet); the rates of Japan are extremely low; and the developing countries show rising rates. Eastern Europe — Romania included — belongs today to the regions with high cardiovascular mortality, which gives this chapter its immediate national relevance.

25.4. Aetiology and risk factors

The aetiology is **multifactorial**, and the risk grows with the number of factors present. The factors are divided into:

- **non-modifiable factors (risk markers):** age; male sex; family history; genetic constitution and personality;
- **modifiable factors (risk factors):** smoking; hypertension; serum cholesterol; diabetes; obesity; sedentary habits; stress.

Smoking is a major CHD risk factor, responsible for about 25% of CHD deaths under 65 years in men. The risk is directly related to the number of cigarettes per day, and smoking acts **synergistically** with the other risk factors — in the smoker who is also hypertensive and hypercholesterolaemic, the risks do not add, they multiply.

Hypertension accelerates the atherosclerotic process, especially in the presence of hyperlipidaemia. Systolic blood pressure is a better predictor of CHD than the diastolic one; both, however, are important risk factors.

Serum cholesterol. Populations with a high burden of CHD have high mean cholesterol levels; cholesterol is a central causal factor, and the **LDL fraction is the one most directly related to CHD**. The classical ATP III classification of lipids and lipoproteins is summarised in the following tables.

LDL cholesterol (mg/dl)	Category
< 100	Optimal
100–129	Near optimal / above optimal
130–159	Borderline high
160–189	High
≥ 190	Very high

HDL cholesterol (mg/dl)	Category
< 40	Low
≥ 60	High (protective)

Total cholesterol (mg/dl)	Category
< 200	Desirable
200–239	Borderline high
≥ 240	High

Serum triglycerides (mg/dl)	Category
< 150	Normal
150–199	Borderline high
200–499	High
≥ 500	Very high

The causes of elevated triglycerides include: obesity and overweight; physical inactivity; cigarette smoking; excess alcohol intake; high-carbohydrate diets (over 60% of the energy intake); several diseases — type 2 diabetes, chronic renal failure, the nephrotic syndrome; certain drugs — corticosteroids, oestrogens, retinoids, higher doses of beta-blockers; and various genetic dyslipidaemias.

When the serum triglycerides are elevated (≥ 200 mg/dl), the **non-HDL cholesterol** — the sum of VLDL and LDL cholesterol, calculated as total cholesterol minus HDL cholesterol — becomes the secondary target of therapy; VLDL cholesterol denotes the atherogenic remnant lipoproteins, and the non-HDL cholesterol goal is set 30 mg/dl above the LDL goal.

Other risk factors: diabetes mellitus — CHD is 2–3 times more frequent in diabetics; the family history of premature CHD; physical inactivity; the type A personality; high alcohol intake; oral contraceptives; and the hormonal difference between men and women, which contributes to the sex gap described above.

25.5. Prevention

CHD is preventable, and its prevention deploys the complete hierarchy of levels.

Primary prevention comprises: (1) the control of the risk factors in the whole population — dietary changes (the reduction of the intake of saturated fats and cholesterol; the avoidance of alcohol consumption), the smoke-free society, the control of blood pressure, the promotion of physical activity; and (2) the identification of the high-risk groups, who receive specific, intensified advice. The two approaches — the *population strategy* and the *high-risk strategy*

— are complementary: the first shifts the whole distribution of risk slightly, with a large collective effect; the second concentrates large individual benefits on the few.

Secondary prevention aims to prevent the recurrence and to obtain the regression of the constituted disease: the screening of the high-risk groups with suitable treatment; drugs, coronary surgery, pace-makers; and the continued control of the risk factors — smoking, hypertension, diabetes, diet, exercise.

Tertiary prevention is the rehabilitation of the cardiac function: changes in behaviour, habits, life-style and diet; the use of drugs; occupational rehabilitation; the control of risk factors; psychological rehabilitation — returning the coronary patient to an active and confident life.

Box 25.1. From risk factors to risk charts (supplementary). The concept of the cardiovascular *risk factor* was born with the Framingham study (1948), and its current practical expression is the **total (global) risk estimation**: rather than treating each factor in isolation, modern guidelines estimate the absolute risk of a cardiovascular event over 10 years — in Europe with the SCORE2 and SCORE2-OP charts, which use sex, age, smoking status, systolic blood pressure and non-HDL cholesterol — and calibrate the intensity of intervention accordingly; Romania belongs to the *high-risk* country group of these charts. The therapeutic corollary of the LDL hypothesis has meanwhile been confirmed by the statin megatrials and by the newer agents (ezetimibe, PCSK9 inhibitors): "the lower, the better" — current European guidelines recommend LDL targets below 55 mg/dl for very-high-risk patients. The population counterpart is summarised in the WHO "best buys": tobacco taxation and smoke-free laws, salt reduction, the elimination of industrial trans-fats, and accessible hypertension treatment — the measures with the greatest number of infarctions prevented per unit of cost.

25.6. Coronary disease today: global risk, modern evidence and the Romanian burden

The burden. Cardiovascular diseases remain the leading cause of death worldwide, with **at least 19 million deaths in 2021** — of which ischaemic heart disease is the largest single component — accounting for about a third of global mortality [1]. The classical statement that CHD is "the epidemic of the industrialised world" is now historically inaccurate: the great majority of cardiovascular deaths occur in low- and middle-income countries, where the epidemic is ascending while the high-income countries continue the decline that began in the late 1960s.

Romania. The national figures give this chapter its immediate relevance. **Cardiovascular diseases caused 56% of all deaths in Romania in 2022**, against 17% for cancer; treatable mortality is the highest in the European Union, at 215 deaths per 100,000, with mortality from hypertension-related causes approximately six times the EU average; and preventable mortality, at 304 per 100,000, is the third highest [2]. Romania is classified in the **high-risk** region of the European SCORE2 charts. No other set of numbers in this book argues more directly for the population measures of Chapter 23 and for the strengthening of primary care.

From risk factors to total risk, and from total risk to treatment. The methodological advance summarised in Box 25.1 — the shift from treating individual factors to estimating **absolute 10-year cardiovascular risk** — is now embodied in the SCORE2 and SCORE2-OP algorithms, calibrated by country risk region [3] and using age, sex, smoking, systolic blood pressure and non-HDL cholesterol. Two consequences follow for practice: a moderately elevated single factor in a young person without other risks may warrant no drug treatment, while the same value in an older person with several risks warrants intensive management; and risk communication with the patient should use absolute risk and the expected benefit of treatment, not the isolated laboratory value.

The LDL hypothesis, confirmed. The classical account correctly identifies LDL cholesterol as the fraction most directly related to CHD. The evidence since has become as strong as epidemiology ever achieves, by the convergence of three independent lines: observational cohorts; **Mendelian randomisation** studies, in which genetic variants that lower LDL from birth are associated with proportionally lower lifetime risk — evidence that is free of confounding by lifestyle, and that indicates that the *duration* of exposure to LDL matters as much as the level; and randomised trials of statins, ezetimibe and PCSK9 inhibitors, meta-analysed by the Cholesterol Treatment Trialists' Collaboration, showing that each 1 mmol/L (≈39 mg/dL) reduction in LDL produces about a 22% proportional reduction in major vascular events per year of treatment, with benefit proportional to absolute risk and no threshold below which lowering ceases to help [4]. Current European guidelines therefore set LDL targets below 55 mg/dL for very-high-risk patients — the practical translation of "the lower and the earlier, the better".

Blood pressure. The **SPRINT** trial demonstrated that, in high-risk non-diabetic hypertensive patients, targeting a systolic pressure below 120 mmHg rather than below 140 mmHg reduced major cardiovascular events and all-cause mortality, at the cost of more hypotension and electrolyte disturbance [5]; the debate on the optimal target continues, but the direction of the evidence — lower is better in high-risk patients, with individualisation in the frail elderly — is established. At population level, the **SSaSS** cluster-randomised trial in 21,000 Chinese villagers showed that replacing ordinary salt with a potassium-enriched substitute reduced stroke, major cardiovascular events and death [6] — one of the few population dietary interventions with randomised evidence of hard outcomes, and a model of the "best buy" logic.

Smoking. The 25% attributable fraction quoted in the classical text is consistent with modern estimates; what has been added is the demonstration, from the 50-year follow-up of the British Doctors Study, that **cessation before the age of 40 avoids almost the whole of the excess mortality**, and that persistent smokers lose about a decade of life [7]. Tobacco control at population level — taxation, smoke-free legislation, plain packaging, advertising bans — remains the intervention with the largest documented effect on cardiovascular mortality, and the acute drop in myocardial infarction admissions following smoke-free laws is one of the fastest public health effects ever measured.

Diabetes and the cardiovascular continuum. The classical 2–3-fold excess risk in diabetics remains, but the therapeutic landscape has changed: SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated reductions in cardiovascular and renal outcomes independent of their glycaemic effect, and semaglutide reduced major adverse cardiovascular events by 20% in patients with obesity and established cardiovascular disease without diabetes [8]. Cardiovascular prevention, diabetes care and obesity management have consequently converged into a single clinical enterprise — the practical expression of the "multifactorial causation" with which this Part began.

What remains classical. None of this displaces the doctrine of Section 25.5. The greater part of the decline in CHD mortality in the countries that achieved it has been attributed, in the IMPACT modelling analyses, roughly half to changes in population risk factors and half to treatment — that is, prevention and cure in about equal measure, with the prevention half achieved largely by measures that never reached a doctor's consulting room.

References

1. World Health Organization. Noncommunicable diseases — key facts. Geneva: WHO; 2025 (data for 2021).
2. OECD/European Observatory on Health Systems and Policies. *România: Profilul de țară din 2025 în ceea ce privește sănătatea*. Paris/Brussels; 2025.
3. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *European Heart Journal*. 2021. doi:10.1093/eurheartj/ehab484
4. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *The Lancet*. 2010. doi:10.1016/S0140-6736(10)61350-5
5. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *New England Journal of Medicine*. 2015. doi:10.1056/NEJMoa1511939
6. Neal B, Wu Y, Feng X, et al. Effect of salt substitution on cardiovascular events and death (SSaSS). *New England Journal of Medicine*. 2021. doi:10.1056/NEJMoa2105675
7. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004. doi:10.1136/bmj.38142.554479.AE
8. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes (SELECT). *New England Journal of Medicine*. 2023. doi:10.1056/NEJMoa2307563

Chapter 26. Hypertension

26.1. Definition and classification

Hypertension is the most prevalent of the cardiovascular diseases and, at the same time, the most important treatable risk factor for stroke, coronary disease, heart failure and chronic renal failure. The classification used in the course (after JNC-7) is the following:

Category	Blood pressure (mmHg)
Normal	< 120 / < 80
Prehypertension	120–139 / 80–89
Hypertension, stage 1	140–159 / 90–99
Hypertension, stage 2	≥ 160 / ≥ 100

Box 26.1. Current definitions (supplementary). The diagnostic threshold used in current European practice remains the office blood pressure of **≥ 140/90 mmHg**, confirmed by repeated measurements or by out-of-office measurement (ambulatory or home monitoring, with lower corresponding thresholds — e.g. 24-hour mean ≥ 130/80). The American guidelines (ACC/AHA 2017) lowered the definition of hypertension to ≥ 130/80 mmHg, and the recent European guidelines introduced the category of "elevated blood pressure" (120–139/70–89) — differences of classification that matter epidemiologically, because they change overnight the prevalence of "hypertension" without changing anyone's pressure. Whatever the labels, the epidemiological relation is continuous: from 115/75 mmHg upwards, the cardiovascular risk doubles with every increase of 20/10 mmHg.

26.2. The magnitude of the problem

Hypertension is estimated to affect about **20% of the world's adult population, and around 50% of persons over 60 years**. Illustrative national figures for prevalence and control: USA — prevalence about 18%, control about 34%; Canada — 22% and 16%; Egypt — 26% and 8%; China — 14% and 3%. The socioeconomic implications are enormous: in the USA, the cost of hypertension has been estimated at 47.2 billion dollars (NHLBI), for some 50 million affected persons.

The comparison of the American NHANES surveys illustrates what an organised health system can achieve in time: between 1976–1980 and 1999–2000, awareness of hypertension among the affected rose from 51% to 70%, the treated share from 31% to 59% and the controlled share from about 10% to 34% — while the data available for Romania in the same era (prevalence around 20%, awareness around 27%, control around 20% among the treated, with many unknowns) show the distance that remained to be covered.

In the developing countries — and not only there — the problem has specific dimensions:

1. public and professional awareness is greatly lacking;
2. the issue is not adequately addressed by any organisation;
3. an open market exists for all possible drugs, without coherent guidance;
4. many misconceptions circulate among the public regarding hypertension and its treatment;
5. the medical professionals belong to too many "schools", with diverse treatment traditions and standards;
6. hypertension is not adequately recognised as an important life-long risk for other, more "attractive" diseases — chronic renal failure, stroke, myocardial infarction.

All of the above affect every aspect of the management of hypertension.

26.3. Where the problems lie — the "rule of halves"

The chain of care of hypertension loses patients at every link: **awareness** is severely lacking among the public and the professionals, despite the significance of the disease for public health; **treatment** — guidelines exist but are not applied; **control** — only a small percentage of those identified and treated actually reach the target values (of the order of 20%); and the **holistic approach** — the management of the hypertensive patient with consideration of co-morbidities and of the associated risk factors — is inconsistent. This cascade is known classically as the "rule of halves": half of the hypertensives are unaware, half of the aware are untreated, half of the treated are uncontrolled — and although modern systems have improved upon it, its logic still describes the situation of many countries.

The special cruelty of hypertension as a public health problem lies in its silence: the disease does not hurt, the treatment is lifelong, and the benefit — the stroke that did *not* occur — is invisible to the patient. Its control is therefore, before all, a problem of organisation and of education, not of pharmacology.

26.4. What is needed

The strategic needs identified are:

- educating the professionals in the prevention and treatment of hypertension;
- improving the teaching of life-style modification, addressed to the medical profession and to the general public;
- improving the general public's awareness of the importance of a normalised blood pressure;
- cooperating with the policy makers to project a multitude of actions against hypertension throughout society, all year long;
- developing training packages for the health care providers in the primary care centres;
- cooperating with national and international organisations, to learn from each other's experience.

26.5. The management plan

The management plan of the hypertensive patient comprises:

1. establishing a good patient–doctor relationship — the foundation of decades of adherence;
2. educating the patient and the family on the consequences of uncontrolled hypertension;
3. encouraging the self-monitoring of blood pressure;
4. setting the blood pressure goal;
5. non-pharmacological therapy — salt reduction, weight loss, physical activity, moderation of alcohol, smoking cessation — which is the first step in every patient and the sufficient step in many;
6. pharmacological therapy;
7. simplifying the drug regimen — the fewer daily doses, the better the adherence;
8. the particular approach of the elderly, in whom isolated systolic hypertension dominates and treatment, correctly conducted, is at least as beneficial as in the young.

26.6. Hypertension today: the global report and what it demands

The figures. The first WHO global report devoted to hypertension, published in 2023, gives the current dimensions of the problem and supersedes the older survey data quoted above: **1.3 billion adults live with hypertension — one adult in three — a doubling from 650 million in 1990** [1]; nearly half are unaware of their condition; **approximately four out of every five are not adequately treated**; and only about **one in five has it controlled**. More than three quarters of adults with hypertension live in low- and middle-income countries [2].

The report's central calculation is the one worth remembering: if the coverage of effective treatment were scaled up to the level already achieved by the best-performing countries, **76 million deaths could be averted between 2023 and 2050**, together with 120 million strokes, 79 million heart attacks and 17 million cases of heart failure — at a return of the order of 18 to 1 on the investment [2]. Hypertension is thus, by a wide margin, the condition in which the gap between what is known and what is done is largest.

The Romanian dimension. Romania's mortality from hypertension-related causes is approximately six times the EU average, and its treatable mortality — the deaths that should not occur given timely, effective care — is the highest in the Union at 215 per 100,000 [3]. The "rule of halves" described in Section 26.3 is not a historical curiosity here but a current description, and the deficit lies overwhelmingly in the detection, the treatment and the *control* of an asymptomatic condition in primary care.

What modern evidence has added to the classical account.

Measurement. The single most consequential technical change is the recognition that a diagnosis must not rest on office readings alone: **out-of-office measurement** — 24-hour ambulatory monitoring or standardised home measurement — identifies white-coat hypertension (avoiding unnecessary lifelong treatment) and masked hypertension (avoiding a missed diagnosis with full cardiovascular risk), and predicts outcomes better than office readings. Automated office blood pressure with the patient unattended reduces the white-coat effect. The correct technique — seated, back supported, arm at heart level, correct cuff size, after five minutes of rest, at least two readings — is not pedantry: an incorrectly sized cuff can produce errors of 10–20 mmHg, enough to create or abolish a diagnosis.

Targets. The SPRINT trial and its successors have moved the therapeutic target downwards for high-risk patients; current European guidance recommends, for most treated patients who tolerate it, a systolic pressure of 120–129 mmHg, with individualisation in the frail and very old [4, 5].

Treatment strategy. Three changes have improved control rates where they have been adopted: **initiation with a single-pill combination of two agents** rather than sequential monotherapy, which achieves control faster and improves adherence; the use of **simplified, standardised protocols** with a limited formulary — the core of the WHO **HEARTS** technical package — which allows the great majority of patients to be managed in primary care by trained non-specialists [6]; and systematic **team-based care** with task-sharing, in which nurses and pharmacists conduct measurement, titration and follow-up under protocol. The evidence that these organisational measures raise control rates is stronger than the evidence distinguishing one modern drug class from another.

Population prevention. Salt reduction remains the principal population lever, and the **SSaSS** trial provided randomised evidence that potassium-enriched salt substitution reduces stroke, cardiovascular events and death [7]. WHO's global sodium benchmarks for packaged foods, mandatory reformulation targets and front-of-pack labelling are the policy instruments; potassium-enriched salt is a rare intervention that acts on the whole distribution of blood pressure — a textbook example of Rose's population strategy.

A note on communication. The reason hypertension is "the silent killer" is not only physiological. The patient feels nothing before treatment and nothing after it; the benefit is an event that does not occur; and the treatment lasts for life. Adherence is therefore the central clinical problem, and the measures that improve it are known and unglamorous: simplify the regimen to one pill once daily where possible, explain the absolute benefit in comprehensible terms, use home monitoring to give the patient a role, review at intervals that make sense, and never treat a number without treating the person attached to it.

References

1. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019. *The Lancet*. 2021. doi:10.1016/S0140-6736(21)01330-1
2. World Health Organization. *Global report on hypertension: the race against a silent killer*. Geneva: WHO; 2023; and WHO news release, 19 September 2023.
3. OECD/European Observatory on Health Systems and Policies. *România: Profilul de țară din 2025 în ceea ce privește sănătatea*. Paris/Brussels; 2025.
4. SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. *New England Journal of Medicine*. 2015. doi:10.1056/NEJMoa1511939
5. McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *European Heart Journal*. 2024. doi:10.1093/eurheartj/ehae178
6. World Health Organization. *HEARTS technical package for cardiovascular disease management in primary health care*. Geneva: WHO; 2020.
7. Neal B, Wu Y, Feng X, et al. Effect of salt substitution on cardiovascular events and death (SSaSS). *New England Journal of Medicine*. 2021. doi:10.1056/NEJMoa2105675

Chapter 27. Diabetes Mellitus

27.1. Definition and classification

Diabetes mellitus (DM) is a chronic disease due to the deficiency, or the diminished effectiveness, of insulin. The disease affects the metabolism of carbohydrates, proteins, fats, water and electrolytes — a truly systemic metabolic disorder, whose vascular complications make it simultaneously a cardiovascular disease.

The classification used in the course distinguishes:

1. **Diabetes mellitus proper:**
   - **insulin-dependent (type 1, juvenile-onset, IDDM)** — the consequence of the autoimmune destruction of the insulin-producing beta cells;
   - **non-insulin-dependent (type 2, maturity-onset, NIDDM)** — the combination of insulin resistance with the progressive failure of secretion;
2. **Impaired glucose tolerance** — the intermediate state between diabetes and normality; pregnancy, obesity and stress may precipitate this condition;
3. **Gestational diabetes** — induced by pregnancy.

The severity of the two principal types differs: **type 1 is the most lethal form, with an abrupt onset**; **type 2 is the commonest presentation**, with a gradual onset and a milder nature, compatible with long living under adequate control.

27.2. Diagnostic criteria

The biochemical criteria for the diagnosis of type 2 diabetes are summarised below:

Biochemical index	Diabetes	Impaired glucose tolerance	Normal
Fasting blood glucose	≥ 7.0 mmol/l (≥ 126 mg/dl)	6.1–6.9 mmol/l (111–125 mg/dl)	< 6.1 mmol/l (< 110 mg/dl)
2-hour OGTT glycaemia	≥ 11.1 mmol/l (≥ 200 mg/dl)	7.7–11.0 mmol/l (140–200 mg/dl)	< 7.7 mmol/l (< 140 mg/dl)
Random plasma glucose	≥ 11.1 mmol/l (≥ 200 mg/dl) with symptoms	—	—

Box 27.1. Current criteria (supplementary). The present ADA/WHO criteria retain the thresholds above and add **glycated haemoglobin (HbA1c) ≥ 6.5%** as a diagnostic criterion, with the band 5.7–6.4% defining prediabetes (together with impaired fasting glucose and impaired glucose tolerance). Globally, the International Diabetes Federation estimates that over **half a billion adults live with diabetes** — the majority type 2, and up to half of them undiagnosed — a prevalence roughly one order of magnitude above the "2–6%" of the classical era, driven by the epidemics of obesity and sedentarism and by the ageing of populations.

27.3. Magnitude

Diabetes is among the most common metabolic diseases of human beings; its worldwide prevalence has classically been estimated at two to six per cent. In the developing countries, DM is masked by the communicable diseases and by malnutrition; the higher recorded rates of occurrence are found in the developed countries. DM is the eighth leading cause of death in the USA — but its true weight is larger, hidden in the cardiovascular and renal deaths it produces. Diabetics are incapacitated by many serious complications: the atherosclerotic diseases, renal failure, neuropathy and blindness — diabetes being the leading cause of blindness, of end-stage renal disease and of non-traumatic amputation in the industrialised world [1].

27.4. Aetiology

The fundamental cause remains unknown; several theories suggest different causative mechanisms, and inherited and exposure factors accumulate to produce the disease. The primary defect may be: an insulin deficiency of genetic or pancreatic origin; an insulin present in normal amounts but of defective nature; or the decreased sensitivity of the peripheral tissues to insulin (insulin resistance — the core of type 2).

Diseases and factors incriminated in the aetiology of DM include:

1. **viruses** — rubella, mumps, Coxsackie, cytomegalovirus — incriminated as triggers of the autoimmune destruction of type 1;
2. **endocrine diseases** — acromegaly, Cushing's syndrome, thyrotoxicosis — producing secondary diabetes through counter-regulatory hormones;
3. **behaviour and stress** — the lack of exercise, and stress in its widest sense (trauma, surgery, psychic troubles) may bring out the disease in the predisposed.

27.5. Diabetes and pregnancy

Two situations must be distinguished: (a) adult-type DM manifesting itself for the first time during pregnancy; and (b) **gestational DM**, which disappears with the end of the pregnancy — but marks the woman, for life, with a high risk of later type 2 diabetes.

It has been estimated that 10,000 babies are born to women with diabetes every year in the developed countries; the possibility of occurrence rises with the parity and the age of the pregnant woman, and the incidence of diabetes in pregnancy ranges from 0.1 to 0.5 per 100 pregnancies. The morbid effects are double: **maternal complications** — a higher incidence of pre-eclampsia, eclampsia, infections and postpartum haemorrhage; and **foetal and child morbidity** — from birth trauma (macrosomia), deranged metabolism (neonatal hypoglycaemia) and congenital anomalies. Hence the obligation of screening for gestational diabetes and of the rigorous control of glycaemia throughout pregnancy.

27.6. Descriptive epidemiology

Person. DM increases with age. Among the young there are more male diabetics; in middle age women become more affected, partly through the diabetogenic role of pregnancies. The **genetic factor** is undisputed — the aggregation of cases in families is characteristic. The **immune mechanism** — cell-mediated autoimmunity — defines type 1. **Body weight** — obesity — and **diet** dominate the risk of type 2.

Place. DM is commoner in the developed countries, through the different age structure of the population, the better facilities of diagnosis, stress, and the sedentary occupations — an epidemiology now being replicated, at accelerated speed, by the urbanising developing world.

Time. DM is on the increase, due to the prolongation of the life span, the changing life-styles, the better diagnosis and the improved medical care (which keeps diabetics alive — prevalence rising even where incidence is stable). A **seasonality** has been recorded for type 1, with a peak incidence in the winter months, suggesting the participation of fluctuating viral diseases.

27.7. Prevention

Primary prevention rests on two pillars:

- **the identification of those at risk:** persons with a positive family history; persons over 40 years of age; obese individuals; women with a suggestive obstetric history (macrosomic babies, gestational diabetes); cases with premature atherosclerosis;
- **health education:** the maintenance of the optimal body weight; the promotion of physical exercise; diet modification; the avoidance of diabetogenic drugs (contraceptive pills, corticosteroids); family-life education, classically including counselling regarding marriage among diabetics and the prevention of pregnancy in high-risk situations — recommendations which modern practice has replaced with individualised genetic and preconception counselling.

Secondary prevention comprises:

- **screening.** The preventive significance of early detection is twofold: the discovery of the disease in its pre-symptomatic state, followed by adequate treatment, minimises the danger of complications such as coma and infection; and early therapy slows the progress of the disease and may reverse the pathological changes — chronic hyperglycaemia itself exhausting the already weakened islets of Langerhans. Diabetics with no or minimal complications at the time of diagnosis have a death rate less than one third of that of the patients with serious complications at diagnosis. All risk groups should therefore be screened periodically. As screening tests, the classical approach used the detection of glucose in urine two hours after a meal — with the caveat that mild cases escape (up to 50% false negatives, when glycosuria is absent) — and the confirmation with blood glucose two hours after an oral glucose load, 180 mg/dl being the classical threshold; any organised community group can be the target of a screening programme — insured

workers, mothers attending mother-and-child centres, school children, factory workers. (Modern screening uses fasting plasma glucose and HbA1c — Box 27.1.)

- **treatment**, whose aim is to maintain the serum glucose within normal limits: by diet modification alone; by diet and oral hypoglycaemic drugs; or by diet and insulin. Well-controlled diabetics have a life expectancy approaching that of the general population.
- **health education**, in individual counselling or organised group sessions, covering: the maintenance of the ideal body weight; the training of the diabetic for **self-care** — crucial for a good prognosis — including adherence to treatment and the recognition of danger signs and symptoms; the diabetic should be able to test his own blood, choose his diet, regulate his physical activity, and administer — and even adjust — his daily insulin dosage; and the use of the diabetic card.

Tertiary prevention means treating the complications and rehabilitating the patient towards a life as normal as possible: periodic check-ups of visual acuity (retinopathy), of the renal functions (nephropathy) and of the peripheral sensation (neuropathy); and the diabetic card, providing the information needed in emergencies — the hypoglycaemic and ketoacidotic episodes.

27.8. Diabetes today: the Atlas figures, prevention trials and modern therapy

The magnitude, in current numbers. The 11th edition of the IDF Diabetes Atlas gives, for 2024, a picture that is an order of magnitude beyond the "2–6% worldwide prevalence" of the classical text: **589 million adults aged 20–79 are living with diabetes — one adult in nine — projected to reach 853 million by 2050**, or one in eight. **Some 252 million, that is 43%, are undiagnosed**, and almost 90% of these live in low- and middle-income countries. Diabetes caused **3.4 million deaths in 2024** — one every six seconds in this age group — and accounted for about **USD 1.015 trillion in health expenditure**, a 338% increase over seventeen years. A further **635 million adults have impaired glucose tolerance** and 488 million impaired fasting glucose; **one live birth in five is affected by hyperglycaemia in pregnancy**; and **four out of five adults with diabetes (81%) live in low- and middle-income countries** [2].

Diagnosis. To the criteria of Section 27.2 must be added **HbA1c ≥ 6.5%** as a diagnostic threshold, with 5.7–6.4% defining one form of prediabetes [3]; HbA1c requires no fasting, is less affected by acute illness, and reflects the preceding two to three months, but it is unreliable in haemoglobinopathies, in anaemia and in conditions altering erythrocyte survival — in which case glucose criteria must be used. The classical screening test cited in the older text, glycosuria, is obsolete for the reasons given there: it misses up to half of cases.

Primary prevention has moved from exhortation to evidence. Two landmark randomised trials established that type 2 diabetes is preventable in persons with impaired glucose tolerance. The **Finnish Diabetes Prevention Study** and the American **Diabetes Prevention Program** both showed that an intensive lifestyle intervention — modest weight loss (5–7%), 150 minutes

a week of physical activity, dietary change — **reduced the incidence of diabetes by about 58%**, substantially more than metformin (about 31%) in the DPP [4, 5]. The long-term follow-up studies (DPPOS, Da Qing) showed persistence of the benefit for decades. These results converted "health education" into a costed, deliverable intervention, and they are the basis of the national diabetes prevention programmes now operating in several countries.

Remission of established type 2 diabetes. The **DiRECT** trial demonstrated that a structured total diet replacement programme delivered in primary care achieved remission of type 2 diabetes — normal glycaemia off all antidiabetic medication — in 46% of participants at one year and 36% at two years, the probability of remission being closely related to the weight lost [6]. Type 2 diabetes, long taught as inexorably progressive, is therefore, in its early years and in association with substantial weight loss, a potentially reversible condition — a change of paradigm with direct implications for what is said to the newly diagnosed patient.

Therapy has become cardio-renal protection. The classical aim of Section 27.7 — maintaining glycaemia within normal limits — remains, but the evidence of the past decade has shown that the *choice* of agent matters beyond glycaemic control: **SGLT2 inhibitors** reduce heart failure hospitalisation, cardiovascular death and the progression of chronic kidney disease, and **GLP-1 receptor agonists** reduce major adverse cardiovascular events, both in patients with diabetes and, for semaglutide, in obesity without diabetes [7]. Metformin remains the usual first agent, but treatment is now selected according to the patient's cardiovascular and renal profile rather than by glycaemia alone. **Continuous glucose monitoring** has transformed the management of type 1 diabetes, and automated insulin delivery ("closed-loop") systems are becoming standard of care in that condition.

Screening and secondary prevention. The principle of Section 27.7 is confirmed by the modern evidence and by the Atlas figures: with 43% of cases undiagnosed, and with complications frequently present at diagnosis in type 2 diabetes, opportunistic screening of risk groups — age above 40, overweight or obesity, family history, gestational diabetes, hypertension, dyslipidaemia — is the practical instrument, using fasting glucose or HbA1c. Tertiary prevention has its own established schedule: annual retinal screening (with growing use of automated image analysis), annual assessment of renal function and albuminuria, foot examination with risk stratification, and cardiovascular risk management — the complications that make diabetes the leading cause of blindness of working age, of end-stage renal disease and of non-traumatic amputation being largely preventable by exactly these unglamorous routines.

Gestational diabetes. The classical account understated the frequency: with modern criteria, hyperglycaemia affects about one pregnancy in five worldwide [2]. Treatment reduces macrosomia, pre-eclampsia and shoulder dystocia; and the postpartum follow-up is not optional, since a substantial proportion of affected women develop type 2 diabetes within a decade — the single most identifiable high-risk group available for the primary prevention described above.

References

1. World Health Organization. Diabetes — fact sheet; *Global report on diabetes*. Geneva: WHO.
2. International Diabetes Federation. *IDF Diabetes Atlas*, 11th edition. Brussels: IDF; 2025 (data for 2024).
3. American Diabetes Association. Standards of Care in Diabetes (annual). *Diabetes Care*.
4. Tuomilehto J, Lindström J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine*. 2001. doi:10.1056/NEJM200105033441801
5. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002. doi:10.1056/NEJMoa012512
6. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *The Lancet Diabetes & Endocrinology*. 2019. doi:10.1016/S2213-8587(19)30068-3
7. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes (SELECT). *New England Journal of Medicine*. 2023. doi:10.1056/NEJMoa2307563

Chapter 28. Cancer

28.1. Definition and magnitude

Cancer has emerged as a major public health problem not only in the developed countries but also in many developing countries. It can be regarded as a group of diseases characterised by: (1) the abnormal growth of cells; (2) the ability to invade adjacent tissues and even distant organs (metastasis); and (3) the eventual death of the affected patient, if the tumour has progressed beyond the stage at which it can be successfully removed.

All forms of cancer together cause about 9% of deaths throughout the world. At the beginning of the twentieth century cancer was the sixth cause of death in the developed countries; today it is the **second leading cause of death, next to the cardiovascular diseases**, in these countries, and it ranks fourth in the developing world. There is a steady increase in incidence and mortality, explained by: (1) the improved techniques of case-finding and detection; (2) the control of the communicable diseases — which allows people to live long enough to develop cancer; (3) the marked demographic ageing; and (4) the changes in life-style and environment. Cancer is thus, in part, the price of victories won elsewhere in public health — which makes its prevention, not its mere treatment, the rational answer.

28.2. Descriptive epidemiology

Place

The international variations in the pattern of cancer are attributed to multiple factors: environmental, food habits, life-style, genetics, the inadequacy of detection and reporting, and the population structure. Cancer of the stomach is common in Japan and has a low incidence in the United States; breast cancer, on the contrary, is common in the United States and has a low incidence in Japan. In Egypt, owing to the prevalence of bilharzia (schistosomiasis), bladder cancer is more common than in the areas free of bilharzia — an instructive example of an infection-caused cancer. It has also been observed that cancer mortality is highest in the urban and industrial communities and lowest in mountain areas. The migrant studies — showing that the descendants of migrants progressively acquire the cancer pattern of the host country — have demonstrated that these geographical differences are predominantly environmental, not racial: in other words, that most cancer is, in principle, preventable.

Person

Age. Mortality is low during infancy and the preschool years, drops to its minimum during the subsequent childhood period, and at older ages rises consistently to a peak; more than half of the cancer deaths today occur in persons aged 65 years and over.

Sex. In general, cancer occurs more frequently in females than in males; however: (a) the incidence of cancer of the lip, larynx, lung, bronchus, tongue, pharynx and oesophagus is higher among males — the map of tobacco and alcohol; (b) cancer of the thyroid and of the biliary

passages is more frequent among females; (c) the gastro-intestinal cancers are equally distributed among the sexes.

Ethnic background. Cancer is, overall, more frequent among non-whites, attributable to the higher incidence of the cancers of the digestive and genital systems, especially in males; skin cancer, on the other hand, is more frequent among the white race — the melanin protection being the biological explanation.

Religion. Both Jewish and Moslem women have very low rates of cervical cancer — a point variously ascribed to the hygienic practices associated with sexual habits and to male circumcision; in modern terms, to differences in the transmission of the human papillomavirus.

Marital status. Cancer of the cervix occurs more in sexually active women, while breast cancer is more common among the unmarried — the mirror-image pair that pointed, long before the aetiological confirmations, towards a sexually transmitted factor in cervical cancer and towards the protective role of early full-term pregnancies in breast cancer.

Socio-economic status. There is an inverse association between cervical cancer and socio-economic status; on the contrary, breast cancer occurs more commonly among women of high social standing. These differences reflect the differences in life-style, dietary pattern, marital practices, fertility pattern and personal hygiene.

28.3. Aetiology

As with the other chronic diseases, cancer has a **multifactorial aetiology**:

1. the genetic factor;
2. personal habits — above all tobacco, responsible for the largest single share of preventable cancers, and alcohol;
3. dietary factors;
4. occupational exposures — the historical chimney-sweeps' scrotal cancer, asbestos, aromatic amines, benzene, ionising radiation;
5. infection — the viruses and other agents associated with human cancers;
6. physical agents — ultraviolet and ionising radiation;
7. chemical agents — the environmental and industrial carcinogens.

Box 28.1. Infections as causes of cancer — and vaccines as cancer prevention (supplementary). About one in eight human cancers worldwide is attributable to infectious agents [1], the principal ones being: *Helicobacter pylori* (gastric cancer), the human papillomaviruses (cancer of the cervix and other anogenital and oropharyngeal cancers), the hepatitis B and C viruses (hepatocellular carcinoma), the Epstein–Barr virus (Burkitt lymphoma, nasopharyngeal carcinoma), HIV (through immunosuppression — Kaposi's sarcoma, lymphomas), and the schistosomes (bladder cancer). The practical consequence is historic: **two vaccines now prevent cancer** — the hepatitis B vaccine, and the HPV vaccine, which, administered before the beginning of sexual life, prevents the great majority of cervical cancers; upon it, together with screening, rests the WHO strategy for the *elimination of cervical cancer* as a public health problem. In Romania, HPV vaccination is offered free of charge through the national programme — its promotion belonging to the daily preventive duties of every physician.

28.4. Cancer prevention

Cancer prevention comprises a series of measures based on medical knowledge in the fields of prevention, detection, diagnosis, treatment, after-care and rehabilitation, aimed at reducing the number of new cases, increasing the number of cures and reducing the invalidism due to cancer. It is estimated that **at least one third of all cancers are preventable** — and current estimates place the preventable fraction higher still, at around 40%.

Primary prevention:

- **health education** — against tobacco and alcohol; for hygiene; for immunisation (hepatitis B, HPV — Box 28.1); for the early presentation of warning signs;
- **industrial and occupational control** — the elimination or strict limitation of the exposure to occupational carcinogens;
- **the control of environmental pollution**.

Secondary prevention:

- **the early detection of cases** — the organised screening programmes: cervical cytology (and HPV testing) for cervical cancer, mammography for breast cancer, the endoscopic and stool-based tests for colorectal cancer — the three screenings with demonstrated mortality benefit at population level;
- **treatment** — prompt, adequate, in organised oncological networks.

Tertiary prevention:

- **pain relief** — palliative care being an integral, and too often neglected, part of cancer control;
- **rehabilitation and psychological support** — returning the cured or stabilised patient to family, work and society.

The four components — prevention, early detection, treatment and palliation — form together the modern concept of the **national cancer control programme**, in which the epidemiologist's cancer registry provides the measuring instrument of every advance.

28.5. Cancer today: GLOBOCAN, prevention that works, and the elimination of a cancer

The global figures. The GLOBOCAN estimates of the International Agency for Research on Cancer give, for the most recent year, approximately **20.6 million new cancer cases and 9.8 million cancer deaths worldwide**, with a five-year prevalence of about 54 million people. The five most frequent cancers by incidence are **lung** (2.64 million cases, 12.8%), **breast** (2.43 million, 11.8%), **colorectum** (2.04 million, 9.9%), **prostate** (1.55 million, 7.5%) and **stomach** (0.98 million, 4.8%); by mortality, **lung** (1.86 million deaths, 19.1%), **colorectum** (0.92 million), **liver** (0.73 million), **breast** (0.69 million) and **stomach** (0.64 million) [2]. Lung cancer has thus returned to first place in both incidence and mortality — a direct consequence of the tobacco epidemic described in Chapter 23 — and breast cancer accounts for about a quarter of all cancers in women.

The projections are demographic before they are biological: with population growth and ageing, global incidence is expected to exceed 35 million new cases a year by 2050, with the steepest increases in low- and middle-income countries, where survival is lowest and where the shortfall in radiotherapy, pathology and systemic therapy is greatest. This is why cancer control, as Section 28.4 states, is a matter of programmes rather than of individual therapeutic advances.

The attributable causes, quantified. The multifactorial aetiology of Section 28.3 can now be given proportions. Roughly 40% of cancers in high-income countries are attributable to known modifiable risk factors: **tobacco** remains the largest single cause (about a fifth of all cancer deaths worldwide, and the cause of some 85% of lung cancers); **infections** account for about 13% of cancers globally, rising above 20% in some regions [1]; then **alcohol**, classified as a Group 1 carcinogen by IARC [3] and causally implicated in cancers of the oral cavity, pharynx, larynx, oesophagus, liver, colorectum and breast, with no threshold of "safe" consumption identified for cancer risk; **excess body weight**, causally linked to at least thirteen cancers; **ultraviolet radiation**; **air pollution**, classified as carcinogenic by IARC; **ionising radiation**; and **occupational exposures**, which continue to account for a substantial number of preventable cancers.

The infectious causes and the two anticancer vaccines. The principle of Box 28.1 has become an operational strategy. The leading infectious causes are *Helicobacter pylori* (gastric cancer — for which eradication strategies are being trialled at population level), the **human papillomaviruses** (virtually all cervical cancers and a growing share of oropharyngeal cancers), the **hepatitis B and C viruses** (hepatocellular carcinoma), Epstein–Barr virus, HIV through immunosuppression, and the schistosomes.

The demonstration of population effect is now available. In England, the national HPV vaccination programme was followed by a reduction in cervical cancer incidence of the order of **87% in the cohorts offered vaccination at ages 12–13**, together with a comparable fall in grade 3 cervical intraepithelial neoplasia [4]; analyses of national mortality data to 2024 have begun to show the corresponding decline in cervical cancer deaths [5]. On this evidence rests the **WHO global strategy for the elimination of cervical cancer**, with its 90–70–90 targets by 2030 (90% of girls fully vaccinated by 15; 70% of women screened with a high-performance test at 35 and 45; 90% of those with disease treated) [6] — the first time in history that the elimination of a common cancer has been a declared and technically feasible objective.

Romania is precisely the country where this matters most. HPV vaccination coverage among 15-year-old girls stood at about **23% in 2024, against an EU average of 63%** [7], while Romania has long carried one of the highest cervical cancer incidence and mortality rates in the European Union. The gap between the available technology and its uptake is, in this instance, measurable in future deaths — and closing it belongs to the daily practice of every physician who sees adolescents and their parents.

Screening. The evidence and the pitfalls are set out in Chapter 9; the three programmes with demonstrated mortality benefit at population level remain cervical (now by primary HPV testing), breast (mammography) and colorectal (FIT or colonoscopy), to which low-dose CT screening for lung cancer in heavy smokers has been added on the strength of randomised trials, and is being introduced progressively in Europe. The recurrent lesson of implementation is that **organised programmes with systematic invitation and quality assurance achieve what opportunistic screening does not** — including equity of access, without which screening widens rather than narrows the social gradient in cancer mortality.

Treatment and survival. Although outside the scope of an epidemiology course, three developments have altered the survival statistics that epidemiologists measure: immune checkpoint inhibitors, molecularly targeted therapy directed by genomic profiling, and the improvement of radiotherapy. Their epidemiological consequence is a widening survival gap between countries with and without access to them — which makes the availability of essential cancer medicines, radiotherapy and pathology a public health indicator in its own right, and cancer registration the instrument by which any of this can be known.

References

1. de Martel C, Georges D, Bray F, Ferlay J, Clifford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. *The Lancet Global Health*. 2020. doi:10.1016/S2214-109X(19)30488-7
2. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*. 2024. doi:10.3322/caac.21834; and IARC Global Cancer Observatory factsheets.
3. International Agency for Research on Cancer. *IARC Monographs on the Identification of Carcinogenic Hazards to Humans*. Lyon: IARC.
4. Falcaro M, Castañon A, Ndlela B, et al. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. *The Lancet*. 2021. doi:10.1016/S0140-6736(21)02178-4
5. Cervical cancer mortality trends following HPV vaccination in England, 2001–24: an analysis of population-based mortality data. *The Lancet*. 2026. doi:10.1016/S0140-6736(26)00918-9
6. World Health Organization. *Global strategy to accelerate the elimination of cervical cancer as a public health problem*. Geneva: WHO; 2020.
7. OECD/European Observatory on Health Systems and Policies. *România: Profilul de țară din 2025 în ceea ce privește sănătatea*. Paris/Brussels; 2025.

Chapter 29. The Global Response to the Chronic Disease Epidemic

29.1. Misunderstandings and realities

The chronic disease epidemic is rapidly evolving, while the global recognition of and response to it have not kept pace. The obstacle is not only material but conceptual: a series of widespread misunderstandings about chronic diseases, which can be dispelled by the strongest evidence. The principal realities, opposed point by point to the common prejudices, are the following:

- *"Chronic diseases are diseases of the rich countries."* In reality, the projections by World Bank income groups show that the great majority of chronic disease deaths occur in the **low- and middle-income countries**, and within every country **chronic diseases are concentrated among the poor** — who both fall ill more and, facing illness, sink into deeper poverty, in a vicious circle of disease and deprivation.
- *"Chronic diseases are diseases of old age."* A large share of chronic disease deaths occur at active ages, between 30 and 69 years — premature deaths, with maximal social and economic cost.
- *"The sick have only themselves to blame; life-style is a free choice."* In reality, **the poor and the children have a limited choice**: the food environment, advertising, education, urban conditions and income decide, to a great extent, in their place — and the next generation is being shaped by the same forces.
- *"Nothing can be done."* In reality, **80% of premature heart disease, stroke and type 2 diabetes, and 40% of cancer, are preventable**, and **inexpensive and cost-effective interventions exist**; the individuals who escape risk without any intervention are the rare exceptions, not the model.
- *"Everybody has to die of something."* Death is indeed inevitable — but it does not need to be **slow, painful or premature**, which is what uncontrolled chronic disease condemns millions to.

29.2. The global goal

Upon these realities WHO founded the global goal: **a 2% annual reduction in the chronic disease death rates worldwide, per year, over 10 years** [1]. The scientific knowledge to achieve this goal already exists. Its achievement was projected to avert tens of millions of deaths within a decade — **9 out of 10 of the lives saved being in the low- and middle-income countries** — and to produce economic gains of billions through the labour supply preserved.

29.3. What works

Comprehensive and integrated action is the means to prevent and control chronic diseases: acting on the common risk factors (tobacco, diet, inactivity, alcohol) across the whole population and across sectors — health, finance, education, agriculture, urban planning — while the health system reorients itself towards prevention, screening and the long-term management of the chronic patient, with primary care at the centre.

Box 29.1. From the global goal to the current targets (supplementary). The strategy summarised above has since been consolidated into the WHO Global Action Plan for the prevention and control of NCDs and into the United Nations Sustainable Development Goals, whose target 3.4 demands the reduction by one third, by 2030, of premature mortality from non-communicable diseases. The operational instrument is the list of **"best buys"** — interventions of proven cost-effectiveness [2]: the taxation of tobacco, alcohol and sugar-sweetened beverages; smoke-free environments and advertising bans; salt reduction and the elimination of industrial trans-fats; the promotion of physical activity; hypertension and diabetes management and secondary prevention with accessible essential medicines in primary care; hepatitis B and HPV vaccination; and cervical, breast and colorectal cancer screening. For the sixth-year student, the final lesson of this book is precisely the unity of its parts: the same epidemiological reasoning — source or risk factor, route or mechanism, susceptible population, and the levels of prevention — serves the physician equally before an outbreak of measles, a case of tetanus, or the silent epidemic of hypertension in his or her own list of patients.

29.4. Where the global response stands, and what remains to be done

The commitments and the measured progress. The "global goal" of a 2% annual reduction in chronic disease death rates, formulated in the WHO report on which this chapter is based, has been succeeded by the more precise commitment of **Sustainable Development Goal target 3.4**: to reduce by one third, by 2030, premature mortality from non-communicable diseases [3]. The WHO NCD Progress Monitor, which assesses every country against a standard set of indicators [4], shows the pattern that has become familiar: near-universal adoption of policies on paper, and very uneven implementation in practice — with tobacco control the most widely implemented and the fiscal measures on alcohol and unhealthy foods the least. On current trajectories, only a minority of countries will reach the 2030 target.

Why the trajectory is off track is not mysterious, and the reasons should be stated plainly because they define what the next generation of physicians will have to change. First, the **interruption caused by the COVID-19 pandemic**: two years in which screening, chronic disease follow-up and elective care were disrupted worldwide, whose consequences are now being counted in later-stage cancer diagnoses and in deteriorated control of hypertension and diabetes. Secondly, the **financing gap**: NCDs receive a share of development assistance for health that is grossly disproportionate to the burden they represent. Thirdly, the **commercial determinants of health** — the industries of tobacco, alcohol, ultra-processed food and fossil fuels [5] — whose products and marketing shape the risk factors described in Part IV, and whose lobbying has repeatedly delayed the fiscal and regulatory measures that constitute the

"best buys". Fourthly, the **weakness of primary health care**, which is where the whole of chronic disease management must ultimately take place.

What demonstrably works. The evidence assembled through this Part identifies a short list of measures with documented population effect: **tobacco taxation and smoke-free legislation**, whose effect on myocardial infarction admissions is measurable within a year; the **elimination of industrial trans-fats**, now covering a majority of the world's population; **salt reduction and potassium-enriched salt substitution**, with randomised evidence of stroke and mortality reduction; **taxation of sugar-sweetened beverages**, with documented reductions in purchases; **HPV and hepatitis B vaccination**, the two anticancer vaccines; **organised cancer screening** with quality assurance; and **standardised, protocol-driven hypertension and diabetes management in primary care**, of which the WHO HEARTS and PEN packages are the operational form. None of these is expensive relative to its benefit; all of them require political decision rather than scientific discovery.

The equity dimension. The realities set out in Section 29.1 — that chronic diseases concentrate among the poor, that the poor and children have limited choice, that the deaths are premature — have been amplified rather than contradicted by the subsequent data: **82% of premature NCD deaths occur in low- and middle-income countries** [6], and within every country the social gradient in NCD mortality is steep and, in several, widening. A prevention strategy that relies exclusively on individual behaviour change will, predictably, widen that gradient, because the capacity to act on advice is itself unequally distributed [7]. This is the strongest argument for the population and structural measures listed above — and it is an argument from evidence, not from ideology.

29.5. A concluding note for the student

This book has moved from the general laws of the epidemiological process, through the methods by which those laws are established, to the two great families of disease that occupy contemporary medicine. Its structure could suggest that these are separate subjects. They are not, and the final lesson is the unity of the reasoning.

Whether the physician faces an outbreak of measles in a village, a case of tetanus in an unvaccinated elderly man, a patient with untreated hypertension, or a population in which cervical cancer remains common, the same four questions organise the response: **what is the source or the risk factor; by what route or mechanism does it reach people; who is susceptible, and why; and at which level of prevention can the chain be broken?** The instruments differ — chlorination, a vaccine, a tax on tobacco, a screening programme, a single-pill combination — but the analysis does not.

To that analytical unity the practice of the past decade has added three habits that this book has tried to teach alongside the facts: to **measure** before asserting, and to know which measure answers which question; to **weigh the evidence by the design that produced it**, remembering

that the strength of a conclusion is the strength of the study behind it; and to **communicate honestly**, including the uncertainty — because trust, as the epidemics of the past few years have shown, is itself an epidemiological variable, and one that the individual physician does more than any institution to build or to destroy.

References

1. World Health Organization. *Preventing Chronic Diseases: A Vital Investment*. Geneva: WHO; 2005.
2. World Health Organization. *Tackling NCDs: best buys and other recommended interventions for the prevention and control of noncommunicable diseases*. Geneva: WHO.
3. United Nations. Political declaration of the high-level meeting of the General Assembly on the prevention and control of non-communicable diseases. New York: UN.
4. World Health Organization. *Noncommunicable diseases progress monitor 2025*. Geneva: WHO; 2025.
5. Kickbusch I, Allen L, Franz C. The commercial determinants of health. *The Lancet Global Health*. 2016. doi:10.1016/S2214-109X(16)30217-0
6. World Health Organization. Noncommunicable diseases — key facts. Geneva: WHO; 2025 (data for 2021).
7. Rose G. *The Strategy of Preventive Medicine*. Oxford University Press; 1992.

PART V. EPIDEMIOLOGY AT THE BEDSIDE

Chapter 30. Clinical Epidemiology and Evidence-Based Practice

30.1. Why this chapter closes the book

Everything in the preceding parts concerned populations. The physician, however, works with one patient at a time, and the natural question of the sixth-year student is what any of it changes in the consulting room. **Clinical epidemiology** is the answer: it is the application of the methods of Part II to the decisions of clinical practice — diagnosis, prognosis, treatment and prevention in the individual patient. This chapter sets out the small number of quantitative habits that convert epidemiological knowledge into better clinical decisions.

30.2. Diagnosis: probability before and after the test

The single most consequential idea in clinical epidemiology is that **a test does not establish a diagnosis; it modifies a probability**. Three quantities express this:

- the **pre-test probability** — the probability of the disease before the test, derived from prevalence in the setting, from the history and from the examination;
- the **likelihood ratio** of the result — LR+ = sensitivity/(1 − specificity) for a positive result, LR− = (1 − sensitivity)/specificity for a negative one;
- the **post-test probability**, obtained by combining the two.

The practical rules of thumb are simple: a likelihood ratio above 10 or below 0.1 usually changes management; one between 0.5 and 2 rarely does. And the pre-test probability dominates: the same test result means different things in different patients, which is why Box 9.1 — the demonstration that the predictive value of a test collapses when prevalence is low — is a clinical, not merely an epidemiological, lesson. Ordering a test in a patient with a very low pre-test probability generates false positives, further investigation, anxiety, cost and occasionally harm; this is where **quaternary prevention** (Section 1.7) begins.

Two further distinctions belong here. **Diagnostic thresholds** are decisions, not facts: the test threshold below which no test is done and the treatment threshold above which treatment starts depend on the consequences of missing the disease and of treating unnecessarily. And a test must be judged not only by its accuracy but by whether using it changes outcomes — the question addressed by randomised trials of diagnostic strategies rather than by accuracy studies.

30.3. Treatment: expressing benefit in usable numbers

The results of a therapeutic trial can be expressed in ways that convey very different impressions of the same fact, and the physician must be able to translate between them.

- **Relative risk reduction (RRR)** = (risk in controls − risk with treatment)/risk in controls. It is the figure most often quoted, and it is largely independent of baseline risk — which is exactly why it is misleading on its own.

- **Absolute risk reduction (ARR)** = risk in controls − risk with treatment. It depends on the patient's baseline risk and is therefore the clinically meaningful figure.
- **Number needed to treat (NNT)** = 1/ARR — the number of patients who must receive the treatment for one to benefit, over the period of the trial.
- **Number needed to harm (NNH)** = 1/absolute risk increase of the adverse effect.

The relation between them contains the whole argument for individualising treatment. A therapy with a constant relative risk reduction of 25% produces, in a patient whose 10-year risk is 40%, an absolute reduction of 10 percentage points and an NNT of 10; in a patient whose risk is 2%, the same relative reduction gives an absolute benefit of 0.5 percentage points and an NNT of 200. Identical drug, identical trial, entirely different clinical decisions — and the reason why modern cardiovascular guidelines calibrate treatment to total risk (Section 25.6) rather than to a single threshold value.

The comparison of NNT with NNH, weighted by the severity of the outcomes, is the quantitative form of the benefit–harm judgement that every prescription implies.

30.4. Prognosis and natural history

Prognostic questions differ from aetiological ones: the aim is not to identify a cause but to predict a course. The instruments are **cohort studies of inception cohorts** (patients assembled at a common, early point in the disease), **survival analysis** (Kaplan–Meier curves, hazard ratios), and **prognostic models** validated in populations other than the one in which they were derived. Two errors recur: confusing a prognostic marker with a therapeutic target (a factor that predicts an outcome need not, when modified, change it), and applying a model outside the population in which it was validated.

The physician should also retain from Chapter 9 the vocabulary of the biases that flatter apparent prognosis: **lead time**, **length time**, and **overdiagnosis** — because they operate not only in screening programmes but every time an earlier or more sensitive diagnostic technology is introduced.

30.5. Reading a paper: a practical sequence

Evidence-based practice is often described as the integration of the best available evidence with clinical expertise and with the patient's values and circumstances [1]. Its operational core is the ability to read a study critically, and a workable sequence is short [2]:

1. **The question.** Formulate it in PICO terms — Population, Intervention (or exposure), Comparator, Outcome. A vague question cannot be answered by any literature.
2. **The design.** Is it appropriate to the question? Therapy and prevention: randomised trial or systematic review of trials. Aetiology and harm: cohort or case-control. Diagnosis: cross-sectional study against a reference standard, in a population resembling the intended clinical use. Prognosis: inception cohort.

3. **The internal validity.** For a trial: was allocation truly random and concealed; were the groups comparable at baseline; was there blinding; was the analysis by intention to treat; was follow-up complete; was the primary outcome pre-specified? For an observational study: how were participants selected, how was exposure measured, which confounders were considered, and how were they controlled?
4. **The results.** What is the *size* of the effect and how *precise* is it — that is, what does the confidence interval contain? Is the outcome one that matters to patients (a death, a stroke, a symptom) or a **surrogate** (a laboratory value, an image)? The history of medicine contains many surrogates that improved while patients did not.
5. **The applicability.** Does the patient in front of me resemble those studied? Is the intervention feasible here? What is the baseline risk of *my* patient, and therefore the expected absolute benefit?

To this sequence, contemporary appraisal adds attention to the ecology of the literature itself: **publication bias**, **selective outcome reporting**, **conflicts of interest**, and the **reproducibility crisis** — the demonstration, in several fields, that a substantial proportion of published findings do not replicate [3]. The remedies now standard — trial registration, pre-specified protocols and analysis plans, reporting guidelines (CONSORT for trials [4], STROBE for observational studies [5], PRISMA for systematic reviews, STARD for diagnostic accuracy) and data sharing — are the profession's structural answer, and the reader who checks whether a study followed them has already performed a substantial part of the appraisal.

30.6. From evidence to guidelines, and back to the patient

Guidelines translate bodies of evidence into recommendations, and the **GRADE** system makes explicit both the certainty of the evidence and the strength of the recommendation [6]. A **strong** recommendation means that almost all well-informed patients would choose the option; a **conditional** one means that choices will legitimately differ, and that the decision belongs with the patient. Recognising which of the two is in front of you is what distinguishes the informed use of a guideline from its mechanical application.

The final step is **shared decision-making** [7]: presenting absolute benefits and harms in comprehensible terms (natural frequencies — "out of 100 people like you, about 3 will..." — are understood far better than percentages, and far better than relative risks [8]), eliciting what matters to the person, and reaching a decision together. This is not a softening of the evidence; it is its correct use, because a treatment whose expected benefit is small and whose burden is large is not obviously right for everyone, and only the patient can supply the missing values.

30.7. Conclusion: the epidemiological habits of mind

If a single paragraph must survive from this book, let it be this. In front of every patient, and every population, the physician who has learned epidemiology asks: **How frequent is this,**

here and now? Where does it come from, and how does it travel? Who is susceptible, and why? How certain is the evidence I am relying on, and what design produced it? What is the absolute benefit for this person, and what is the harm? And at which level of prevention could this have been avoided altogether? These questions do not require a computer or a database; they require a habit. They are what this discipline exists to teach, and they will remain valid long after every figure printed in this volume has been superseded.

References

1. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312:71–72.
2. Guyatt G, Rennie D, Meade MO, Cook DJ. *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. 3rd ed. McGraw-Hill; 2015.
3. Ioannidis JPA. Why most published research findings are false. *PLoS Medicine*. 2005. doi:10.1371/journal.pmed.0020124
4. Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010. doi:10.1136/bmj.c332
5. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. *The Lancet*. 2007. doi:10.1016/S0140-6736(07)61602-X
6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008. doi:10.1136/bmj.39489.470347.AD
7. Elwyn G, Frosch D, Thomson R, et al. Shared decision making: a model for clinical practice. *Journal of General Internal Medicine*. 2012. doi:10.1007/s11606-012-2077-6
8. Gigerenzer G, Gaissmaier W, Kurz-Milcke E, Schwartz LM, Woloshin S. Helping doctors and patients make sense of health statistics. *Psychological Science in the Public Interest*. 2007. doi:10.1111/j.1539-6053.2008.00033.x

APPENDICES

Appendix A. Glossary of Epidemiological Terms

Anthroponosis. Disease specific to humans, transmitted from human to human (measles, rubella, syphilis, viral hepatitis).

Anthropozoonosis. Disease in which the animal and the human sources of infection have comparable importance; influenza is the classical example.

Attack rate. Cumulative incidence computed for a defined group over the period of an outbreak. The **secondary attack rate** is the proportion of contacts of a primary case who develop the disease within the maximum incubation period; it measures contagiousness.

Attributable risk (risk difference). The excess incidence in the exposed compared with the unexposed; the number of cases per unit population that removal of the exposure would prevent. Measure of public health impact.

Basic reproduction number (R□). Mean number of secondary cases produced by one case in a wholly susceptible population. The **effective reproduction number (R_t)** is the same quantity in the population as it actually is.

Bias. Any systematic error in the design, conduct or analysis of a study that produces an estimate deviating from the truth. Principal families: selection bias, information (measurement) bias.

Carrier. Person who harbours and excretes a pathogen without manifest disease. Sub-types: pre-infectious (incubatory), convalescent, chronic, healthy; permanent, intermittent or closed (encysted) according to the pattern of excretion.

Case definition. Set of clinical, epidemiological and laboratory criteria by which a case is classified as possible, probable or confirmed; the instrument that makes surveillance data comparable.

Case-fatality (fatality). Deaths from a disease divided by the cases of that disease; a measure of severity. Not to be confused with **lethality (proportionate mortality)**, the share of a given cause among all deaths.

Cluster. Aggregation of cases in space and/or time, which may or may not exceed the expected number.

Cohort study. Analytical observational design starting from the exposure and following participants forward to the outcome; yields incidence, relative risk and attributable risk.

Case-control study. Analytical observational design starting from the outcome and comparing past exposure between cases and controls; yields the odds ratio.

Confounding. Distortion of an association by a third factor associated with the exposure and independently a risk factor for the outcome, not lying on the causal pathway.

Contagiousness index. Percentage of susceptible persons exposed to the infection who develop the typical disease (over 95% for measles; about 40% for scarlet fever).

Contamination. Presence of a pathogen on a surface or in an organism before multiplication has begun; distinct from infection.

DALY (disability-adjusted life year). Years of life lost through premature death plus years lived with disability, weighted by severity; one DALY is one lost year of healthy life.

Determining factors of the epidemiological process. The source of infection, the transmission route and mechanism, and the receptive population; all three are necessary.

Endemic. Constant presence of a disease in a territory at a relatively low and uniform level. **Hyperendemic**: intense, persistent transmission affecting all age groups.

Epidemic. Occurrence of cases in excess of what is expected in a given community, place and time.

Epidemiological focus. The infectious process together with all its links to previous and subsequent infectious processes; the concrete unit of the epidemiological process.

Epidemiological process. The totality of physiopathological and social phenomena occurring in a population traversed by a pathogen; a succession of connected epidemiological foci.

Eradication. Worldwide disappearance of the disease and of its agent (smallpox). **Elimination**: disappearance of the disease from a defined territory, the agent persisting elsewhere.

Favouring factors. Natural, socio-economic and biological conditions which do not create the focus but modify the form of manifestation of the epidemiological process.

Herd immunity (herd protection). Indirect protection of susceptible individuals resulting from a sufficient proportion of immune individuals in the population; the threshold is approximately $1 - 1/R_0$.

Iceberg phenomenon. The relation between the few clinically manifest cases and the large submerged mass of inapparent infections (poliomyelitis, West Nile fever).

Incidence. Number of new cases in a population over a period; **cumulative incidence** (risk) relates them to persons at risk, **incidence rate** to person-time.

Incubation period. Interval between infection and the appearance of the first symptoms; determines the duration of quarantine and the reading of the epidemic curve.

Infection, latent. Infection with biological and histopathological changes but without clinical signs.

Odds ratio. Ratio of the odds of exposure in cases to that in controls; approximates the relative risk for rare diseases.

One Health. Integrated approach to the health of humans, animals and the environment; the framework of zoonosis and antimicrobial resistance control.

Overdiagnosis. Detection, usually by screening, of a condition that would never have produced symptoms or death in the person's lifetime.

Pandemic. Epidemic extending over several countries or continents, affecting a large number of people. Since the 2024 amendments to the IHR, a **pandemic emergency** is a formal legal category above the PHEIC.

PHEIC (Public Health Emergency of International Concern). Extraordinary event which constitutes a public health risk to other States through international spread and may require a coordinated international response; declared by the WHO Director-General under the IHR.

Population attributable fraction. Proportion of cases in the whole population attributable to an exposure; depends on both the relative risk and the prevalence of exposure.

Prevalence. Number of existing cases (point or period) related to the population; approximately incidence × duration.

Prevention: primordial (prevents the appearance of risk factors), **primary** (acts on risk factors before disease), **secondary** (early detection — screening), **tertiary** (limits complications and disability), **quaternary** (protects against unnecessary medical intervention).

Quarantine. Restriction of activity of healthy persons exposed to a case, for the maximum incubation period; distinct from **isolation**, which applies to the ill.

Receptivity. State of the organism permitting the survival and multiplication of the pathogen.

Relative risk. Ratio of the incidence in the exposed to that in the unexposed; measures the strength of the association.

Screening. Presumptive identification of unrecognised disease by tests applied to apparently healthy persons; not a diagnosis.

Sensitivity / specificity. Proportion of the diseased correctly identified by a test / proportion of the non-diseased correctly excluded. **Predictive values** depend additionally on the prevalence.

Sporadic. Small number of cases without apparent connection, dispersed in space and time.

Standardisation. Procedure removing the effect of the differing composition (usually age) of populations being compared; direct (standardised rate) or indirect (standardised mortality ratio).

Superspreading. Marked heterogeneity of transmission, in which a minority of cases generate the majority of secondary infections (overdispersion).

Surveillance. Continuous, systematic collection, analysis and interpretation of health data, integrated with dissemination to those who must act — "information for action".

Syndemic. Synergistic co-occurrence of two or more epidemics in a population, aggravated by social conditions.

Vector. Living organism transmitting a pathogen; **mechanical (passive)** or **biological (active)**; **monovalent**, **polyvalent** or **universal** by specificity.

Zoonosis. Disease transmissible under natural conditions from vertebrate animals to humans.

Appendix B. Essential Formulae

Measure	Formula	Notes
Cumulative incidence (risk)	new cases / persons at risk at start	dimensionless; state the period
Incidence rate	new cases / person-time at risk	per 100,000 person-years
Prevalence	existing cases / population	≈ incidence × duration
Case-fatality	deaths from disease / cases of disease	severity
Relative risk (RR)	$I_{exposed} / I_{unexposed}$	strength of association
Attributable risk (AR)	$I_{exposed} - I_{unexposed}$	public health impact
Attributable fraction, exposed	$(RR - 1) / RR$	share of exposed cases due to exposure
Population attributable fraction	$P(exp)\cdot(RR - 1) / [1 + P(exp)\cdot(RR - 1)]$	depends on exposure prevalence
Odds ratio (OR)	$(a \times d) / (b \times c)$	case-control studies
Sensitivity	TP / (TP + FN)	property of the test
Specificity	TN / (TN + FP)	property of the test
Positive predictive value	TP / (TP + FP)	depends on prevalence
Negative predictive value	TN / (TN + FN)	depends on prevalence
Herd immunity threshold	$1 - 1/R_0$	proportion immune needed
Standardised mortality ratio	observed deaths / expected deaths × 100	indirect standardisation

Appendix C. Incubation Periods and Isolation of the Principal Diseases Studied

Disease	Usual incubation	Contagious period	Isolation / principal measure
Influenza	1–4 days	from ~1 day before onset, 3–5 days	home isolation; vaccination
Measles	10–14 days	4 days before to 4 days after rash	isolation to disappearance of rash; MMR
Rubella	14–21 days	7 days before to 7 days after rash	isolation; MMR; protect pregnancy
Mumps	16–18 days	2 days before to ~9 days after onset	isolation ~10 days; MMR
Scarlet fever	2–5 days	until 24–48 h of effective antibiotic	isolation; penicillin
Diphtheria	2–5 days	2–3 days after starting antibiotic	strict isolation; antitoxin; vaccine
Pertussis	7–10 days	catarrhal phase to 3 weeks (untreated)	isolation 5 days on macrolide; vaccine
Meningococcal disease	2–10 days	24–48 h after effective antibiotic	droplet precautions; chemoprophylaxis of contacts
Tuberculosis	weeks to years	while sputum positive; falls ~2 weeks after treatment	airborne precautions; treat
Hepatitis A	15–50 days	2 weeks before to 1 week after jaundice	hygiene; immunoglobulin/vaccine
Hepatitis B	45–180 days	while HBsAg positive	standard precautions; vaccine
Cholera	hours–5 days	during illness, briefly after	contact-type isolation; rehydration
Typhoid fever	8–14 days (up to 3 weeks)	while excreting; 2–5% become chronic carriers	isolation until clearance; carrier follow-up
Dysentery (Shigella)	1–7 days	during illness and up to weeks after	isolation; three negative coprocultures
Poliomyelitis	7–14 days	pharyngeal 1 week; faecal 3–6 weeks	isolation; disinfection of faeces; IPV
Tetanus	3–21 days	not transmitted between humans	wound care; ATPA ± immunoglobulin
COVID-19	2–5 days (Omicron)	~2 days before to ~5 days after onset	isolation of cases; ventilation; vaccination

The values are didactic ranges; the current national methodological norms govern practice.

Appendix D. The Romanian National Immunisation Programme (structure)

Age	Vaccine
First 24 hours	Hepatitis B
2–7 days	BCG
2 months	Hexavalent (DTPa-IPV-Hib-HepB) + pneumococcal conjugate
4 months	Hexavalent + pneumococcal conjugate
11 months	Hexavalent + pneumococcal conjugate
12 months	MMR
5 years	MMR (second dose)
6 years	DTPa-IPV
14 years	dTpa
Target age groups	HPV (girls and boys); influenza in risk groups

Structure as provided by the national programme; the schedule is periodically amended by order of the Ministry of Health, and the version in force must always be verified.

Appendix E. Self-Assessment Questions

Part I — General epidemiology

1. Define the epidemiological focus and distinguish it from the infectious process and from the epidemiological process.
2. A person recovered from typhoid fever excretes *S. typhi* four months after the acute episode. Classify this carrier and state the measures required.
3. Explain why the aerogenous route is described as "the most efficient and the hardest to block".
4. A disease has R□ = 15. What proportion of the population must be immune to interrupt transmission, and what does this imply for a vaccine of 95% effectiveness?
5. Distinguish sporadic, endemic, epidemic and pandemic manifestation, giving one example of each from the diseases studied.
6. List the five levels of prevention and give one measure of each for cervical cancer.

Part II — Methods

1. A disease has an incidence of 10 per 1,000 per year and a mean duration of 5 years. Estimate the prevalence and explain the relation used.
2. Why can a case-control study not measure incidence, and what does it measure instead?
3. A screening test has 95% sensitivity and 95% specificity. Compute the positive predictive value in a population with 1% prevalence and comment.
4. Name the three biases that make survival comparisons between screen-detected and symptom-detected cases invalid.
5. State the Bradford Hill viewpoints and identify the only one that is strictly necessary.
6. Outline the ten steps of an outbreak investigation and explain when control measures should begin.

Part III — Infectious diseases

1. Explain antigenic drift and shift, and relate each to the epidemic and pandemic manifestation of influenza.
2. What is meant by "U = U", and what are its epidemiological consequences?
3. Compare the source of infection, transmission and prevention of hepatitis A and hepatitis B.
4. A child presents with a wound contaminated with soil; the vaccination history is unknown. Describe the complete prophylactic conduct.
5. Why is poliomyelitis eradicable and tetanus not?
6. Describe the measures to be taken in a school where a case of measles has been confirmed.

7. What distinguishes tuberculosis infection from tuberculosis disease, and what is the practical consequence for contacts?
8. State the four principles of antimicrobial stewardship that a clinician can apply at the bedside.

Part IV — Chronic non-communicable diseases

1. Enumerate the six epidemiological peculiarities of chronic non-communicable diseases.
2. Explain the "prevention paradox" and its consequence for the choice between the population and the high-risk strategy.
3. Why do predictive values of a screening test differ between a high-risk group and the general population?
4. List the WHO "best buys" and identify those applicable in Romania with the greatest expected impact.
5. Explain why treating obesity pharmacologically does not solve the obesity epidemic.

General Bibliography and Further Reading

The references specific to each subject are listed at the end of the corresponding chapter. What follows is the general bibliography of the volume — the textbooks, treatises and permanent sources of data to which the reader should turn for a fuller treatment of any topic.

1. The lecture courses of the Discipline of Epidemiology, "Victor Babeș" University of Medicine and Pharmacy, Timișoara (Courses 1–7 and the course of chronic non-communicable disease epidemiology), which constitute the foundation of the present text.
2. Ivan A. (ed.). *Tratat de epidemiologie a bolilor transmisibile.* Iași: Polirom; 2002.
3. Bocșan I.S. *Epidemiologie practică pentru medicii de familie.* Cluj-Napoca: Editura Medicală Universitară "Iuliu Haţieganu"; 1999.
4. Celentano D.D., Szklo M. *Gordis Epidemiology.* 6th ed. Philadelphia: Elsevier; 2019.
5. Park K. *Park's Textbook of Preventive and Social Medicine.* 26th ed. Jabalpur: Banarsidas Bhanot; 2021.
6. Heymann D.L. (ed.). *Control of Communicable Diseases Manual.* 21st ed. Washington, DC: American Public Health Association; 2022.
7. Bennett J.E., Dolin R., Blaser M.J. (eds.). *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases.* 9th ed. Philadelphia: Elsevier; 2020.
8. Orenstein W.A., Offit P.A., Edwards K.M., Plotkin S.A. (eds.). *Plotkin's Vaccines.* 8th ed. Philadelphia: Elsevier; 2023.
9. Centers for Disease Control and Prevention. *Principles of Epidemiology in Public Health Practice.* 3rd ed. Atlanta: CDC; 2012.
10. Porta M. (ed.). *A Dictionary of Epidemiology.* 6th ed. New York: Oxford University Press; 2014.
11. World Health Organization. *Preventing Chronic Diseases: A Vital Investment.* Geneva: WHO; 2005.
12. World Health Organization. *Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013–2020* (extended to 2030). Geneva: WHO.
13. World Health Organization. *Global Hepatitis Report.* Geneva: WHO; 2024.
14. UNAIDS. *Global AIDS Update.* Geneva: Joint United Nations Programme on HIV/AIDS; 2024.
15. World Health Organization. Fact sheets: Noncommunicable diseases; Obesity and overweight; Hypertension; Diabetes; Cancer; Cholera; Typhoid; Measles; Poliomyelitis; Hepatitis A–E; HIV/AIDS; Influenza (seasonal, zoonotic, pandemic). Geneva: WHO (www.who.int).

16. European Centre for Disease Prevention and Control. Surveillance reports and factsheets on measles, diphtheria, pertussis, invasive meningococcal disease, hepatitis and influenza (www.ecdc.europa.eu).
17. The Romanian National Institute of Public Health (INSP/CNSCBT). Methodologies for the surveillance of communicable diseases and the National Immunisation Programme (www.insp.gov.ro).

Note. Epidemiological figures, vaccination schedules and therapeutic recommendations evolve continuously; for clinical practice, the current editions of the national methodological norms and of the international guidelines must always be consulted.