Epidemics 17 (2016) 56–63

Contents lists available at ScienceDirect

Epidemics

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

Research paper

Impact of waning acquired immunity and asymptomatic infections on case-control studies for enteric pathogens

Arie H. Havelaar[a,b,*], Arno Swart[c]

[a] Emerging Pathogens Institute, Institute for Sustainable Food Systems, Animal Sciences Department, University of Florida, Gainesville, FL, USA
[b] Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands
[c] Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

ARTICLE INFO

Article history:
Received 14 July 2016
Received in revised form
26 November 2016
Accepted 27 November 2016
Available online 28 November 2016

Keywords:
Case-control studies
Bias
Acquired immunity
Asymptomatic infections
Mathematical model

ABSTRACT

Case-control studies of outbreaks and of sporadic cases of infectious diseases may provide a biased estimate of the infection rate ratio, due to selecting controls that are not at risk of disease. We use a dynamic mathematical model to explore biases introduced in results drawn from case-control studies of enteric pathogens by waning and boosting of immunity, and by asymptomatic infections, using *Campylobacter jejuni* as an example. Individuals in the population are either susceptible (at risk of infection and disease), fully protected (not at risk of either) or partially protected (at risk of infection but not of disease). The force of infection is a function of the exposure frequency and the exposure dose. We show that the observed disease odds ratios are indeed strongly biased towards the null, i.e. much lower than the infection rate ratio, and furthermore even not proportional to it. The bias could theoretically be controlled by sampling controls only from the reservoir of susceptible individuals. The population at risk is in a dynamic equilibrium, and cannot be identified as those who are not and have never experienced disease. Individual-level samples to measure protective immunity would be required, complicating the design, cost and execution of case-control studies.

1. Introduction

Foodborne pathogens such as *Campylobacter* spp., non-typhoidal *Salmonella* spp. and other enteric pathogens continue to be of public health importance in developed and developing countries alike (Havelaar et al., 2016). To inform a rational choice of intervention methods, source attribution models are increasingly applied (Pires et al., 2009). The ultimate goals of such studies are to identify the most important sources of exposure for intervention, and to monitor if interventions have been successful. Epidemiologic approaches to source attribution include case-control studies of outbreaks and of sporadic cases. The underlying assumption in case-control studies is that the observed exposure distributions in cases and controls are reflective of the infection incidence rate ratios. However, such relationships may be biased by acquired immunity or asymptomatic infections, due to selecting controls that are not at risk of disease (Havelaar et al., 2009). Swift and Hunter (2004) developed a mathematical model suggesting that given lifetime exposure to infectious disease agents at different intensities, risk ratios for high exposure are biased to the null by constant low exposures and that high exposure may even apparently become protective. The model assumes lifelong immunity, which may not be realistic for many enteric pathogens such as *Campylobacter* spp., to which protective immunity is of limited duration. As a consequence, an individual may not be at risk of disease at some point in time, but subsequently lose protective immunity and be at risk again. Hence, both the population of potential cases and of eligible controls varies over time and individuals may leave and enter the cohort repeatedly. It is suggested that the confounding effects of immunity may be controlled by the usual array of methods used in study design and data analysis (Rothman and Mahon, 2004). Such methods would, however, require information on the exposure history of the study population, which is rarely available.

Swart et al. (2012) have developed a simple mathematical model to quantify the impact of acquired immunity on the population dynamics of campylobacteriosis and concluded that due to the effects of waning and boosting of immunity, an increasing force of infection does not necessarily lead to an increase in the incidence of disease. Under certain conditions, a decrease of the force of infec-

* Corresponding author at: Emerging Pathogens Institute, Institute for Sustainable Food Systems, Animal Sciences Department, University of Florida, Gainesville, Florida, USA.
E-mail address: ariehavelaar@ufl.edu (A.H. Havelaar).

http://dx.doi.org/10.1016/j.epidem.2016.11.004

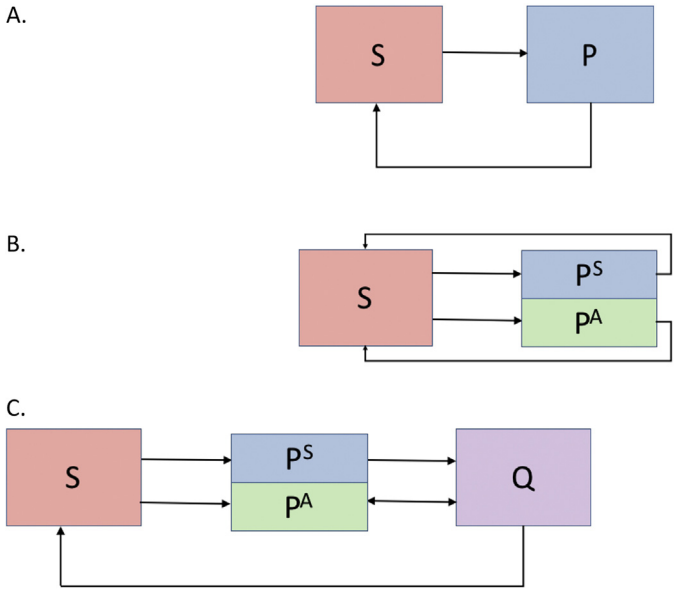

Fig. 1. Conceptual models for dynamics of enteric illness without (A) and with (B, C) asymptomatic infection and without (A, B) and with (C) waning acquired immunity.

tion may in fact lead to an increase of the incidence of disease. The model also includes the possibility of asymptomatic infection, leading to temporary protection without illness symptoms occurring. This model was subsequently used by Havelaar and Swart (2014) to explore the impact of acquired immunity in quantitative microbial risk assessment studies by explicitly including the frequency of exposure and the ingested dose into the estimation of the force of infection and the probability of (a)symptomatic infection. In this paper, we proceed to use this model as a basis to explore biases introduced in case-control studies of enteric pathogens by waning and boosting of immunity, and by asymptomatic infections, using *Campylobacter jejuni* as an example.

2. Model

To evaluate the selection bias by acquired immunity and asymptomatic infections in case-control studies, we present several compartmental models. Panel A in Fig. 1 represents a basic model in which susceptible individuals (S) may become infected (defined as a state in which the pathogen has established itself and actively multiplies in the host, measurable by production of antibodies by the host), with all infected individuals becoming ill, who subsequently recover and become susceptible again. This model is similar to the standard SIS model (Anderson and May, 1991) but in our case the focus is on illness rather than infectivity, hence we use the symbol P (for protected) rather than I for this compartment and the symbol Q (sequential to P) for the partially protected compartment. This basic model also represents the assumptions in a standard analysis of case control studies: all individuals with clinical signs of illness are classified as cases and all asymptomatic cases are classified as controls. Note that typically, duration of protective immunity is longer than of clinical symptoms, hence even in this basic model, some asymptomatic individuals may be misclassified. We assume that this misclassification is countered by the usual practice to exclude persons with a recent history of gastrointestinal disease from the study, e.g., (MacDonald et al., 2015). Implicitly, this assumes that the average duration of protection in P is the same as the exclusion period in the epidemiological study.

A more detailed consideration of the nature of infectious diseases leads to the need to refine the simple SPS model:

a. Even upon first exposure, infection may not lead to illness, i.e. the probability of illness given an S → P transition is less than 1, depending on the ingested dose and other factors; see the panel B in Fig. 1. Asymptomatic, infected individuals (P^A) are protected from disease and hence potentially incorrectly classified as controls for estimating the infection rate ratio, while symptomatic individuals (P^S) are correctly classified as cases. We refer to this model as the SP^AS model.

b. After infection, individuals may be partially protected by acquired immunity, implying they may be re-infected but the reinfection does not lead to disease, see panel C in Fig. 1. Individuals in this state of partial protection (Q) are potentially incorrectly classified as controls for estimating the infection rate ratio as they are not at risk of disease. We refer to this model as the SP^AQS model.

As in Swart et al. (2012), we assume for the full SP^AQS model that:

- All individuals are born susceptible (S);
- Individuals may become (asymptomatically) infected with force of infection λ; incorporating both the intensity of exposure and the dose-response function;
- When infected, there is a probability π of developing symptomatic illness;
- an infected individual is immediately fully protected (P) against subsequent infection;
- Waning of immunity is represented by transitions from P to a state of partial protection (Q) with rate α and then back to S with rate γ;
- When a partially protected individual is re-exposed to the same pathogen, a transition to the fully protected state (P) takes place with rate λ given the same frequency and dose of exposure as for the S → P transition;

We first consider the distribution of individuals over the different compartments in a closed cohort. At the start of the study, we have unknown fractions of the population in S, P, Q denoted s_0, p_0, q_0, and $s_0 + p_0 + q_0 = 1$. The evolution of the numbers of individuals as a function of time in the compartments, in the absence of birth and death, is given by

$$\begin{pmatrix} s(t) \\ p(t) \\ q(t) \end{pmatrix} = \frac{1}{(\alpha+\lambda)(\gamma+\lambda)} \begin{pmatrix} \gamma\alpha \\ \lambda(\gamma+\lambda) \\ \lambda\alpha \end{pmatrix} +$$

$$\frac{\lambda - (\alpha+\lambda)p_0}{(\alpha-\gamma)(\alpha+\lambda)} \begin{pmatrix} -\gamma \\ \gamma-\alpha \\ \alpha \end{pmatrix} e^{-(\alpha+\lambda)t} +$$

$$\frac{\alpha\lambda s_0 - \alpha\gamma p_0 + \gamma(\lambda+\gamma-\alpha)q_0}{(\alpha-\gamma)(\gamma+\lambda)} \begin{pmatrix} 1 \\ 0 \\ -1 \end{pmatrix} e^{-(\gamma+\lambda)t} \quad (1)$$

Note that when working with age instead of time, and setting $(s_0, p_0, q_0) = (1, 0, 0)$, we retrieve the equations from Swart et al. (2012).

Individual components can be obtained from the above equation, e.g.

$$s(t) = \frac{\gamma\alpha}{(\alpha+\lambda)(\gamma+\lambda)} + \frac{\gamma}{(\alpha-\gamma)} \left\{ \left[p_0 - \frac{\lambda}{(\alpha+\lambda)} \right] e^{-(\alpha+\lambda)t} + \left[\frac{\alpha}{\gamma} s_0 + q_0 - \frac{\alpha}{(\gamma+\lambda)} \right] e^{-(\gamma+\lambda)t} \right\} \quad (2)$$