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Modeling rates of infection with transient maternal antibodies and waning active immunity: Application to *Bordetella pertussis* in Sweden

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HIGHLIGHTS

- We modeled age-specific forces of infection when immunity wanes in Sweden
- We used a cross-sectional survey of anti-PT after a 17-year vaccination hiatus
- Using Finnish contact rates, we estimated probabilities of infection on contact
- We also estimated the infection rates, $\mathfrak{R}_0$, and age-specific contributions
- Our $\mathfrak{R}_0$ approximates the ratio of longevity and age at first infection

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ABSTRACT

Serological surveys provide reliable information from which to calculate forces (instantaneous rates) of infection, but waning immunity and clinical consequences that depend on residual immunity complicate interpretation of results. We devised a means of calculating these rates that accounts for passively acquired maternal antibodies that decay or active immunity that wanes, permitting re-infection. We applied our method to pertussis (whooping cough) in Sweden, where vaccination was discontinued from 1979 to 1995. A national cross-sectional serosurvey of antibodies to pertussis toxin, which peak soon after infection and then decay, was conducted shortly after vaccination resumed. Together with age-specific contact rates in Finland, contemporary forces of infection enable us to evaluate the recent assertion that the probability of infection upon contact is age-independent. We find elevated probabilities among children, adolescents and young adults, whose contacts may be more intimate than others. Products of contact rates and probabilities of infection permit transmission modeling and estimation of the intrinsic reproduction number. In contrast to another recent estimate, ours approximates the ratio of life expectancy and age at first infection. Our framework is sufficiently general to accommodate more realistic sojourn distributions and additional lifetime infections.

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1. Introduction

Ever since Muench (1959) pioneered catalytic modeling, epidemiologists have used functions that increase at decreasing rates over the unit interval to estimate forces of infection among susceptible persons from cross-sectional serological surveys. This approach was elaborated by others (Grenfell and Anderson, 1985; Griffiths, 1974), as well as Farrington (1990), who subsequently concluded that, however unrealistic biologically, the equilibrium assumption underlying this approach was inconsequential (Whitaker and Farrington, 2004). But these methods ignore passively acquired maternal antibodies

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Abbreviations and symbols

wP, aP	whole-cell and acellular pertussis vaccines
PT, FHA	pertussis toxin and filamentous haemagglutinin
EU	enzyme-linked immunosorbent assay (ELISA) units
BFGS	an iterative method for solving unconstrained nonlinear optimization problems
pdf	probability density function
p, q	proportions susceptible and protected via antibodies
$\lambda(a)$, λ_i	hazard rate or force of infection at continuous age a or in group i
$\omega(a)$	hazard rate at which antibodies decay or immunity wanes at age a
$F(a)$	cumulative probability of infection among children aged a
$R(a)$	probability of being immune at age a
$P_S(a)$, $P_I(\tau)$, $P_R(\sigma)$	probabilities of remaining susceptible at age a, infected τ time units after first infection, and immune σ time units after recovering
$-P'_S(a), -P'_I(\tau), -P'_R(\sigma)$	probability density functions (pdf) of first infection at age a, recovery τ time units after infection, and being susceptible to re-infection σ time units after recovery
$I_1(a)$, $I_2(a)$	probabilities of being infected (for the first and second times) at age a
γ	recovery rate or reciprocal of the duration of infectiousness (fixed in the analyses reported here)
ρ	possible diminution in the risk of subsequent infection by virtue of having been previously infected (fixed in the analyses reported here)
a, b, c, d	parameters of Farrington's (1990) function for the force of infection
a_i	activity, the average *per capita* contact rate of members of age group i
β_i	susceptibility of members of age group i, their probability of infection on contact with an infectious person
c_{ij}	proportion of group i contacts that are with members of group j
$y_j = I_j/N_j$	proportion with antibodies indicating recent infection, the attack "rate" or probability that a randomly contacted member of group j is infectious
N_i	number of people in group i
C_{ij}	number of face-to-face conversations reported by members of group i with members of group j
$\mathfrak{R}_0$, $\mathfrak{R}_{0i}$	basic or intrinsic reproduction number, average number of effective contacts, or infections in a wholly susceptible population, while infectious; *per capita* contribution from group i
$\mathfrak{R}$, $\mathfrak{R}_i$	realized reproduction number or average number of secondary infections per primary infection; *per capita* contribution from group i
K	next-generation matrix
n	number of age groups
A_{ij}	a function defined in the appendix
θ, μ	specific or *per capita* ageing and mortality rates
L	longevity, or average age at death

that may protect infants from infectious diseases while their immune systems develop, and they assume that active immunity lasts a lifetime. Maternal antibodies always decay and the waning of active immunity is an essential feature of the epidemiology of some viral and most bacterial diseases.

Pertussis (whooping cough) is caused by the bacterium *Bordetella pertussis*. Infection causes symptoms that range from paroxysmal to mild coughing depending on immunity, which wanes at rates that may depend on means of acquisition. Unvaccinated infants may develop life-threatening disease several months after birth, whereas vaccinated or previously infected older children, adolescents and young adults commonly develop atypical and less severe disease. Contacts between infants and the adults caring for them are so frequent, intimate, and prolonged that infected caregivers lacking apparent symptoms may nonetheless infect infants with severe or even fatal results. While the concept of immunity-modified disease is not new (Cherry, 2003), school-based outbreaks among adolescents in Massachusetts, which had sustained higher vaccine coverage longer than other states in the U.S.A., captured the attention of clinicians and public health practitioners alike (Marchant et al., 1994; Yih et al., 2000).

Infants began being vaccinated with whole-cell pertussis vaccines (wP) throughout the developed world in the mid-20th century, specifically in Sweden in 1953. However, Swedish authorities discontinued vaccination with wP in 1979, partly because pertussis resurged despite high vaccine coverage (Romanus et al., 1987). Unproven allegations (Institute of Medicine, 1991) about the safety of wP motivated the development of acellular products (aP), several of which were evaluated in Sweden (Ad hoc group for the study of pertussis vaccines, 1988; Gustafsson et al., 1996; Olin et al., 1997; Trollfors et al., 1995), where pertussis was again endemic.

Here we elaborate on Farrington's (1990) approach to account for the temporary protection of some infants by passively acquired maternal antibodies, and for active immunity that wanes, allowing re-infection with clinical consequences that depend on residual immunity. We apply our models to pertussis in Sweden, where a cross-sectional serological survey of antibodies to pertussis toxin (anti-PT) was conducted shortly after vaccination resumed in 1996 (Olin et al., 2004). Because immunity to pertussis is short-lived and exposure is most common among schoolchildren, we doubt that wP vaccination prior to 1979 appreciably affected survey results, especially given its apparent ineffectiveness during the mid-1970s.

In the EU's PolyMod project, face-to-face conversations were studied as a proxy for contacts by which the pathogens causing respiratory diseases such as pertussis might be transmitted from infectious to susceptible people (Mossong et al., 2008). We derived the contact rates used in our calculations from conversations in Finland, another Nordic country whose social system resembles that of Sweden. Together with this information, our estimated forces of infection in an essentially unvaccinated contemporary population permit us to calculate age-specific probabilities of infection with *B. pertussis*, as well as the infection rates and reproduction number required to model pertussis transmission.

A glossary of symbols and abbreviations accompanies the next section.

2. Methods

2.1. Maternal antibodies

We begin by allowing a proportion p of infants to be susceptible at birth and $1-p=q$ to be immune by virtue of passively acquired

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