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Review

Colonisation endpoints in *Streptococcus pneumoniae* vaccine trials

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ABSTRACT

Evaluating vaccine efficacy for protection against colonisation (VE_{col}) with bacterial pathogens is an area of growing interest. In this article, we consider estimation of VE_{col} for colonisation with *Streptococcus pneumoniae* (the pneumococcus). Colonisation is a common, recurrent and multi-type endpoint that requires both careful definition of the vaccine efficacy parameter and the corresponding method of estimation. We review recent developments in the area and provide practical guidelines for choosing the estimand and the estimation method in trials with a colonisation endpoint. We concentrate on methods that are based on a cross-sectional study design, in which only one nasopharyngeal sample is obtained per study subject.

Contents

Abbreviations: OR, odds ratio; PCV, pneumococcal conjugate vaccine; VE_{col}, vaccine efficacy against colonisation; VE_{acq}, vaccine efficacy against acquisition of colonisation; VE_T, combined vaccine efficacy against acquisition and duration of colonisation; VT, vaccine (sero)type(s); NVT, non-vaccine (sero)type(s).

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1. Introduction

Evaluating vaccine efficacy for protection against colonisation (VE_{col}) with *Streptococcus pneumoniae* (the pneumococcus) and other bacterial pathogens is an area of growing interest, because the biological basis for indirect immunity and for replacement colonisation with non-vaccine types is due to the impact of vaccination on colonisation. Bacterial colonisation of the nasopharynx leads to a generally asymptomatic carrier state, which acts as the source for person-to-person transmission. Colonisation with more than one serotype at a time is relatively common, and competition between serotypes for colonisation of the human host is known to occur. Therefore, following initial observations that bacterial conjugate vaccines reduce nasopharyngeal colonisation with vaccine serotypes (VT) [1–3], the implication that this would have on disease was intriguing. Use of bacterial conjugate vaccines in infant immunisation programmes has in addition to direct protection, resulted in an observed reduction in invasive disease in both unvaccinated children and adults [4,5]. In some settings the indirect effect seen accompanying the use of pneumococcal conjugate vaccines (PCV) in infants has been responsible for more disease reduction than the direct effect [6] and has thus driven cost effective calculations. The consequence of reducing or even eradicating the most prevalent pneumococcal serotypes from the nasopharynx has been an increase (replacement) in colonisation by non-vaccine serotypes that have the potential to cause disease (there are approximately 94 different pneumococcal types (serotypes) identified).

Colonisation endpoints are important in phase III or IV pneumococcal vaccine studies for a variety of biologic and practical reasons. Firstly, because pneumococcal colonisation is a precondition to pneumococcal disease, vaccine effects on colonisation may at the individual level serve as markers of vaccination-induced protection against various disease manifestations [7]. Secondly, the public health impact of pneumococcal vaccination in the wider population, including the indirect and overall effectiveness of vaccination, depends on the level of direct protection against colonisation. Thirdly, because the incidence and prevalence of pneumococcal colonisation are higher than those of disease, studies with a colonisation endpoint are easier to conduct and require smaller sample sizes than studies with a disease endpoint. Fourthly, in phase III trials, in which the direct vaccine efficacy is of interest, indirect effects of vaccination or other confounding factors are less likely to interfere with the measurement of vaccine efficacy due to the shorter time period for data collection. Finally, unlike the currently applied immunological criteria for PCV licensure [8,9], colonisation endpoints can be more directly estimated for each serotype and may thus serve as a better assessment of true biological efficacy.

Despite the obvious relevance of colonisation data, the interpretation of efficacy against colonisation across different studies may be confounded by the variability of study designs employed [10]. Colonisation differs from most other clinical outcomes used in vaccine efficacy trials in that it is common, recurrent and observed only in its prevalent state, i.e. the actual acquisition events cannot be directly observed. Moreover, estimation of vaccine efficacy for a colonisation endpoint may need to be adjusted for interactions between the multiple strains of the pathogen as they compete in colonising the human hosts. Study subjects may be sampled for colonisation with long sampling intervals or only once. All these aspects should impact the choice of specific colonisation endpoint (e.g. acquisition, duration, or density of colonisation), vaccine efficacy parameter, and the appropriate methods for estimation.

Here and in the accompanying article [14] we discuss the choice of colonisation endpoints for PCV and other pneumococcal vaccine efficacy studies and the associated issues of estimation methods, adjustment for competing non-vaccine type acquisition, control vaccine, timing of colonisation measurements, implications of multiple serotype colonisation, and sample size. We distinguish between vaccine efficacy against acquisition of colonisation (VE_{acq}), vaccine efficacy regarding duration (VE_{dur}) or density of colonisation. A combined efficacy (VE_T) is defined accounting effects on both acquisition and clearance. For these and other possible vaccine efficacy parameters, vaccine efficacy against colonisation (VE_{col}) is used as an umbrella concept. We concentrate on methods that can be used in a cross-sectional study, i.e. based on only one observation of the current colonisation per study subject. The combined efficacy then turns out to be the parameter that requires the smallest set of underlying assumptions.

The statistical methodology reviewed here is based on two previous articles ([10,11]). These methods are related to the nested case-control design that could be used to estimate vaccine efficacy in a setting with multiple possible endpoints (i.e. colonisation with any of the >90 pneumococcal serotypes), whilst avoiding the need for identifying the actual acquisition events. Related statistical methods for estimation of vaccine efficacy against colonisation or disease in a setting with multiple serotypes include the indirect cohort method [12] and sieve analysis [13]. Our approach generalises the indirect cohort method to the analysis of transient and recurrent (colonisation) events with appropriate adjustment for replacement carriage within the host. The main difference between our approach and the sieve analysis is that the outcomes in the latter method are non-transient.

This work is framed with PCV in mind, however the methods are applicable for newer vaccines such as the protein vaccines. The accompanying article discusses more practical design questions, including the timing of colonisation measurement with respect to the time of vaccination, choice of control vaccine and the statistical power of colonisation endpoint trials [14].

2. Colonisation endpoints in vaccine studies

Several characteristics of pneumococcal colonisation may be affected by vaccination and could thereby serve as endpoints in a vaccine study (Table 1). Firstly, vaccination may reduce the individual's susceptibility to acquisition of colonisation. In general, susceptibility to acquisition is quantified by the rate of acquisition in those not colonised or otherwise considered susceptible to acquire the target (vaccine) serotypes (cf. [11,15]). Secondly, vaccination may enhance the clearance of colonisation so that duration of future colonisation is shortened. Thirdly, vaccination may decrease the density of future colonisation, i.e. the quantitative load of pneumococcal carriage in the nasopharynx, as compared to a non-vaccinated carrier.

All these three primary endpoints (acquisition, duration, density) can be considered either specific to the individual protective components of the vaccine or "overall" in an aggregate manner. For example, for PCVs, the serotypes included in a vaccine formulation can be considered either individually or as a set of all vaccine serotypes. Although the main interest often lies in estimating the aggregate efficacy against all vaccine serotypes, vaccine effects on non-vaccine serotypes are also important if serotype replacement is considered (see Section 3).

In addition to the primary endpoints, various summary endpoints can be used to quantify vaccine effects on colonisation. In particular, a combined endpoint involving both acquisition and duration proves to have many desirable epidemiological properties. It is defined as

$$T = (\text{hazard rate of acquisition}) \times (\text{mean duration of colonisation}).$$

The risk of T is related to a susceptible individual's expected (i.e. future) time spent colonised and thereby capable of spreading the organism. If transmissibility varies over the course of the