

Contents

<i>Foreword</i>	xix
<i>Preface</i>	xxiii
1 Practical Experience with an Integrated Syndromic Surveillance System in the Medical, Veterinary, Nursing, and Emergency Response Communities	1
<i>William Stanhope, Tigi Ward, R. Michael Ragain, Gary Simpson, and Alan Zelicoff</i>	
1.1 More Than Half of All Human Infectious Agents are Zoonotic	1
1.2 Syndrome Reporting Information Systems	3
1.2.1 Examples	6
1.2.2 Some Successes with SYRIS	11
1.2.3 Actionable Information: The SYRIS Advantage	12
1.3 Conflict of Interest Disclosure	14
2 Environmental Surveillance for Polioviruses in Israel: Bioerror, Bioterror, or just Mother Nature	17
<i>Lester M. Shulman, Yossi Manor, Danit Sofer, and Ella Mendelson</i>	
2.1 The Silent Presence or Circulation of Polioviruses in Poliomyelitis-Free Communities	17
2.2 Global Eradication of Poliomyelitis	18
2.3 The Need for Routine Surveillance	20
2.4 The Program of Environmental Surveillance for Poliovirus in Israel	20
2.5 Polioviruses Isolated from Environmental Samples in Israel	23

2.6	Molecular Analysis Yields Epidemiological Information	23
2.7	The Contribution of Routine Surveillance toward Understanding One Potential Route for Reemergence of Neurovirulent Polioviruses	27
2.8	Monitoring Silent Poliovirus Infections: The Contribution of Sewage Surveillance and Molecular Epidemiology	30
3	Filoviruses: Deadly Pathogens and Potential Bioweapons	35
	<i>Michael Schümann and Elke Mühlberger</i>	
3.1	Emergence of Marburg and Ebola Viruses	35
3.2	The Virus and the Disease	36
3.3	Filovirus Biology	37
3.4	Pathogenesis and Clinical Presentation	38
3.5	The Bioweapon Potential of Filoviruses	40
	3.5.1 Dissemination and Transmission	41
	3.5.2 Mortality and Impact on Public Health	43
	3.5.3 Public Panic and Social Disruption	45
	3.5.4 Public Health Preparedness	46
	3.5.4.1 Vaccination	46
	3.5.4.2 Treatment	50
	3.5.4.3 Diagnostics	53
3.6	Future Perspectives	55
4	Bridging Diagnostics Research, Development, and Commercialization: Diagnostics for the Developing World	65
	<i>Rosanna W. Peeling</i>	
4.1	Lack of Access to Diagnostics as a Contributor to the Burden of Infectious Diseases	65
4.2	Role of Diagnostic Tests	66
4.3	Diagnostic Landscape in the Developing World	67
4.4	Lack of International and National Regulatory Standards for Approval of Diagnostics	68
4.5	The Ideal Diagnostic Tool	68
4.6	Development of Diagnostic Tests	70
4.7	Challenges in the Availability of Quality-Assured Diagnostic Tests in the Developing World	70
4.8	Opportunities for a Better Future	73

4.8.1	Technological Advances	73
4.8.2	More Funding and More Players	73
4.8.3	Increased Efforts at Capacity Building	75
4.9	Bridging Research, Product Development, and Commercialization	75
5	Oropouche Fever: An Overview of the Epidemiological and Molecular Aspects in the Brazilian Amazon Region	79
	<i>Pedro F. C. Vasconcelos and Marcio R. T. Nunes</i>	
5.1	Oropouche Outbreaks	79
5.2	The Oropouche Virus	81
5.3	Geographic Distribution	83
5.4	Molecular Biology of the OROV	85
6	Is Avian Influenza Subtype H5N1 a Cause for Concern? A Critical Analysis	97
	<i>Alan P. Zelicoff</i>	
6.1	Specter of Panzootics	97
6.2	The Nature of Influenza A Predisposes It to Pandemics	98
6.3	A Brief History of the H5N1 Panzootic and Human Cases	102
6.4	Review of Epidemiology of H5N1 in Humans	105
6.4.1	The Basis of the Concern for H5N1 as a Pandemic Threat	106
6.4.2	Critique of the Pandemic Hypothesis	107
6.5	Are There Asymptomatic H5N1 Infections?	110
6.6	Do Humans Have Some Immunity to H5N1?	111
6.7	Experimental Data: Vaccination and Challenge Experiments in Animals Using H5N1	114
6.8	Transmission of Reassortment Variants of H5N1	116
6.9	Was the 1918 Pandemic Different from Others?	117
7	Diagnostics of Viral Respiratory Diseases	127
	<i>Tamar Amir, Guy Gubi, and Leslie Lobel</i>	
7.1	Viral Respiratory Diseases	127
7.2	Respiratory Viruses	128
7.3	Diagnostic Techniques	132
7.3.1	Immunoassays	135
7.3.2	Molecular Techniques	136

7.3.3	Multiplex PCR-Based Assays in Use Today	139
7.3.4	Point-of-Care Tests	142
8	Reverse Genetics as a Tool for Detection of Negative-Stranded RNA Viruses	149
	<i>Pavel Naumenko, Leslie Lobel, and Robert S. Marks</i>	
8.1	Dangerous Viruses Easily Accessible	149
8.2	Negative-Stranded RNA Viruses	150
8.2.1	Genome Structure	150
8.3	Reverse Genetics System Development	153
8.4	Choosing the Promoter	155
8.5	Applications	156
8.6	Detection of Negative-Stranded RNA Viruses	157
8.7	Reverse Genetics-Based Detection	159
8.8	Where Do We Go from Here?	164
9	Diagnostics of Ebola Hemorrhagic Fever Virus	169
	<i>Ariel Sobarzo, Robert S. Marks, and Leslie Lobel</i>	
9.1	Ebola Virus	169
9.2	Etiology and Epidemiology	170
9.3	Disease Transmission and Clinical Behavior	170
9.4	Therapy	171
9.5	The Fear of Ebola	171
9.6	Current Methods in Ebola Diagnostics	172
9.6.1	Culture Virus Isolation	174
9.6.2	Electron Microscopy	174
9.6.3	Serological Assays	175
9.7	Nucleic Acid-Based Techniques	176
9.8	Engineered Recombinant Proteins	177
9.9	New Trends in Ebola Diagnostics	179
9.10	Future Diagnostics	182
9.11	The Effort Continues	186
10	Pathogen Detection Using Spatially Focused Microwaves and Metal-Enhanced Fluorescence	201
	<i>Kadir Aslan and Chris D. Geddes</i>	
10.1	Ultrafast and Sensitive Detection of Anthrax with Focused Microwave and Metal-Enhanced Fluorescence	201
10.2	Metal-Enhanced Fluorescence	202

10.3	Microwave-Accelerated Metal-Enhanced Fluorescence	206
10.3.1	Proof-of-Principle Demonstration of the MAMEF Technique	207
10.3.2	Application of the MAMEF Technique to Pathogen Detection Based on DNA Hybridization Assays	210
10.4	Spatially Focused Microwaves and Metal-Enhanced Fluorescence for Pathogen and Virus Detection	213
10.5	Summary and Future Outlook	220
11	Lyssavirus Surveillance and Diagnostics: Focus on Africa	227
	<i>Wanda Markotter and Louis H. Nel</i>	
11.1	Introduction	227
11.2	The Etiological Agent	228
11.3	Lyssaviruses in Africa	231
11.4	Pathogenesis of Lyssaviruses	233
11.5	Lyssavirus Diagnostics	235
11.5.1	Detection of Negri Bodies	236
11.5.2	Fluorescent Antibody Test	236
11.5.3	Enzyme-Linked Immunosorbent Assay	238
11.5.4	Direct Rapid Immunohistochemical Test	238
11.5.5	Rapid Lateral Flow Immunochromatography	238
11.5.6	Detection of Lyssavirus RNA	239
11.5.7	Virus Isolation	240
11.5.8	Antibody Detection	241
11.6	Challenges for the Developing World	242
12	Detection of Human Pathogens under Basic Laboratory Conditions by DNA Hybridization Arrays	253
	<i>Roman Wölfel</i>	
13	Differentiation between Viral and Bacterial Respiratory Infections Using Chemiluminescence of Polymorphonuclear Leukocytes	263
	<i>Daria Prilutsky, Mark Last, Leslie Lobel, and Robert S. Marks</i>	
13.1	The Innate Immune System and Participating Cells	263

13.2	Phagocytosis as a First-Line Defense Mechanism against Pathogens	265
13.2.1	Respiratory Burst: Mechanisms, Localization, and Techniques for Detection	266
13.2.1.1	Main mechanisms, products and enzymes of the respiratory burst	266
13.2.1.2	Techniques used to measure reactive oxygen species	267
13.2.1.3	Localization of the luminol-dependent CL reaction	269
13.2.1.4	Stimulation of the respiratory burst	271
13.2.2	Priming	272
13.2.3	Characterization of the Dynamic Component Chemiluminescent Approach for Assessment of Functional States of Phagocytes	274
13.2.4	Components of Chemiluminescent Kinetics	275
13.3	Functional States of Phagocytes	277
13.3.1	Dynamic Assessment of Phagocytes' Functional States	279
13.3.1.1	fMLP priming	280
13.3.1.2	Aging as a priming factor	280
13.3.2	Functional States of Phagocytes Associated with Different Clinical States	281
13.3.3	Phagocytic Function in Viral Infection	282
13.3.4	Phagocytic Function in Bacterial Infection	283
13.4	Data Mining Techniques in Clinical Groups' Differentiation	284
13.5	Differentiation between Viral and Bacterial Respiratory Infections Using a Chemiluminescent Approach	285
13.5.1	Description of an Experiment	285
13.6	Data Mining Algorithms and CL Information Can Differentiate between Clinical Groups and Assess Functional States of Phagocytes	286
13.7	Prospects	290

14	Phage Display for Viral Diagnostics	299
	<i>Danit Atias, Leslie Lobel, and Robert S. Marks</i>	
14.1	Phage Display for Advanced Diagnostics	299
14.2	Biology of Phages	301
14.3	Filamentous Phages	302
	14.3.1 Structure of the Filamentous Phage Virion	303
	14.3.2 Life Cycle of the Filamentous Phage	305
	14.3.3 Filamentous Phage Display	307
14.4	T7 Phage: Structure of the Virion	308
	14.4.1 Life Cycle of T7	310
	14.4.2 T7 Phage Display	311
14.5	Principles and Applications of Phage Display	313
	14.5.1 Phage Display of Natural Peptides	314
	14.5.2 Phage Display of Random Peptides	314
	14.5.3 Phage Display of Proteins or Protein Domains	315
	14.5.4 Multiple-Display Phages	316
14.6	Use of Phage-Displayed Epitopes for Viral Diagnostics	317
	14.6.1 ELISA and Phage Display	318
	14.6.2 Dot Blot Assay and Phage Display	318
	14.6.3 PCR, Immuno-PCR, and Phage Display	319
	14.6.4 Electrochemical Phage Immunosensors	320
14.7	Prospects for Use of Phage Display in Biosensors and Biochips	321
15	Nanolithography and Biochips' Role in Viral Detection	333
	<i>Inbal Tsarfati-BarAd and Levi A. Gheber</i>	
15.1	The Need for Portable Biochips for Viral Detection	333
15.2	Arrayed Biosensors: Biochips	334
15.3	The Need for Miniaturization	334
15.4	Nanolithography	335
15.5	SPM-Based Nanolithography Methods	336
	15.5.1 Nanografting	337
	15.5.2 Dip-Pen Nanolithography	337
	15.5.3 Nano-Fountain Pen	338
15.6	Problems Associated with Miniaturization	339
15.7	Conclusions	341

16 Optical Fiber Immunosensors and Genosensors for the Detection of Viruses	343
<i>Yael Liebes and Robert S. Marks</i>	
16.1 Issues in Biothreat Detection	343
16.2 Optical Fibers as Optical Transducers: Why Optical Fibers to Begin With?	344
16.2.1 Optical Fibers: Pros and Cons	345
16.2.2 The Basic Physics behind Optical Fiber Operation	346
16.2.2.1 Snell's law and TIR	346
16.2.3 Relevance of Optical Fibers as a Waveguide to Chemiluminescence	350
16.2.4 Evanescent Wave Principles Useful in Fluorescence-Based Optical Fiber Sensors	351
16.3 Bioreceptor Immobilization: Chemical Modification to Optical Fibers	353
16.3.1 Immobilization to Solid Supports	353
16.3.2 Immobilization via Functional Group-Terminated Silane Reagents	356
16.3.3 Immobilization via Electrochemical Procedures	356
16.3.4 Immobilization via an Avidin-Biotin Bridge	359
16.4 Signal Measurements: State-of-the-Art Photodetectors	362
16.4.1 Evolution of Photodetector Instrumentations	364
16.5 Fiber Optic Immunosensors Applications for Use in Viral Infections	365
16.5.1 Biosensors under Research or Development: Antibody Detection	365
16.5.1.1 Detection of anti-West Nile virus IgG antibodies	365
16.5.1.2 Detection of viral antibodies using an "electroptode"	368
16.5.2 Virus Detection	369
16.5.2.1 Newcastle disease virus	369
16.5.2.2 MS2 bacteriophage	370
16.5.3 Detection of Oligionucleotides	370

16.6	Commercial Products	372
16.7	Issues in Developing Fiber Optic-Based Immunosensors	375
16.8	The Future Role of Optical Fiber Biosensors	376
17	Aptamers, a New Class of Binders, with Particular Focus on Diagnostics and Bioactivity in the Field of Virology	385
	<i>Andreas Kage and Leslie Lobel</i>	
17.1	General Facts about Aptamers	385
17.2	Selection Procedures	386
17.3	Aptamers for Analytical Purposes (Detection and Quantification)	387
17.4	Polyvalent, Polyspecific Aptamer Constructs	387
17.5	Aptamers for Therapeutic Purposes	388
17.6	Aptamers in Virology	388
	17.6.1 General Facts about Aptamers in Virology	388
	17.6.2 Next Steps into the Future of Aptamers in Virology	390
17.7	AptaRes AG: MonoLex Aptamers	391
18	Pseudotyped Viruses: A New Sero-Diagnostic Tool	395
	<i>Jean-Michel Garcia</i>	
18.1	Brief Historical Review of Pseudotyped Viruses	395
18.2	Present Lentiviral Production Technologies and Their Limitations	396
18.3	Pseudoparticles Characterization and Titration	399
18.4	Applications to a Neutralization-Based Sero-Diagnostic Assay	401
18.5	Perspectives for the Use of Pseudoparticles in Serology and Other Applications	402
19	Nucleic Acid Isothermal Amplification Technologies and Point-of-Care Diagnostics	409
	<i>Tanya M. Ferguson and Angelika Niemz</i>	
19.1	Isothermal Amplification Technologies	411
	19.1.1 Target Detection via RNA Transcription	411
	19.1.2 Target Detection via DNA Replication	414
	19.1.3 Target Detection via Strand Displacement	416

19.2	NAAT-NAAT-Compatible End-Point Detection Platforms Suitable for Point-of-Care in Low-Resource Settings	420
20	Recent Ebola and Marburg Viral Hemorrhagic Fever Outbreaks in Uganda: The Need for Quick, Reliable Diagnostic Tests	427
	<i>Julius Julian Lutwama</i>	
20.1	Introduction	427
20.2	Outbreak Experience	429
20.2.1	The 2000–2001 Ebola Outbreaks: Gulu, Masindi, and Mbarara Districts	429
20.2.2	The 2007 Marburg Outbreaks in the Kamwenge District	433
20.2.3	The 2007–2008 Ebola Outbreak in the Bundibugyo District	435
20.3	The Challenges	438
20.3.1	Time Spent on Receiving Information and Time Spent before a Response Is Made	438
20.3.2	Time Spent without Confirmation of an Outbreak	439
20.3.3	Numbers of People Infected and Deaths	440
20.3.4	Numbers of Health Workers Infected and Deaths	440
20.3.5	The Need for Quick Diagnostic Tests	441
20.3.5.1	The needed capacities	441
20.3.5.2	Infrastructural capacities	441
20.3.6	Trained Personnel	442
20.3.7	Availability of Funds	442
20.3.8	The Complexity of the Present Tests and the Need for Simplification	442
20.4	Way Forward for Uganda	444
21	Amperometric Immuno- and DNA Sensors for Rapid and Specific Identification of Viruses	453
	<i>Rodica E. Ionescu, Serge Cosnier, Vasile Magearu, and Robert S. Marks</i>	
21.1	Introduction	454

21.2	Theoretical Aspects for Amperometric Enzyme Biosensors	461
21.2.1	Introduction to Basic Electrochemical Principles	461
21.2.2	Voltammetry	462
21.2.3	Amperometry	463
21.2.4	Amperometric Biosensors' Classes	465
21.2.4.1	First class of amperometric biosensors	465
21.2.4.2	Second class of amperometric biosensors	466
21.2.4.3	Third class of amperometric biosensors	468
21.3	Classification of Amperometric Biosensors	468
21.3.1	Immunosensors	468
21.3.2	DNA Sensors	470
21.4	Viral Detection Using Amperometry	471
21.4.1	Variola Virus	471
21.4.2	<i>Retroviridae</i> Family	472
21.4.2.1	Bovine leukemia virus	472
21.4.3	The <i>Orthomyxoviridae</i> Family	474
21.4.3.1	Parainfluenza and influenza A viruses	474
21.4.4	The <i>Flaviviridae</i> Family	475
21.4.4.1	Japanese encephalitis virus	475
21.4.4.2	West Nile virus	476
21.4.4.3	Hepatitis C virus	477
21.4.4.4	Bovine viral diarrhea virus	478
21.4.5	The <i>Hepadnaviridae</i> Family	479
21.4.5.1	Hepatitis B virus	479
21.4.6	The <i>Bunyaviridae</i> Family	481
21.4.6.1	Hantaviruses	481
21.4.7	The <i>Paramyxoviridae</i> Family	482
21.4.7.1	Newcastle disease virus	482
21.5	Future Directions	483
	<i>Index</i>	493