Birkhäuser Advances in Infectious Diseases
A. Schmidt, M.H. Wolff, S.H.E. Kaufmann
Series Editors

The Grand Challenge for the Future

Vaccines for Poverty-Related Diseases from Bench to Field

Stefan H. E. Kaufmann
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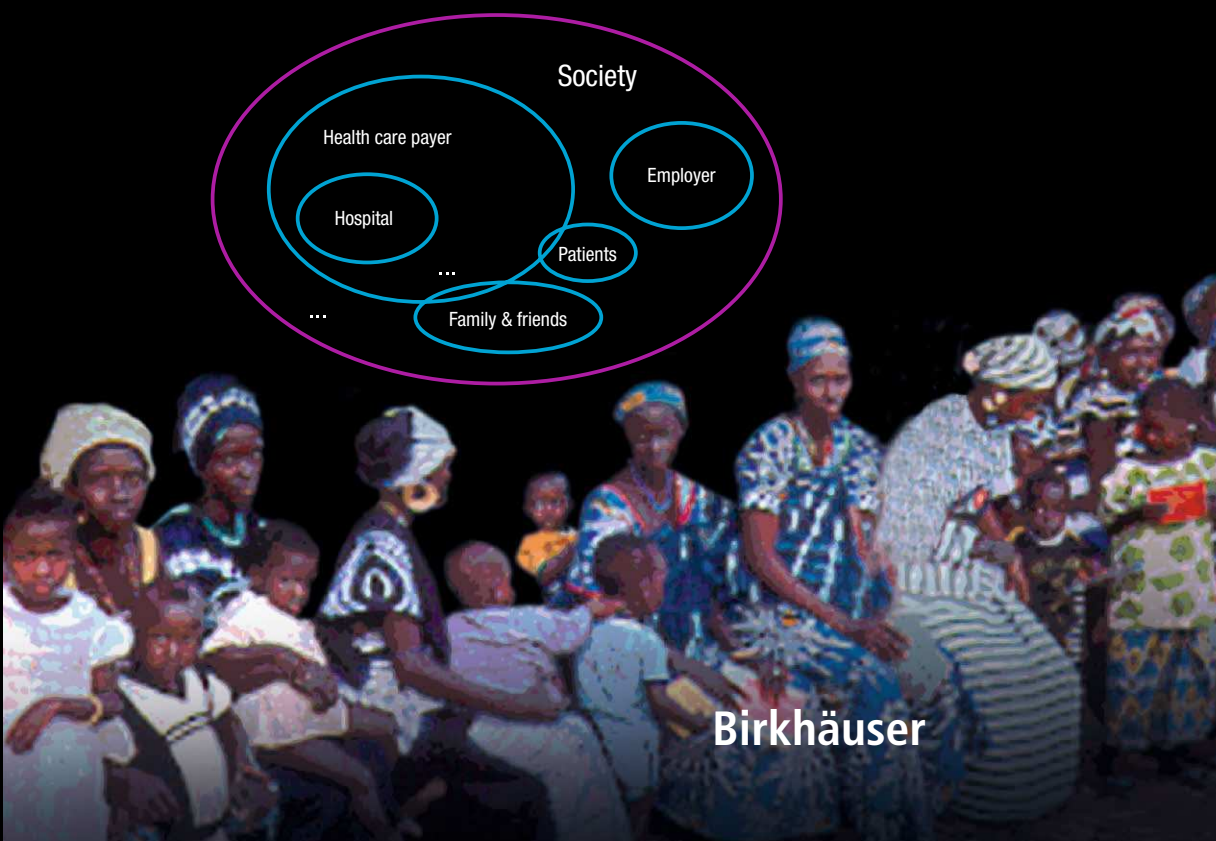

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Series Editors

Axel Schmidt
University Witten/Herdecke
Faculty of Medicine
Alfred-Herrhausen-Str. 50
58448 Witten
Germany

Manfred H. Wolff
University Witten/Herdecke
Faculty of Biosciences
Stockumer Str. 10
58448 Witten
Germany

Stefan H.E. Kaufmann
Max-Planck-Institut für Infektionsbiologie
Department of Immunology
Schumannstrasse 21/22
10117 Berlin
Germany

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Edited by S. H. E. Kaufmann and P.-H. Lambert

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Editors
Stefan H.E. Kaufmann
Max Planck Institute for Infection Biology
Schumannstrasse 21-22
D-10117 Berlin
Germany

Paul-Henri Lambert
CMU – Centre of Vaccinology
1 rue Michel Servet
CH-1211 Geneva 4
Switzerland

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List of contributors

Carl R. Alving, Department of Vaccine Production and Delivery, Division of Retrovirology, Walter Reed Army Institute of Research, U.S. Military HIV Research Program, 1600 East Gude Drive, Rockville, MD 20850, USA; e-mail: calving@hivresearch.org

Ann M. Arvin, Departments of Pediatrics and Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA 94305-5164, USA; e-mail: Aarvin@stanford.edu

Adwoa D. Bentsi-Enchill, Vaccine Assessment and Monitoring, Department of Immunization, Vaccines and Biologicals, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; e-mail: bentsienchilla@who.int

Philippe Beutels, Department of Epidemiology and Community Medicine, University of Antwerp, Universiteitsplein 1, 2610 Antwerpen, Belgium, and National Centre for Immunisation Research

Royal Alexandra Hospital for Children & University of Sydney, Australia, e-mail: philippe.beutels@ua.ac.be

Bjarne Bjorvatn, Centre for International Health, University of Bergen, Armauer Hansen Building, Haukeland University Hospital, 5021 Bergen, Norway; e-mail: bjarne.bjorvatn@cih.uib.no

John D. Clemens, International Vaccine Institute, SNU Research Park, San 4-8 Bongcheon-7-dong, Kwanak-gu, Seoul, Korea 151-818; e-mail: jclemens@ivi.int

Philippe Duclos, Vaccine Assessment and Monitoring, Department of Immunization, Vaccines and Biologicals, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; e-mail: duclosp@who.int

Brian Greenwood, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, UK; e-mail: brian.greenwood@lshtm.ac.uk

Arnd Hoeveler, European Commission, Unit for Poverty-related Diseases, DG Research, 1049 Brussels, Belgium; e-mail: arnd.hoeveler@cec.eu.int

Luis Jodar, International Vaccine Institute, SNU Research Park, San 4-8 Bongcheon-7-dong, Kwanak-gu, Seoul, Korea 151-818; e-mail: ljodar@ivi.int

Maria Lattanzi, Chiron Vaccines, Via Fiorentina 1, 53100 Siena, Italy; e-mail: maria-lattanzi@chiron.com

David B. Lewis, Department of Pediatrics and Program in Immunology, Stanford University School of Medicine, Stanford, CA 94305-5164, USA; e-mail: dblewis@stanford.edu

Gary R. Matyas, Department of Vaccine Production and Delivery, Division of Retrovirology, Walter Reed Army Institute of Research, U.S. Military

HIV Research Program, 1600 East Gude Drive, Rockville, MD 20850, USA; e-mail: GMatyas@hivresearch.org

Hanna M. Nohynek, National Public Health Institute, Department of Vaccines, Clinical Unit, Mannerheimitie 166, 00300 Helsinki, Finland; e-mail: hanna.nohynek@ktl.fi

R. Leon Ochiai, International Vaccine Institute, SNU Research Park, San 4-8 Bongcheon-7-dong, Kwanak-gu, Seoul, Korea 151-818; e-mail: rlochiai@ivi.int

Ole F. Olesen, European Commission, Unit for Poverty-related Diseases, DG Research, 1049 Brussels, Belgium; e-mail: ole.olesen@cec.eu.int

Dina Pfeifer, Vaccine Assessment and Monitoring, Department of Immunization, Vaccines and Biologicals, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; e-mail: pfeiferd@who.int

Stanley A. Plotkin, University of Pennsylvania, and Sanofi Pasteur, 4650 Wismer Road, Doylestown, PA 18901, USA; e-mail: Stanley.Plotkin@Sanofipasteur.com

Rino Rappuoli, Chiron Vaccines, Via Fiorentina 1, 53100 Siena, Italy; e-mail: rino_rappuoli@chiron.com

James M. Robinson, Industrial Operations, Sanofi Pasteur, Inc, Discovery Drive, Swiftwater, PA 18370, USA

Veronica L. Tallo, Research Institute for Tropical Medicine, Department of Health, Filinvest Corporate City, Alabang, Muntinlupa 1781, The Philippines; e-mail: vltallo@pacific.net.ph

François Verdier, Sanofi Pasteur, Campus Mérieux, 1541 avenue Marcel Mérieux, 69280 Marcy l'Etoile, France; e-mail: francois.verdier@sanofipasteur.com

Introductory remarks: Towards relevant vaccinology

It is a dream for all scientists engaged in vaccine research to quickly identify a gene product or genetically engineer a microorganism and to find out that this product represents a potential vaccine against a major infectious disease. It is often a nightmare for the same scientist to experience the hurdles that have to be overcome to move this marvellous product towards clinical trials. Most distressful may even be the rising awareness that a fully successful candidate may end up on the list of vaccines waiting for the unlikely introduction into vaccination programs.

The main goal of this book is to review various aspects related to vaccinology and to appreciate how they apply to major infectious diseases associated with poverty. This approach will take us from vaccine research and development efforts for malaria, AIDS and tuberculosis vaccines to issues critical to introduction of these candidates into national vaccination programs.

These reviews show how, within a few decades, vaccinology has emerged as a unique discipline through the increasing confrontation of the scientists who deal with vaccine research with the intricate network of multiple obstacles to be overcome. Issues range from immunology to epidemiology, from genetics to ecology, from economics to industrial engineering, from social sciences to primary health care. Until a few years ago, a vaccine would largely be developed on the basis of its technical feasibility within a decent time frame. Surprisingly little consideration was given at onset to the relative need for the vaccine at public health level or to specific practical issues that could direct its future use. This often led to wrong market analyses. For example, initial marketing studies for a hepatitis B vaccine concluded that use in high-risk groups and medical personnel would be the primary indications. The mere fact that this vaccine was becoming available, however, led public health experts to realize its potential benefit for developing countries where the disease is highly endemic, and to recommend universal vaccination programs.

This development has had remarkable consequences. It is now inconceivable to engage at any level of vaccine R&D for poverty-associated infectious diseases without some knowledge of the broad range of related issues which have to be considered.

Novel vaccination strategies for poverty-related diseases must deal at a global and comprehensive level with the specific issues related to both the target microorganism and the target population.

Antigenic diversity, naturally occurring mutations and microbial selection under immunological pressure do influence the global epidemiology of microbial pathogens targeted by novel vaccination strategies. This is well appreciated for influenza and a major impediment to the design of optimal vaccination strategies for diseases intrinsically associated with antigenic variation, including HIV and malaria. The multiplicity of antigenic variants may open the way to "replacement" strains. For example, new pneumococcal vaccines, which only prevent a limited number of dominant serotypes, can effectively decrease the infant carrier rate for the serotypes covered by the vaccine. However, this may lead to colonization by pneumococci of different serotypes not included in the vaccine formulation. Such replacement phenomena necessitate the continuing monitoring of pneumococcal strains and, if needed, regular changes in the vaccine formulation.

Equally important, the nature of the target population influences the selection of vaccination strategies in conjunction with the definition of epidemiological patterns. For a number of childhood diseases, the period of greatest vulnerability to infection and disease is within the first few years after birth. Vaccine-induced long-term memory is not always critical, since after a basic level of vaccination, re-exposure to the antigens or re-infection can 'boost' the immune response. However, when dealing with poverty-related diseases, one has to face the fact that infants and adults, throughout much of their lifetime, can be at risk for infection. How long can a vaccine given in early life confer protection? Can we expect that infant immunization protects against HIV/AIDS for 20–30 years? How can immunological memory be generated and sustained? Can it be achieved with subunit vaccines, or will immunization with live, attenuated vectors be necessary, with potentially greater risks of adverse effects? Or should we favour combinatory strategies comprising heterologous prime-boost regimes? These are just a few of the questions that do await answers in the near future.

We have learned a great deal about how to deliver vaccines to toddlers and infants to protect them against childhood infectious diseases. Extraordinary logistical challenges had to be solved and ways of integrating immunization programs into public health and primary care programs had to be developed. As one of the results of these efforts, the level of vaccine coverage in developing countries is now far better for vaccines given soon after birth (e.g., BCG, hepatitis B, polio) than for those given later in life. Thus, in addition to protecting against early-occurring infections, any new poverty-related disease vaccine that is found to be efficacious in the first weeks of life will have a remarkable competitive advantage. As discussed in this book, the immunological challenge of engendering potent protective immune responses in newborns is far from negligible.

Vaccination of immunodeficient individuals also poses unique problems. The risk of adverse events needs to be carefully evaluated, particularly if live attenuated vaccines cannot be controlled and cause disease in immunocompromised vaccinees. Because of the long latency of HIV infection before symptoms of AIDS develop, the possibility exists to induce significant protection prior to major immunodeficiency. However, should the level of vaccine-induced immunity fall short of that achieved in the general population, potential implications for transmission and persistence of infection need to be assessed.

Additional challenges reside in the pressing need for rapid assessment of clinical efficacy. Vaccine trials represent a long, complex and expensive endeavour. Surrogates of protection do exist for a number of vaccines currently in use, because they are thought to provide protection by means of neutralizing antibodies which can be easily assessed. However, protection against major poverty-related disease is likely to require multiple and complex mechanisms, including antibodies and cell-mediated immunity. The definition of relevant correlates of protection in these infections remains an area of considerable concern which needs to be addressed in the near future.

In several industrialized countries, public resistance to the addition of new vaccines to the existing paediatric schedule is on the rise. This is often reflected by parental rejection of what is resented as medical "aggression" for their healthy child. It is also directly related to the number of injections required for completing infant vaccination plans. In several European countries, this feeling is reinforced by particular medical groups, who are proponents of new "natural" preventive or therapeutic approaches. These negative reactions partly mirror a decreased perception of the risk of infectious disease in countries where efficient disease control or elimination strategies have been successful.

Although it is likely that such considerations have a lower penetration in developing countries, misperceptions of vaccine safety increasingly contribute to vaccine failures as illustrated by the recent re-emergence of polio in Kano (Nigeria/Niger) following suspension of polio vaccination. Better information is the key to success in this area and this is the topic of an important chapter of this volume.

Finally, numerous challenges are economic in nature. At the industrial level, vaccines increasingly appear as low-profit products, with an increasing litigation risk, as compared to some of the new high-return blockbusting drugs, often produced by another section of the same giant pharmaceutical company. In many developing countries, economic obstacles still limit the use of existing vaccines and no rapid solution can be expected without international aid and significant financing plans. It is hoped that the true value of preventive vaccination will be taken into proper consideration at political and general public levels in both developing and industrialized countries. Greater recognition of the social value of prophylactic vaccina-

tion will be essential in order to let humankind benefit from the considerable scientific and economic efforts that underpin the development of new vaccines against poverty-related diseases.

We are now at a time when relevant vaccinology should prevail. The scientific community is developing an understanding of how to engage the immune response in molecular and cellular terms to provide protection against the target disease. However, the specific needs for the vaccine, the various epidemiological patterns to be faced, the target population foreseen for vaccination and related economic aspects should be equally considered at the time of vaccine design. How will the new and effective vaccine be used? How will target populations be reached? What could be the public acceptance? Will high priority be given to this vaccine in public health policies? These are the realms of knowledge that we see as the "grand challenge" for vaccines and vaccination.

We would like to sincerely thank the staff of Birkhäuser Publishers, and notably Dr. Beatrice Menz, for editing this volume of the "Advances in Infectious Diseases" series, as well as our secretaries Yvonne Bennett, Souraya Sibaei and Gaby Roetzer for their extraordinary help. Most of all we would like to thank all our colleagues who generously shared their knowledge in the broad interdisciplinary field of relevant vaccinology with us. It is only through their in-depth knowledge and their willingness to share their experience with us that we were able to compile this volume on the grand challenge for the future, namely vaccine development for poverty-related diseases from the bench to the field.

Berlin/Geneva, January 2005

Stefan H. E. Kaufmann
Paul-Henry Lambert

Background