Preface

This book is intended for statisticians working in clinical vaccine development in the pharmaceutical industry, at universities, at national vaccines institutes, etc. Statisticians already involved in clinical vaccine trials may find some interesting new ideas in it, while colleagues who are new to vaccines will be able to familiarize themselves quickly with the statistical methodology.

A good knowledge of statistics is assumed. The reader should be familiar with hypothesis testing, point and confidence interval estimation, likelihood methods, regression, mathematical and statistical notation, etc. A book that would provide the necessary background is: Armitage P., Berry G. and Matthews J.N.S. Statistical Methods in Medical Research, 4th edition, Blackwell Science, New York, 2001.

The scope of the book is practical rather than theoretical. Many real-life examples are given, and SAS codes are provided, making application of the methods straightforward. SAS codes are also given for accurate sample size estimation, including codes for the estimation of required sample sizes for equivalence and noninferiority vaccine trials.

The first two chapters are introductions to the immunology of vaccines, and they will provide the reader with the necessary background knowledge. In Chap. 1, the fundamentals of vaccination, the immune system and vaccines are presented. The principle of vaccination is explained, and the major infectious microorganisms are introduced. The primary defence mechanism of microorganisms – antigenic variation – is discussed. A sketch of the immune system is given so that the reader will understand roughly how it works, including the distinction between the innate and the adaptive immune system. The chapter proceeds with a short section on the basics of tumour immunology. An overview of the several types of vaccines for viruses and bacteria, from the first generation live-attenuated vaccines to third generation vaccines such as recombinant vector vaccines, DNA vaccines and virus-like particles vaccines is given. As an example of a parasite vaccine, a summary of the state of affairs of malaria vaccine development is given. Therapeutic vaccines for noninfectious diseases are briefly touched upon. Humoral immunity, the component of the immune system involving antibodies that circulate in the humor, and cellular immunity, the component that provides immunity by action of cells, are explained. Antibody titres and antibody concentrations are introduced, and two standard assays for humoral immunity, the haemagglutination inhibition test and ELISA, are dis-
cussed. The distinction between T helper cells and T killer cells and their different roles are explained. A number of assays for cellular immunity are briefly introduced, including the ELISPOT assay.

Chapter 3 is the central one of the book. The four standard statistics to summarize humoral and cellular immunogenicity data are introduced, and in the sections on the statistical analysis of proportions the use of Wilson-type confidence intervals is promoted rather than the more familiar Wald-type intervals. It is explained how exact confidence intervals for the risk difference and the relative risk can be obtained.

In Chap. 4, two types of possible bias for antibody titres are discussed. The first type of bias is due to how antibody titres are defined. An alternative definition is proposed, the mid-value definition. With this definition, the bias is properly corrected. This type of bias is largely of theoretical interest only. That cannot be said of the second type of bias, which is of major practical importance. It occurs when titres above (or below) a certain level are not determined. If this bias is ignored, the geometric mean titre will be underestimated. It is shown how the method of maximum likelihood estimation for censored observation can be applied to eliminate this bias.

Pre-vaccination or baseline antibody levels need not to be zero. Examples of infectious diseases for which this can be the case are tetanus, diphtheria, pertussis and tick borne encephalitis. Imbalance in pre-vaccination state, i.e., a difference in baseline antibody levels between vaccine groups, can complicate the interpretation of a difference in post-vaccination antibody values. A standard approach to this problem is analysis of covariance. But in case of antibody values one of the assumptions underlying this analysis, homoscedasticity, is not met. The larger the baseline value the smaller the standard deviation of the error term. In Chap. 5, a solution to this problem is offered. It is shown that the heteroscedasticity can be modeled. A variance model is derived, and it is demonstrated how this model can be fitted with SAS.

Many vaccine immunogenicity trials are conducted in an equivalence or noninferiority framework. The objective of such trials is to demonstrate that the immunogenicity of an investigational vaccine is comparable or not less than that of a control vaccine. In Chap. 6, the statistical analysis of such trials is explained, both for trials with an antibody response as endpoint and trials with seroprotection or seroconversion as endpoint. The standard analysis of lot consistency data is known to be conservative, but a simple formula is presented which can be used to decide if the lot sample sizes guarantee that the actual type I error rate of the trial is sufficiently close to the nominal level. The chapter is concluded with a discussion of sample size estimation for vaccine equivalence and noninferiority trials, including lot consistency trials. Recommendations are given how to avoid that the statistical power is overestimated.

Chapter 7 considers vaccine field efficacy trial. The aim of a field efficacy trial is to demonstrate that a vaccine protects against infection or disease. First, an overview of the different effects vaccines can produce is given. Next, some critical aspects of such field efficacy trials are discussed. The three most common incidence measures for infection are presented: the attack rate, the infection rate and the force of infection. The statistical analysis of field efficacy trials using these estimators is
explained. The chapter then continues with the statistical analysis of recurrent infection data, which is known to be complex. The chapter is concluded with a discussion of sample size estimation for vaccine field efficacy trial. It is shown that the standard method to estimate the sample size for a trial comparing two attack rates and with the aim to demonstrate super efficacy is highly conservative. An SAS code to compute sample sizes for trials comparing two infection rates is presented.

A correlate of protection is an immunological assay that predicts protection against infection. The concept is the topic of Chap. 8. In clinical vaccine, trials correlates of protection are widely used as surrogate endpoints for vaccine efficacy. The function specifying the relationship between log-transformed immunogenicity values and the probability of protection against infection, conditional on exposure to the pathogen, is called the protection curve. It is demonstrated how the parameters of the protection curve can be estimated from challenge study data and vaccine field efficacy data. Also explained is how a threshold of protection can be estimated from the protection curve. The generalizability of estimated protection curves is discussed.

The final chapter, Chap. 9, addresses vaccine safety. To proof the safety of a vaccine is much more difficult than proving its efficacy. Of many vaccines millions of doses are administered, which can bring very rare but serious adverse vaccine events to light. In this chapter, some statistical aspects of vaccine safety are addressed. Vaccine safety surveillance is briefly discussed, and some recent controversies are recalled. The notorious problem of vaccine safety and multiplicity is discussed at great length. Four different methods to handle this problem are presented, including the recently proposed double false discovery method. The performance of the different methods is illustrated with the help of simulation results. The second part of the chapter is dedicated to the analysis of reactogenicity data.

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Jos Nauta
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Nauta, J.
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