

Meningococcal Vaccines

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Meningococcal Vaccines

Methods and Protocols

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Foreword

Since the first recognition of outbreaks of cerebrospinal or spotted fever at the end of the nineteenth and the beginning of the twentieth centuries, the menace of the meningococcus has been high on the list of public health priorities. Few if any pathogens surpass the meningococcus in the rapidity and severity with which it devastates previously healthy individuals. The challenge of understanding the biology of this fascinating microbe is immense, but few will doubt that successful control of meningococcal meningitis and septicemia will only transpire through the application of a body of extraordinary detailed information, including key minutiae of its molecular biology.

In the first of two companion volumes, *Meningococcal Vaccines*, the team of experts gathered by Andy Pollard and Martin Maiden converge to provide an impressive accumulation of molecular tools with which to lay bare the secrets of the meningococcus. The results of this ambitious and welcome volume represent an exciting and much needed resource for all of us in the field. Time and again, on reading through the carefully prepared texts, I found the contents not only enlightening and relevant to my own research program, but also a source of new ideas and approaches—with the wherewithal to move forward all there in front of me!

Despite the pernicious behavior of the meningococcus in causing devastating disease, the new developments and tools afforded by molecular microbiology and epidemiology can surely be used to turn the tide on this pathogen. No scholar or investigator of *Neisseria meningitidis* will want to be without the riches contained within this work whose pages, I predict, will rapidly show evidence of repeated use in the many laboratories and offices of those who pursue the challenges of the meningococcus.

E. Richard Moxon, MB, BChir

Preface

Meningococcal disease, which occurs chiefly as either septicemia or meningitis, represents a major health problem worldwide. In Europe, the Americas, and Australasia these syndromes, which can occur by themselves or in combination, are principally diseases of early childhood and adolescence, whereas in Africa and Asia, especially China, large-scale epidemic or pandemic outbreaks can involve the whole community. In many industrialized countries there are few childhood diseases that parents fear more than “meningitis,” the term commonly used to refer to meningococcal disease.

There are a number of good reasons for this fear. Meningococcal disease is sporadic, unpredictable, and difficult to diagnose. The disease progresses in a matter of hours from apparently trivial symptoms to a life-threatening medical emergency. Even in the presence of treatment, a positive outcome is uncertain and, frequently, victims are left with severe disabling sequelae ranging from brain damage to limb loss. Finally, the apparently most rational approach to controlling meningococcal disease, childhood vaccination, is hindered by the lack of a suitable comprehensive vaccine, a fact that can leave public health officials feeling helpless in the face of meningococcal disease outbreaks.

Many of these factors are a consequence of the natural history of *Neisseria meningitidis*, the causative agent in meningococcal disease. Perhaps the most important consideration in this regard is paradoxical for one of the most feared pathogens: the meningococcus is a normally harmless member of the commensal flora of adult humans. Asymptomatic colonization of the nasopharynx is very common, averaging at about 10% of the population in many countries, peaking at higher levels, 30–40%, in some age groups. Probably as a consequence of this ubiquity, meningococcal populations contain bewildering antigenic and genetic diversity. There are thousands of distinct meningococcal variants described to date and each of these has a sophisticated mechanism for varying its surface coat in response to immune attack. In summary, this bacterium is very well adapted indeed to living with the human immune system. This adaptation is the principal reason for the difficulties in vaccine development.

Safe, effective vaccines against meningococcal disease have been available since the late 1960s. These target the polysaccharide coat of the meningococcus, which is essential for the organism’s survival in the bloodstream. From the dozen or so such coats available to the meningococcus, only five, those which define serogroups A, B, C, Y, and W-135, are associated with disease. Unfortu-

nately, vaccines that include unmodified polysaccharides are poorly immunogenic, eliciting only a temporary immune response in adults and none at all in infants. Serogroup B polysaccharide is problematic because its especially poor immunogenicity may result from immunological identity to human polysaccharides, raising concern about the safety of any vaccine based on this molecule. In addition to these polysaccharides, many research and development programs have targeted the protein components of the meningococcal coat but, as yet, despite some promising reports, none of these has resulted in a wholly satisfactory vaccine.

However, at the beginning of the 21st century, nearly 120 years after the first isolation of the meningococcus and its association with human disease in 1887, there is optimism that solutions to meningococcal disease may be on the horizon, even if comprehensive solutions remain elusive in the short or even medium term. Polysaccharide–protein conjugate vaccines, which will provide infants with life time immunity against meningococci that express the serogroup A, C, Y, and W-135 antigens, are likely to be available soon. The completion of the whole genome sequences of two meningococci and the start of the post-genomic age will provide a host of novel data and approaches to research on the development of new meningococcal vaccines. Molecular methods, combined with phylogenetic and theoretical approaches, promise accurate molecular and epidemiological descriptions of those meningococci responsible for disease, adding further knowledge to the arsenal that can be brought to bear on this difficult problem.

Meningococcal Vaccines is designed to provide a comprehensive discussion of current molecular and cellular methods relevant to meningococcal vaccine development and evaluation. The first two chapters provide the context for the book, by reviewing vaccination strategies and describing the mechanisms of immunity that are relevant to natural and vaccine-induced protection against disease. The succeeding chapters deal in detail with the many approaches available for vaccine design and the assessment of immune responses to vaccine candidates and novel vaccine formulations. The book concludes with a discussion of the implementation of a new meningococcal vaccine, based on recent experience in the United Kingdom. A companion text, *Meningococcal Disease*, is available from Humana Press; this includes overview chapters and detailed methods in the areas of diagnostic microbiology, bacterial characterization, epidemiology, host–pathogen interactions, and clinical studies.

Finally, some words of thanks to the many people who have made this book possible: the series editor, John Walker, and the staff of Humana Press for commissioning this book and seeing it through to press; the chapter authors for

their hard and always enthusiastic work in response to (frequently unreasonable) goading by the editors; our immediate colleagues who, over the years, have generously shared their knowledge, ideas, and expertise with us; and last, but by no means least, the legion of physicians and scientists who have labored in the fight against meningococcal disease since its first definitive description in 1805.

Andrew J. Pollard, md, phd

Martin C. J. Maiden, phd

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