Epidemics 9 (2014) 8–17

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Timing of bacterial carriage sampling in vaccine trials: A modelling study

Pippa Scott[a,*], Sereina A. Herzog[a,b], Kari Auranen[c], Ron Dagan[d], Nicola Low[a], Matthias Egger[a,e], Janneke C.M. Heijne[a]

[a] Institute of Social and Preventive Medicine, University of Bern, Switzerland
[b] Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria
[c] Department of Vaccination and Immune Protection, National Institute for Health and Welfare (THL), Finland
[d] Pediatric Infectious Disease Unit, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel
[e] Centre for Infectious Disease Epidemiology and Research (CIDER), University of Cape Town, Cape Town, South Africa

ARTICLE INFO

Article history:
Received 19 December 2013
Received in revised form 8 May 2014
Accepted 18 August 2014
Available online 26 August 2014

Keywords:
Vaccine efficacy
Bacterial pathogens
Randomised controlled trials
Methodological research
Mathematical modelling

ABSTRACT

Background: Pathogenic bacteria are often asymptomatically carried in the nasopharynx. Bacterial carriage can be reduced by vaccination and has been used as an alternative endpoint to clinical disease in randomised controlled trials (RCTs). Vaccine efficacy (*VE*) is usually calculated as 1 minus a measure of effect. Estimates of vaccine efficacy from cross-sectional carriage data collected in RCTs are usually based on prevalence odds ratios (PORs) and prevalence ratios (PRs), but it is unclear when these should be measured.

Methods: We developed dynamic compartmental transmission models simulating RCTs of a vaccine against a carried pathogen to investigate how *VE* can best be estimated from cross-sectional carriage data, at which time carriage should optimally be assessed, and to which factors this timing is most sensitive. In the models, vaccine could change carriage acquisition and clearance rates (leaky vaccine); values for these effects were explicitly defined (f_{acq}, $1/f_{dur}$). *POR* and *PR* were calculated from model outputs. Models differed in infection source: other participants or external sources unaffected by the trial. Simulations using multiple vaccine doses were compared to empirical data.

Results: The combined *VE* against acquisition and duration calculated using POR ($\widehat{VE}_{acq.dur}$, $(1-POR)\times 100$) best estimates the true *VE* ($VE_{acq.dur}$, $(1-f_{acq}\times f_{dur})\times 100$) for leaky vaccines in most scenarios. The mean duration of carriage was the most important factor determining the time until $\widehat{VE}_{acq.dur}$ first approximates $VE_{acq.dur}$: if the mean duration of carriage is 1–1.5 months, up to 4 months are needed; if the mean duration is 2–3 months, up to 8 months are needed. Minor differences were seen between models with different infection sources. In RCTs with shorter intervals between vaccine doses it takes longer after the last dose until $\widehat{VE}_{acq.dur}$ approximates $VE_{acq.dur}$.

Conclusion: The timing of sample collection should be considered when interpreting vaccine efficacy against bacterial carriage measured in RCTs.

1. Introduction

The estimation of vaccine efficacy (*VE*) from randomised controlled trials (RCTs) is complex because vaccines can act on different stages of the infection dynamics and disease, and because vaccination itself can affect the transmission of disease in the trial population (Smith et al., 1984; Halloran et al., 1997, 1999). Much has been published about complexities in the estimation of *VE* against clinical disease (Smith et al., 1984; Halloran and Struchiner, 1995; Halloran et al., 1997, 1999), but less information is available for other outcomes such as asymptomatic colonisation of the nasopharynx by bacterial pathogens. Asymptomatic colonisation, or carriage, is often measured in RCTs of vaccines that aim to prevent disease caused by bacterial pathogens because carriage is a more common outcome than clinical disease and efficacy of vaccine against clinical disease can be mediated through carriage (Simell et al., 2012). Examples of such pathogens and vaccines include *Streptococcus pneumoniae* and pneumococcal conjugate vaccines

* Corresponding author at: Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, Bern 3012, Switzerland. Tel.: +41 31 631 5640; fax: +41 31 631 35 20.
E-mail address: pscott@ispm.unibe.ch (P. Scott).

http://dx.doi.org/10.1016/j.epidem.2014.08.003

Table 1
Model parameters describing the transmission of the pathogen, and the extent and effect of vaccination.

Parameter	Description	Baseline value	Sensitivity analyses (uni- and multivariate)	Restricted multivariate sensitivity analysis	Sensitivity analysis on steady state assumption	Multiple doses of vaccines	Model validation
		Baseline and constant FOI models	Baseline and constant FOI models	Baseline and constant FOI models	Baseline and constant FOI models	Baseline model	Constant FOI model
Carriage parameters							
$1/\gamma$	Mean duration of carriage in the absence of vaccination (γ, carriage clearance rate)	1.25m[a]	1 day–12m[b]	1 day–12m[b]	1.25m[a]	1.25m[a]	5d, 1.25m 4.3m[c]
P_B	Equilibrium prevalence of carriage in the absence of vaccination	0.25[a]	0.001–0.99	0.001-0.5[d]	0.001–0.99	0.25[a]	VT 0.32[e] VT + 6A 0.37[e]
P_{init}	Prevalence at the start of the model run	Steady state ($P_{init} = P_B$)	Steady state ($P_{init} = P_B$)	Steady state ($P_{init} = P_B$)	0.001–0.99	Steady state ($P_{init} = P_B$)	VT 0.15[f] VT + 6A 0.18[f]
β	Transmission parameter, $\gamma/(1-P_B)$	1.07 [g]	Changes with γ and P_B	Changes with γ and P_B	Changes with γ and P_B	Changes with γ and P_B	Changes with γ and P_B
Vaccine parameters							
VE_{acq}	Vaccine efficacy against acquisition of carriage, $(1 - f_{acq}) \times 100$	60%	0–99%	0–99%	60%	See Table 2	See Table 3
VE_{dur}	Vaccine efficacy against duration of carriage, $(1 - f_{dur}) \times 100$	0%	0–99%	0–20%[h]	0%	See Table 2	See Table 3
$VE_{acq.dur}$	Vaccine efficacy against acquisition and duration of carriage $(1 - (f_{acq} \times f_{dur})) \times 100$	60%	Calculated from f_{acq} and f_{dur}	Calculated from f_{acq} and f_{dur}	60%	Calculated from f_{acq} and f_{dur}	Calculated from f_{acq} and f_{dur}
q	Proportion vaccinated in the trial population	0.33	0.01–0.99	0.1–0.6	0.33	0.33	0.33 vaccinated with each schedule

FOI – force of infection; m – months; VT – 7-valent pneumococcal conjugate vaccine serotypes.

[a] Based on combined estimate for all 7-valent PCV serotypes in 3–59 month olds in Kenya (Abdullahi et al., 2012). Other studies in Denmark, Finland and the United Kingdom did not provide prevalence or duration of carriage data for 7-valent PCV serotypes separately, but duration of carriage for all serotypes combined or individual serotypes were generally similar or longer than in the Kenya data (Auranen et al., 2000, 2010; Raymond et al., 2001; Melegaro et al., 2004).

[b] Range explored in sensitivity analysis reflects a very short duration (1 day) and the longest estimates for the carriage of pneumococcus, *Haemophilus influenzae* type b and *Neisseria meningitidis* (Auranen et al., 1996; Trotter et al., 2006; Abdullahi et al., 2012).

[c] Based on data for 7-valent PCV serotypes in 3–59 month olds in Kenya (Abdullahi et al., 2012). The minimum lower bound for the confidence interval around the mean duration of carriage for any vaccine serotype was 5 days, and the maximum upper bound for the confidence interval around the mean duration of carriage for any vaccine serotype was 130 days.

[d] Carriage prevalence is generally below 50% although it can be higher in some populations (Simell et al., 2012).

[e] Maximum prevalence amongst randomised unvaccinated individuals in the Israeli trial (calculated from individual patient data). These maximums occurred at 12 months of age (Dagan et al., 2012).

[f] Prevalence amongst randomised unvaccinated individuals in the Israeli trial at 2 months of age (calculated from individual patient data). In simulations, model runs were started at 2m of age.

[g] The baseline value for β is calculated from the baseline values of γ and P_B.

[h] Conjugate vaccines have not been observed to have a marked effect on duration of carriage (Barbour et al., 1995; Dagan et al., 2005; O'Brien et al., 2007).

(PCVs) (van Gils et al., 2009; Russell et al., 2010; Ota et al., 2011; Dagan et al., 2012), *Haemophilus influenzae* type B (Hib) and Hib conjugate vaccines (Adegbola et al., 1998), and *Neisseria meningitidis* and meningococcal conjugate vaccines (Daugla et al., 2014).

Vaccines might affect carriage through several mechanisms including reducing susceptibility to acquiring carriage, reducing the duration of carriage, or reducing the density of colonisation (Rinta-Kokko et al., 2009; Mina et al., 2013). In this article, the terms VE_{acq} and VE_{dur} refer to the vaccine efficacy against acquisition and duration respectively, while $VE_{acq.dur}$ captures the combined efficacy against acquisition and duration (Table 1). Some RCTs have attempted to directly estimate VE_{acq} using longitudinal data from repeated nasopharyngeal samples (Dagan et al., 2003, 2012). However, to ensure the detection of each new acquisition and consequently accurately measure the underlying acquisition rate, sampling would need to be more frequent than is feasible in most trials. Instead, carriage is usually assessed cross-sectionally, by sampling once or a few times after vaccination, typically starting one to two months after the last dose (Obaro et al., 2000; Dagan et al., 2003; van Gils et al., 2009; Russell et al., 2010).

Vaccine efficacy is usually estimated using 1 minus a measure of effect that is expressed as a ratio. For cross-sectional carriage data, possible ratio measures are prevalence odds ratios (PORs) and prevalence ratios (PRs). The estimated VE against acquisition and duration ($\widehat{VE}_{acq.dur}$) in a trial can then be calculated as either $(1 - POR) \times 100$ or $(1 - PR) \times 100$. Previous studies have shown that $\widehat{VE}_{acq.dur}$ calculated using the *POR*, once stable, can be used to estimate the "true" $VE_{acq.dur}$ (Rinta-Kokko et al., 2009). The time until the *POR*, and therefore $\widehat{VE}_{acq.dur}$, becomes stable has not been thoroughly investigated (Auranen et al., 2013a) either for when single doses or for when multiple doses of vaccine are given in a vaccine schedule. Previous methods have also assumed that the force of infection (FOI) is constant during trials (Rinta-Kokko et al., 2009; Auranen et al., 2013a,b). The assumption of a constant FOI leads to greater analytical simplicity than allowing the FOI to change over time but it might be an over-simplification as it assumes that vaccination of the trial population has no effect on the FOI.

Many groups including vaccine trial investigators, epidemiologists, mathematical modellers, policy makers and systematic reviewers need to know which ratio measure and sampling points in time can be used to best estimate $VE_{acq.dur}$. We used a dynamic transmission model to investigate how values of $\widehat{VE}_{acq.dur}$ calculated from model outputs compared to the "true" values of $VE_{acq.dur}$ used to parameterise the model. We assessed the optimal time