Waning immunity and sub-clinical infection in an epidemic model: implications for pertussis in The Netherlands

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Abstract

In The Netherlands, an epidemic outbreak of pertussis took place in 1996–1997. Understanding of the causes of the epidemic is hampered by the fact that many cases of infection with *Bordetella pertussis* go by unnoticed, and by the fact that immunity against infection does not last lifelong. Motivated by these observations, we develop and analyze an age-structured epidemic model that takes these factors into account. A distinction is made between infection in immunologically naive individuals, and infection in individuals whose immune system has been primed before by infection or vaccination. While the former often lead to severe symptoms and thus are more often diagnosed and notified, the latter are largely sub-clinical. The main questions are: (1) to what extent do sub-clinical infections contribute to the circulation of *B. pertussis*; and (2) what might be the causes for the recent epidemic? To answer these questions, we first present a new method to estimate the force of infection from notification data. The method is applied to the 1988–1995 case notification data from The Netherlands. Estimates of the force of infection vary greatly, depending on the rate at which immunity is lost, and on the fraction of sub-clinical infections. For the 1988–1995 period, our analysis indicates that if immunity is lost at a small rate and if a majority of infections is sub-clinical, the contribution of infection in adults to the transmission process cannot be neglected. Our results furthermore indicate that a decrease in the duration of protection after vaccination due to a change in the pathogen is the most likely factor to account for the 1996–1997 epidemic.

Keywords: Communicable disease; *Bordetella pertussis*; Notification data; Force of infection; Mathematical model

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1. Introduction

Pertussis (whooping cough) is a highly contagious infection of the respiratory tract. It is caused by the bacteria *Bordetella pertussis* and, less often, *Bordetella parapertussis*. Before the introduction of vaccination pertussis was one of the main causes of infant morbidity and mortality, causing more deaths than all other communicable diseases of childhood taken together. After the introduction of mass vaccination the incidence and severity of pertussis decreased drastically, so that in developed countries pertussis-induced deaths are now rare.

However, pertussis has not been eradicated, and the general incidence of pertussis based on hospital admissions shows an increasing trend in The Netherlands [1,2]. In addition, strong epidemic outbreaks were observed in 1987 and 1996–1997. This is somewhat surprising in view of the fact that vaccination coverage has been high (≈96%) ever since the introduction of the Dutch vaccination program in 1953. Increased incidences have also been reported in other developed countries (e.g. Canada: [3]; USA: [4–6]; UK: [7]).

Vaccination against pertussis is given in the first year of life. Four doses of whole-cell vaccine are administered at 3, 4, 5, and 11 months of age. The intrinsic quality of the Dutch vaccine is constantly measured for each vaccine batch, and satisfies international standards. Nevertheless, the incidence of pertussis in vaccinated infants has increased significantly since 1994. As a result, the vaccine efficacy estimated with the screening method shows a decreasing trend (see [1,2] for details).

Immunity against infection with *B. pertussis* does not last lifelong [7–14]. This is not only so for immunity induced by natural infection, but also for vaccine-induced immunity [10]. In fact, the incidence based on notifications in persons over 7 yr of age in the vaccinated and unvaccinated populations are at present comparable in The Netherlands. This indicates that protection against infection after vaccination may be rather short-lived, on the order of 5–10 yr.

By far, most reported cases of pertussis are in children younger than 15 yr. To illustrate this, Fig. 1 shows the observed number of reported cases stratified by age in the 1988–1995 period, and during the 1996–1997 epidemic. The distribution shows a distinctive pattern. The number of cases is high in (unvaccinated) infants less than 1 yr old, it is much lower in (predominantly vaccinated) infants of 1–2 yr of age, and it reaches a second peak between 4 and 7 yr. Since the age distribution of the Dutch population is relatively uniform (≈200 000 individuals per cohort of a year), the figure is indicative for the incidence based on notification in The Netherlands. In fact, the yearly incidence in children younger than 10 yr was less than 10 per 100 000 in the pre-epidemic period, and exceeded 100 cases per 100 000 during the 1996–1997 epidemic.

The level of circulation of *B. pertussis* in the adult population may also be quite high. For instance, in [10] the yearly incidence of infection in persons over 15 yr in Finland was estimated at 248 per 100 000, and in [11] the incidence of infection in German adults was estimated at 133 per 100 000. Furthermore, in [9] it was found that not less than 26% of college students followed during a 2½ yr period had been infected at least once! This is a potential problem since infected adults may transmit the pathogen to very young children that have not yet been vaccinated, and that are most vulnerable to severe complications. However, the vast majority of infections in adults seem to be sub-clinical, and go by unnoticed [14–16]. As a result, it is very difficult to get a good indication of the total amount of circulation of *B. pertussis* in the population, and in particular of the contribution of circulation in adults.
In this paper we investigate, by means of an age-structured epidemic model, the implications of waning immunity and sub-clinical infections for *B. pertussis* circulation. We present a model that distinguishes between infection in immunologically naive individuals, and infection in individuals whose immune system has been primed before, either by infection or vaccination. Throughout we assume that the latter are more likely to be sub-clinical, and are less infectious than the former.

One of the key ingredients of the model is the so-called force of infection. We present a new method to estimate the force of infection from case notification data. The forte of our method is that the estimation procedure is based on the underlying dynamic model. It allows us to take into account waning immunity in the estimation procedure, and to deal with sub-clinical infections in a consistent manner. The method is applied to the 1988–1995 pertussis incidence data from The Netherlands. The estimates of the force of infection are subsequently incorporated into the

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Fig. 1. Age-specific numbers of notified pertussis cases in The Netherlands. Panel A shows the distribution from 1988 up to 1995 (before the epidemic), while Panel B shows the age distribution in between 1996 and 1997 (during the epidemic). We refer to [1] for details.

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2. Methods and model structure

2.1. Model structure

We consider a model that distinguishes between two types of infection: infection in immunologically naive individuals (henceforth called primary infection), and infection in individuals whose immune system has been primed before by vaccination or infection (henceforth called secondary infection). Fig. 2 gives a schematic structure of the model.

We denote by $S_1(a,t)$ the age-dependent density of susceptible individuals that have not been infected or vaccinated at time $t$. Likewise, $S_2(a,t)$ denotes the density of individuals susceptible after loss of immunity, $I_1(a,t)$ and $I_2(a,t)$ the densities of individuals with a primary or secondary infection, and $R_1(a,t)$, $R_2(a,t)$, and $R_3(a,t)$ the densities of individuals that are recovered and immune after primary infection, secondary infection, or vaccination. Recovery from primary and secondary infection occurs at fixed rates $\rho_1$ and $\rho_2$, respectively. Immunity after primary infection, secondary infection, or vaccination is lost at rates $\sigma_1$, $\sigma_2$, and $\sigma_3$. The age-specific mortality function is given by $\mu(a)$, the age-specific vaccination function by $v(a)$, and the age- and time-dependent force of infection by $\lambda(a,t)$. The equations governing the dynamics of the model are given by

$$
\frac{\partial S_1}{\partial t} + \frac{\partial S_1}{\partial a} = -\mu(a)S_1 - \lambda(a,t)S_1 - v(a)S_1,
$$

$$
\frac{\partial I_1}{\partial t} + \frac{\partial I_1}{\partial a} = -\mu(a)I_1 + \lambda(a,t)S_1 - \rho_1 I_1,
$$

$$
\frac{\partial R_1}{\partial t} + \frac{\partial R_1}{\partial a} = -\mu(a)R_1 + \rho_1 I_1 - \sigma_1 R_1,
$$

$$
\frac{\partial S_2}{\partial t} + \frac{\partial S_2}{\partial a} = -\mu(a)S_2 + \sigma_1 R_1 + \sigma_2 R_2 + \sigma_3 R_3 - \lambda(a,t)S_2,
$$

$$
\frac{\partial I_2}{\partial t} + \frac{\partial I_2}{\partial a} = -\mu(a)I_2 + \lambda(a,t)S_2 - \rho_2 I_2,
$$

$$
\frac{\partial R_2}{\partial t} + \frac{\partial R_2}{\partial a} = -\mu(a)R_2 + \rho_2 I_2 - \sigma_2 R_2,
$$

$$
\frac{\partial R_3}{\partial t} + \frac{\partial R_3}{\partial a} = -\mu(a)R_3 - \sigma_3 R_3 + v(a)S_1.
$$

Fig. 2. Schematic structure of the model.
All individuals are born susceptible. Therefore, the only non-trivial boundary condition is

\[ S_1(0, t) = B(t), \]  

where \( B(t) \) denotes the birth function. We assume that total population size is constant in time (i.e. \( N = N(t) = \int_0^\infty N(a, t) \, da \)). This is ensured by choosing

\[ B(t) = \int_0^\infty \mu(a)N(a, t) \, da, \]

i.e. deaths are balanced by births. We may now interpret \( S_1, I_1, \) etc. in terms of relative frequencies instead of numbers per unit area or densities (i.e. \( S_1 + I_1 + R_1 + S_2 + I_2 + R_2 + R_3 = 1 \)).

The force of infection \( \lambda(a, t) \) denotes the rate at which susceptible individuals acquire infection. We assume that transmission of the pathogen from infecteds to susceptibles is governed by a mass action principle, i.e. the rate at which susceptible \( S_i(a, t) \) individuals acquire infection is proportional to \( S_i(a, t) \) times the prevalence of infecteds.

A contact between a primary or secondary infected (of any age) and susceptible (of any age) leads to transmission of infection from infected to susceptible with probabilities \( \beta_1 \) and \( \beta_2 \), respectively. Hence, the ratio \( \beta_2/\beta_1 \) represents the relative infectiousness of secondary infection to primary infection. Throughout we assume that secondary infections are less infectious than primary infections (i.e. \( \beta_2 < \beta_1 \)). The force of infection \( \lambda(a, t) \) is given by

\[ \lambda(a, t) = \int_0^\infty c(a, a') \{ \beta_1 I_1(a', t) + \beta_2 I_2(a', t) \} \, da'. \]

Here \( c(a, a') \) is the so-called contact function, which represents the number of contacts that a susceptible of age \( a \) makes with an infected of age \( a' \) per unit of time (e.g. [17]). The contact function and the probabilities of infection are determined from estimates of the force of infection (see below and Appendix A).

To arrive at numerical results, we make specific choices for \( \mu(a) \) and \( v(a) \). In the following we assume type 1 mortality (e.g. [18]), i.e. everybody lives to a certain age \( L \), and dies thereafter

\[ \mu(a) = \begin{cases} 0 & \text{if } a < L, \\ \infty & \text{if } a \geq L. \end{cases} \]

Type 1 mortality is a reasonable approximation for developed countries [18]. Moreover, it facilitates analysis of the model. Here, we take \( L = 75 \) yr.

Vaccination is included by assuming that certain fractions \( v_i \) of susceptibles in \( S_1 \) are effectively vaccinated at fixed predefined ages \( a_i \). Hence, \( v(a) \) is given by

\[ v(a) = v_i \sum_{i=1}^n \delta(a_i - a). \]

Here \( \delta(a_i - a) \) denotes Dirac’s delta function \( (\int_{a_i - \Delta}^{a_i + \Delta} \delta(a_i - a) \, da = 1) \), and \( n \) represents the number of vaccination bouts.
Numerical integration of the model was done using the escalator boxcar train method [19]. We refer to [20] for a mathematical description.

3. Model parameters

Vaccination coverage in The Netherlands is about 96%. Estimated vaccine efficacy based on notification data ranged from 0.3 to 1.0 from 1988 to 1995 (see [1,2] for details; [21,22] for interpretation of vaccine efficacy). Mean estimated vaccine efficacy in that period was 0.89 for 1–4 yr old infants, and 0.81 for 5–9 yr old infants. The fraction effectively protected by vaccination is given by the product of vaccination coverage and vaccine efficacy. In the following we assume that 85% of the population is effectively protected after one year of life. Hence, this corresponds to taking $n = 1$, $a_1 = 1$, and $v_1 = 0.85$ in Eq. (6). To check the robustness of the results so obtained we also considered a somewhat more realistic scenario where immunity of the population is gradually built up after each vaccination dose. For this scenario we took $n = 4$, $a_1 = 3/12$, $a_2 = 4/12$, $a_3 = 5/12$, $a_4 = 11/12$, in accordance with the Dutch vaccination schedule. To ensure that approximately 85% of the population is effectively vaccinated after one year of life we took $v_i = 1 − i = 0.85 = 0.38$ ($i = 1, \ldots, 4$), which means that 38% of the susceptible population ($S_1$) is moved to the vaccinated population ($R_3$) per vaccination bout. Qualitatively, the results of the two scenarios were identical. In the following we will adhere to the simpler formulation where a certain fraction $v$ of the population is effectively vaccinated precisely after one year.

The duration of the infectious period is not precisely known, and probably varies widely. Moreover, the duration of infection is likely to be age-dependent [23]. Grenfell and Anderson [24] and Hethcote [25] use a rough estimate of three weeks. This may somewhat overestimate the infectious period, since infected individuals are mainly infectious during the early catarrhal stage, before the appearance of the paroxysmal cough [26]. Here we typically assume that the infectious period lasts for about two weeks ($\rho_1 = \rho_2 = 25$ yr$^{-1}$), but we will also present simulations where the infectious period is four weeks ($\rho_1 = \rho_2 = 12.5$).

Although it is clear that immunity after vaccination or infection does not last lifelong, precise estimates for the duration of protection are lacking. Hethcote [25] assumes that most of the immunity after natural infection is lost after 15 yr on average, while most of the protection after vaccination is lost after 6 yr. As in our model, Hethcote assumes that individuals that have been infected or vaccinated before will not or only very infrequently develop a full infection. In most of the following we assume that immunity after vaccination or infection lasts for 20 yr on average ($\sigma_1 = \sigma_2 = \sigma_3 = 0.05$ yr$^{-1}$), but we will also indicate how the results are affected if, for instance, protection after vaccination lasts for 5–10 yr only. Moreover, we will also consider scenarios in which immunity is not lost at all ($\sigma_1 = 0$).

One of the probabilities of infection ($\beta_1$ or $\beta_2$) is estimated from the force of infection, while the other is chosen in advance. Here we assume that secondary infections have a fixed infectiousness relative to primary infections. Again, not much is known on the infectiousness of mild, sub-clinical infections compared to more severe clinically recognized infections. It may be that severe infections are more infectious because more infectious particles are produced. Alternatively, it may be that severely infected individuals are effectively less infectious because they
stay at home and have fewer contacts with susceptibles. We assume in most of the following
that primary infections are five times more infectious than secondary infections (i.e. \( \beta_2 / \beta_1 = 0.2 \)).

3.1. The force of infection

Reliable estimates of the force of infection are particularly difficult to obtain. In fact, current
estimates for pertussis are all based on incidence data from England and Wales in the pre-vacc-
cination era [18, p. 165;24]. These data lead to the following estimates. The force of infection is
very low during the first year of life, it then increases to reach a peak of 0.4–0.5 (yr\(^{-1}\)) in 5–10 yr
old individuals, after which it decreases to relatively low values of 0.05–0.1 in individuals older
than 15 yr.

It is highly questionable whether the above estimates from the pre-vaccination era describe
the present situation in The Netherlands well. Moreover, the method that is used to estimate the
force of infection [27] has a number of drawbacks. It is based on the assumption that everybody
is immune from a certain age on. This may have been the case 50 yr ago when the infection
pressure was high, but is unlikely to hold at present (see also [21]). Furthermore, Grenfell and
Anderson’s method [27] assumes that the fraction of cases that is notified does not depend on
age (proportional case reports). This assumption is also questionable in the present context
(cf. [28]).

Here we present a new method to estimate the age-dependent force of infection that is based on
the dynamic model (1). In essence, the age-specific force of infection is estimated from age-specific
incidence data and the stable age distribution of the endemic equilibrium of our model. We define
a number of fixed age-classes. Within each age-class we assume that the force of infection is
constant, so that the model reduces to a set of linear ordinary differential equations that can be
solved explicitly. The solution yields relationships between the densities of susceptibles at the left
and right boundary of an age-class, the rate at which immunity is lost, and the force of infection in
that age-class. Given the densities of susceptibles at the left and right boundary of an age-class and
the rate at which immunity is lost, the age-specific force of infection is estimated from the ob-
served incidence in that age-class (see Fig. 1). We assume that a fraction \( p_1 \) of primary infections
and a fraction \( p_2 \) of secondary infections is notified. Given \( p_1 \) and \( p_2 \), the expected densities of
primary and secondary susceptibles at the start of each age-class can be used to convert the
observed incidence in that age-class into an estimated true incidence. The force of infection is
subsequently determined from the estimated true incidence.

We refer to Appendix A for a mathematical description of the method. The method is applied
to the 1988–1995 case notification data from The Netherlands. The results are shown below
(Fig. 3).

3.2. The contact function

The contact function \( c(a, a') \) in (4)) and the probability of primary infection (\( \beta_1 \)) are deter-
mined from a given force of infection. To be able to do so, one has to make additional as-
sumptions on the structure of the contact function. Since not much is known about age-related
mixing patterns, we simply assume that the probability of a contact between a susceptible and infected is given by the product of age-dependent activity levels $l(a)$ of the susceptible and infected involved. This assumption is commonly referred to as proportionate mixing, and has also been used by Hethcote [25]. The force of infection and the contact function have the same shape under the assumption of proportionate mixing (i.e. $\lambda(a) = \text{constant} \times l(a)$). We refer to [17] for a lucid account on the determination of the contact function and probability of infection from a given force of infection.

In our case, the contact function is determined from the estimated force of infection in the 1988–1995 period. As explained above our method assumes that the population was in the endemic vaccination equilibrium in that period. That this cannot be the case is immediately clear from the fact that the Dutch vaccination program is implemented only from 1953 onwards, so that individuals older than 43 yr of age are not vaccinated. However, it appears that estimates of the force of infection in individuals over 45 yr have a marginal impact on the results unless the force of infection in those individuals is very high (results not shown). Once the contact function has been determined from estimates of the force of infection in a given period, the model can be used to reconstruct the past, and to predict the future. Note that this entails the implicit assumption that the contact structure is constant over time.

3.3. Scenarios

We consider four scenarios that differ in the rate at which immunity is lost, and in the fraction of infections that is notified. In Scenarios A and B we assume that immunity after natural infection or vaccination lasts lifelong ($\sigma_i = 0$, $i = 1, 2, 3$). In Scenarios C and D we assume that immunity lasts for 20 yr on average ($\sigma_i = 0.05$ (yr$^{-1}$), $i = 1, 2, 3$). In Scenario A all infections are symptomatic and hence notified ($p_1 = 1$), while in Scenario B only one out of 50 infections is notified ($p_1 = 0.02$). In Scenario C we assume that all primary infections are notified ($p_1 = 1$), while only a small fraction of all secondary infections is notified ($p_2 = 0.1$). In Scenario D only a small fraction of primary infections is notified ($p_1 = 0.1$), and a very small fraction of secondary infections is notified ($p_2 = 0.01$). Table 1 gives an overview of the scenarios.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Rate of loss of immunity ($\sigma_i$)</th>
<th>Fraction of infections notified ($p_i$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario A</td>
<td>0</td>
<td>$p_1 = 1$</td>
</tr>
<tr>
<td>Scenario B</td>
<td>0</td>
<td>$p_1 = 0.02$</td>
</tr>
<tr>
<td>Scenario C</td>
<td>0.05</td>
<td>$p_1 = 1$; $p_2 = 0.1$</td>
</tr>
<tr>
<td>Scenario D</td>
<td>0.05</td>
<td>$p_1 = 0.1$; $p_2 = 0.01$</td>
</tr>
</tbody>
</table>

*Immunity lasts lifelong in Scenarios A and B, and for 20 yr in Scenarios C and D. In Scenario A all infections are notified, while in Scenario B only one out of 50 infections are notified. In Scenarios C all primary infections and one out of 10 secondary infections are notified. In Scenario D one out of 10 primary infections and one out of 100 secondary infections are notified.*
4. Results


Fig. 3 shows the age-dependent force of infection as estimated by the method outlined above. The panels of the figure correspond to the four scenarios. Qualitatively, the force of infection has a familiar shape for all scenarios. It is low in the very young age-classes, it reaches a peak between 5 and 7 yr, and it decreases again to a low level in the older age-classes. This indicates that 5–7 yr old susceptibles are at the highest risk of contracting an infection.

Quantitatively, however, there are large differences between scenarios. If all infections are notified and if immunity lasts lifelong (Scenario A; Fig. 3(A)), the incidence data of Fig. 1 lead to very low estimates for the force of infection. In fact, the force of infection reaches a maximum in five-year-old individuals of only \(0.0015\) (yr\(^{-1}\)). This means that the probability that a five-year-old susceptible infant will be infected in a year is less than 0.15% (\(\approx 1 - e^{-0.0015}\)). In the older age-classes (>15yr) the force of infection is even smaller (<10\(^{-4}\) (yr\(^{-1}\))). In these age-classes the probability of infection is less than 0.01%. Consequently, adult infections cannot play a role in the persistence of \(B.\) pertussis circulation in this scenario.

![Fig. 3](image-url). Age-dependent forces of infection as estimated from the 1988–1995 pertussis incidence data (see Fig. 1). The panels of the figure correspond to the four Scenarios A–D (see Table 1). Note the logarithmic scale on the co-ordinates.
If a significant fraction of infections is sub-clinical (Scenario B; Fig. 3(B)), the estimated force of infection is increased more than 70-fold. In this case the force of infection reaches a peak of almost 0.11 in seven-year-old individuals, which means that about 11% of seven-year-old susceptibles will be infected in a year (≈1−e^−0.11). Moreover, the force of infection in the older age-classes cannot be neglected anymore, and ranges from 2 × 10^−3 to 5 × 10^−3.

Panels C and D of Fig. 3 show the results when immunity is lost after 20 yr on average. In C all primary infections and one out of 10 secondary infections are notified (p_1 = 1, p_2 = 0.1). In D one out of 10 primary infections is notified, and only one out of 100 secondary infections (p_1 = 0.1, p_2 = 0.01). In both panels the force of infection reaches a peak in five-yea-old individuals (\( \lambda^{(5)} = 4.0 \times 10^{-3} \) in C, and \( \lambda^{(5)} = 4.4 \times 10^{-2} \)). In other words, the estimated probability that a five-year-old susceptible is infected is 0.4% in Scenario C, and 4.4% in Scenario D. In C the force of infection in the older age-classes levels off at 2.5 × 10^−5, while in D the force of infection in the older age-classes is about 3.0 × 10^−4.

Note that the relation between the fraction of symptomatic infections and the force of infection need not be straightforward. A high incidence in a certain age-class will in general lead to a high estimate for the force of infection in that age-class. However, it will also leave less susceptibles in the following age-classes. Hence, an increase in the incidence in a certain age-class will not only increase the force of infection in that age-class, but it will also increase the force of infection in all following age-classes. The magnitude of this effect depends on the extent to which the density of susceptibles is decreased by infection. More precisely, it will depend on the number of infections relative to the number of susceptibles. In three of the four scenarios considered here (A, C, and D), the observed incidence is too low to have an appreciable effect on the number of susceptibles. This, however, is not so for Scenario B where the number of susceptible adults is relatively small, and the number of infections relatively large. For this scenario the maximal force of infection is increased more than 70-fold in comparison with Scenario A, while the number of infections is only 50 times higher. In adults the force of infection is even increased from about 2 × 10^−5 in A to 3 × 10^−3 in B, a 150-fold increase.

With estimates of the force of infection at hand, we proceed to investigate the implications for B. pertussis circulation in The Netherlands.


Table 2 summarizes the equilibrium results of the four scenarios, and Fig. 4 shows the simulated age-dependent prevalences of infecteds and susceptibles 43 yr after the introduction of the

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Incidence (100 000 p_1 I_1)</th>
<th>Incidence (100 000 p_1 I_2)</th>
<th>S_1</th>
<th>S_2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario A</td>
<td>5 (8.9 yr)</td>
<td>NA^b</td>
<td>0.16</td>
<td>NA</td>
</tr>
<tr>
<td>Scenario B</td>
<td>193 (7.4 yr)</td>
<td>NA</td>
<td>0.06</td>
<td>NA</td>
</tr>
<tr>
<td>Scenario C</td>
<td>10 (7.4 yr)</td>
<td>14 (15.3 yr)</td>
<td>0.16</td>
<td>0.62</td>
</tr>
<tr>
<td>Scenario D</td>
<td>78 (7.1 yr)</td>
<td>119 (15.3 yr)</td>
<td>0.12</td>
<td>0.63</td>
</tr>
</tbody>
</table>

^a^The mean age at infection is given between brackets.

^b^NA: Not applicable.
vaccination program. The panels of the figure correspond to Scenarios A–D. Since the Dutch immunization program started in 1953, the figure corresponds to the age-dependent prevalences of 1995.

If immunity lasts lifelong ($\sigma = 0$), and without sub-clinical infections ($p_1 = 1$; Panel A), the prevalence of infection is only non-negligible ($> 10^{-5}$, say) in newborns and in 2–7 yr old infants. But even in these age-classes the impact of natural infections on the immune status of the population is negligible, and vaccination is the most important force affecting the prevalence of susceptibles (and hence infecteds). Fig. 4(A) furthermore shows that the prevalence of susceptibles in the age-classes older than 43 yr is very low, owing to a high infection pressure in the pre-vaccination period.

Fig. 4(B) shows the results if there is no waning of immunity ($\sigma = 0$), and if a considerable fraction of infections is sub-clinical and thus not notified ($p_1 = 0.02$). In comparison with Fig. 4(A) the prevalence of infection is increased considerably. In fact, the prevalence of infection in the older age-classes is increased by orders of magnitude. The effect of natural infection on the prevalence of susceptibles cannot be neglected anymore. More specifically, the prevalence of susceptibles that is reduced to approximately 15% by vaccination after the first year of life, is
reduced further by natural infection to approximately 5% at age 20. Here the prevalence of infection in 20–43 yr old persons is about 0.001% (10^-5), which might be within the range of measurement. The prevalence of susceptibles older than 43 yr is now reduced to very low values as a result of a very high infection pressures in the pre-vaccination era (from 1% at 50 yr of age to almost 0.01% at 75 yr of age).

Panels C and D of Fig. 4 show the results when immunity is lost after 20 yr on average. In both panels the total prevalence of secondary susceptibles ($S_2$) is rather high (>60%; Table 2). As a result, the total prevalence of secondary infection is also considerably higher than the total prevalence of primary infection. Especially in adults the prevalence of secondary susceptibles ($S_2$) may be over 80%. This contrasts markedly with Scenarios A and B where most adults are immune. As expected, the mean age at infection is higher for secondary than for primary infections. However, even secondary infections occur mostly in 5–20 yr old individuals. In fact, in C the prevalence of secondary infection in adults is on the order of only 10^-6, while in D it is of the order of 10^-5. Hence, the prevalence of infection in adults (>20 yr) is only non-negligible if the fraction of symptomatic infections is of the order of 1 out of 100 or less. This phenomenon is due to the fact that the estimated force of infection in adults is rather low for both scenarios.

For simplicity, we assumed in all our main scenarios that rate at which immunity is lost is the same after natural infection and vaccination. This is not realistic. Therefore we also considered scenarios where immunity after vaccination is lost after 5 or 10 yr on average. The consequence of this assumption is that the estimates for the force of infection decrease somewhat in the younger age-classes (1–15 yr). At the same time, however, the prevalence of susceptibles in those age-classes increases. Taken together, it appears that estimates for the prevalence of infection in the pre-epidemic period are marginally affected if the duration of immunity after vaccination is decreased from 20 to 10 yr, and slightly more if the duration of protection after vaccination is decreased from 20 to 5 yr (results not shown).

We may conclude that already a small rate of loss of immunity is sufficient to render most adults susceptible, but that sub-clinical infection in adults may only have contributed significantly to pertussis circulation in the 1988–1995 period if the vast majority of secondary infections were sub-clinical.

4.3. The 1996–1997 epidemic

Up to here, our analysis was concerned with the pre-epidemic period from 1988 to 1995. We may now ask what kind of changes in the transmission dynamics of *B. pertussis* can account for the more than 10-fold increase in incidence in 1996–1997, and the change in the relative frequency of infections in infants less than 1 yr old. In particular, we focus on changes that (1) increase the infectious period; (2) increase the relative infectiousness of secondary infections; (3) decrease vaccine efficacy; and (4) decrease the immune period after vaccination. The results are shown in Table 3, and in Figs. 5 and 6.

First, we considered an increase in the infectious period from two weeks ($\rho_1 = \rho_2 = 25$ (yr⁻¹)) to four weeks ($\rho_1 = \rho_2 = 12.5$ (yr⁻¹)). Doubling the infectious period will at least lead to a twofold increase of the prevalence of infection (but not necessarily the incidence, see Scenario B), but it will usually lead to much stronger increase due to extra infections. This effect is particularly
pronounced for Scenarios A and C where the estimated prevalence in the pre-epidemic period is rather low. It is much less marked in Scenarios B and D where the estimated level of circulation before the epidemic is already quite high.

### Table 3
Results of the sensitivity analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scenario A</th>
<th>Scenario B</th>
<th>Scenario C</th>
<th>Scenario D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Default</td>
<td>5/15%</td>
<td>193/21%</td>
<td>10/7.3%</td>
<td>78/6.2%</td>
</tr>
<tr>
<td>$\rho = 12.5$</td>
<td>25/27%</td>
<td>300/36%</td>
<td>263/11%</td>
<td>263/9.2%</td>
</tr>
<tr>
<td>$\beta_2/\beta_1 = 0.4$</td>
<td>NA</td>
<td>NA</td>
<td>108/8.3%</td>
<td>158/7.1%</td>
</tr>
<tr>
<td>$v = 0.7$</td>
<td>400/16%</td>
<td>475/22%</td>
<td>375/8.6%</td>
<td>400/7.3%</td>
</tr>
<tr>
<td>$\sigma_3 = 0.1$</td>
<td>155/6.3%</td>
<td>250/7.7%</td>
<td>83/6.1%</td>
<td>135/5.2%</td>
</tr>
</tbody>
</table>

*a Shown are the equilibrium incidence (in cases per 100,000 per yr) of primary infection, and the proportion of infections in infants less than 1 yr old (in %) for the default parameter setting and four variant parameter settings. Note that, at equilibrium, incidence and prevalence are related through prevalence $(I^*) = incidence \times infectious period (1/\rho)$.

**b NA**: Not applicable.

**Fig. 5.** Simulated prevalence after a decrease in the period of immunity after vaccination from 20 yr ($\sigma_3 = 0.05$) to 10 yr ($\sigma_3 = 0.1$). The panels of the figure correspond to the four Scenarios A–D (see Fig. 3). Black lines denote the prevalence of infecteds (solid line: $I_1$; dashed line: $I_2$). Grey lines denote the fraction of susceptibles (solid line: $S_1$; dashed line: $S_2$).
Second, we considered an increase in the relative infectiousness of secondary infections. A twofold increase in the relative infectiousness of secondary to primary infections usually increases the prevalence of primary infection considerably (see Table 3). However, the extent to which the prevalence of primary infection is increased depends to a large extent on the estimated prevalence of secondary infection in the pre-epidemic period, and hence on the rate at which immunity is lost. If the rate at which immunity is lost is extremely low, an increase in the relative infectiousness of secondary infections cannot alter the prevalence of infection much (results not shown).

Third, there may have been changes associated with the vaccine. In all four scenarios we assumed that 85% of the population is effectively vaccinated at age 1. A decrease of the fraction of the population that is effectively vaccinated from 85% to 70% roughly doubles the frequency of \( S_1 \) susceptibles at age 1 from 15% to 30%. Such a change increases the prevalence of primary infection in infants older than age 1 more than twofold (Table 3).

Another possible vaccination related change is the duration of protection after vaccination. Table 3 and Figs. 5 and 6 show the results after a decrease in the period of protection after vaccination from 20 to 10 yr for all cohorts (also the ones vaccinated before the change took place). In Scenarios A and C this leads to a marked increase in the prevalence of primary
infection. In Scenarios B and D the increase in the prevalence of primary infection is much less pronounced. The magnitude of the increase in prevalence of primary infection strongly depends on the fraction of the population that is susceptible in the pre-epidemic period. If the majority of the population is protected by vaccination, then a decrease in the period of protection will increase the density of susceptibles considerably. As a result, the prevalence of infection will also increase. If, on the other hand, most adults are already susceptible, then a decrease in the duration of protection after vaccination will have a negligible effect on the density of susceptibles, and hence on the prevalence of infection.

As Fig. 5 shows, the prevalence of infection increases rapidly after a decrease in the period of immunity after vaccination. In the long run a new endemic equilibrium is reached. There are some differences between scenarios. First, the frequency and amplitude of the oscillations (epidemics) is higher for Scenarios A and C than for Scenarios B and D. Second, the relaxation time (the time until the endemic situation is reached) is much longer for Scenarios A and C than for Scenarios B and D. These phenomena are due to the fact that the prevalence of infection prior to the change in vaccine efficacy is much lower for Scenarios A and C than it is for Scenarios B and D. This illustrates that the way a change in duration of vaccine protection may affect the Dutch population depends to a large extent on the pre-epidemic situation. A strong epidemic outbreak could occur already for slight changes in the duration of vaccine immunity if the pre-epidemic level of circulation is low. If, on the other hand, the pre-epidemic level of circulation is high, a much larger change is needed to produce an epidemic outbreak.

Fig. 6 shows the age-distribution of infection corresponding to the situation in Fig. 5, 50 yr after the decrease in vaccine efficacy. For all scenarios the prevalence of primary and secondary infection in adults together ranges from $10^{-5}$ to $10^{-4}$. This means that the incidence in adults (computed as $10000 \rho I^a(a)$) will be somewhere between 25 and 250 cases per 100,000. The incidence according to notification in 1996–1997 was about five cases per 100,000 per yr. These observed numbers are not incompatible with the model incidence since the observed incidence should be multiplied by a certain factor to take into account sub-clinical infection. Depending on the assumptions on the fraction of secondary and secondary infections that is notified, and on the relative contribution of primary and secondary infection to the total prevalence, this factor may be anywhere between 5 and 100. Moreover, Fig. 6 refers to the endemic equilibrium instead of the first epidemic peak. Depending on the scenario, the incidence in adults at the first epidemic peak is from 2-fold (Scenario D) to 7-fold (Scenario B) higher than at the endemic equilibrium. Note that the frequency of susceptible adults is still high (82%) in Scenarios C and D due to loss of immunity. It is 55% in Scenario A, and just 30% in Scenario B, where the buildup of immunity by infection balances the waning of immunity.

The most striking feature of the Dutch epidemic is that the relative fraction of cases in infants of less than 1 yr old decreased markedly. However, as shown in Table 3, the relative contribution of infection in infants of age 0 actually increases for most changes that increase incidence in the model. This is so if the infectious period is increased, if the relative infectiousness of secondary infections is increased, and if the fraction of those remaining susceptible after vaccination is increased. However, the opposite pattern is found if one increases the rate at which immunity is lost. Here the contribution of infection in newborns actually decreases, while the general incidence increases. This is particularly so for those scenarios where immunity is not lost at all in the endemic situation (Scenarios A and B).
Table 3 shows the results 50 yr after a change has taken place. We also investigated in more detail the total incidence of infection and the proportion of infection in newborns in the first epidemic peak. It appeared that, qualitatively, the results of Table 3 are remarkably robust. In particular, the fraction of all infections that occurred in newborns is only slightly different in the first epidemic peak as compared to the endemic situation. Hence, we conclude that, among the possible changes in the transmission dynamics of \emph{B. pertussis} considered here, a decrease in the protected period after vaccination is the most likely factor accounting for the 1996–1997 epidemic in The Netherlands.

5. Discussion

We investigated the role of sub-clinical infection and waning immunity in the transmission dynamics of \emph{B. pertussis} using an age-structured epidemic model that distinguishes between two types of infection. To this end we developed a new method to estimate the age-dependent force of infection that is based on the underlying model. Estimates of the force of infection vary greatly, depending on the rate at which immunity is lost, and on the fraction of infections that is sub-clinical. In general, waning immunity tends to increase the prevalence of susceptibles, and therefore tends to decrease the force of infection. On the other hand, if most infections are sub-clinical the true incidence will be higher than the observed incidence, and the force of infection increases. Analysis of the dynamic model indicates that the contribution of sub-clinical infection in adults to the circulation \emph{B. pertussis} in The Netherlands in the pre-epidemic period (1988–1995) could only have been significant if the vast majority of adult infections were sub-clinical.

A sensitivity analysis of the model shows that a variety of factors could have led to the strong increase in the incidence of pertussis in 1996–1997. However, most of these factors also decrease the average age at infection. In particular, most factors that lead to an increased incidence also increase the relative fraction of infections in newborns. This is in striking contrast with the 1996–1997 epidemic: while the general incidence of pertussis increased more than 10-fold, the fraction of infections in infants less than 1 yr of age actually decreased from 19% in 1988–1995 to 6% in 1996–1997. Of the scenarios we studied a sudden decrease in the duration of the immune period after vaccination for all age-classes is the only one that can increase incidence and at the same time decrease the relative fraction of infections in newborns.

Our results indicate that, at least qualitatively, a decrease in the period of protection after vaccination is the most likely explanation for the 1996–1997 epidemic. However, in view of the lack of data on key parameters such as the rate at which immunity is lost, the infectious period, and especially the fraction of primary and secondary infections that is notified, it is at present not really possible to arrive at solid quantitative conclusions. However, our model predictions and the observed incidence of the 1996–1997 epidemic are not at all incompatible. This gives some faith in the model structure, and in our choice of the model parameters. We are currently investigating in more detail various possible explanations for the decrease in the protected period after vaccination (van Boven et al., submitted). An attractive hypothesis is that the decrease in vaccine efficacy may at least in part be due to the appearance of novel \emph{B. pertussis} strains [29,30] for which the vaccine is less effective. Indeed, \emph{B. pertussis} strains circulating in The Netherlands have changed in a number of virulence genes (pertactin and pertussis toxin [29,30]) so that there is a mismatch with the currently used whole-cell vaccine. It is likely that these changes have some adaptive signifi-
cance [30]. Hence, the observed reduction in vaccine efficacy may well be due to changes in the pathogen, rather than changes in the vaccine.

Of course, our model has a number of shortcomings. First, our method to estimate the force of infection assumes that the population is in endemic equilibrium. In the case of pertussis in The Netherlands this assumption is questionable. This problem, however, is shared by other methods (e.g. [21,24,31]). Furthermore, to make the results easily interpretable and to avoid making the model overly complex, we assumed that primary infections are always more infectious than secondary infections, that primary infections are more often notified than secondary infections, and that clinically recognized infections are always notified (and sub-clinical infections never). Although these assumptions are plausible as a starting point, it is not directly clear how our conclusions are affected, for instance, notification and infectiousness are related in a non-obvious way, or if infectiousness is directly related to age. A final point of concern is related to our assumption that immunity against infection is an all or nothing event. This is done for simplicity, and because no reliable quantitative data is available on the relation between the ‘level of immunity’ (which may be reflected by antibody titers) and the probability of infection. It remains to be seen how robust our conclusions are if our model is refined so that the level of immunity decreases gradually, thereby increasing the probability of infection.

By now, it is clear that protection after vaccination or infection against infection with B. pertussis does not last lifelong. Immunity after natural infection seems to be lost after 10–20 yr, while immunity after vaccination might last for 5–10 yr only (e.g. [10]). As a result, we expect that the majority of adults will be susceptible to infection unless the infection pressure is rather high. In view of the situation in the field where very high incidences in adults are sometimes found [9–11], the matter remains unsettled. The main questions that now need to be addressed are: (1) is the majority of the adult population in The Netherlands at present susceptible to infection or immune, and (2) what is the risk that a susceptible adult will contract an infection? We are currently addressing these questions by analyzing pertussis-specific antibody titers in the Dutch population at large [31], and longitudinal trends of antibody titers in individual patients after a clinically recognized infection [J.F.P. Schellekens, unpublished results]. Together, the results of these analyses should give more insight in the incidence of sub-clinical infection, and in its importance in the transmission dynamics of B. pertussis.

Recently, there have been suggestions that boosting the immunity of the population by vaccinating older children and adults may solve the problem of silent transmission of B. pertussis in adults [32–35]. Whether revaccination is useful, however, depends on the immune status of the adult population, on the infection pressure on adults, and on the period of immunity after revaccination. Based on our model results we suspect that revaccination of large parts of the adult population can only be effective if (1) most adults are susceptible to infection, (2) the infection pressure on adults is not too low, and (3) the vaccine gives effective protection for a prolonged period of time. Note that the conditions (1) and (2) are somewhat conflicting: on the one hand it is unlikely that most adults are susceptible if the infection pressure is high, while on the other hand it is unlikely that the infection pressure is high if most adults are susceptible. But even if conditions (1) and (2) are met, the effectiveness of a revaccination program will depend strongly on the duration of protection against infection [36]. Therefore it is essential that the duration of protection provided by the vaccine is taken into account in the evaluation of vaccines and vaccination campaigns aimed at protecting the adult population.
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Appendix A. Estimation of the force of infection

Here we will outline our procedure to estimate the force of infection. Age-dependent estimates for the force of infection can be obtained from serological profiles or from case notification data [26]. Using a very simple model for the age-dependent changes in the fraction of susceptibles, these authors present a maximum likelihood method that is used to fit the model to the data. Their method is based on the assumption that immunity lasts lifelong. Moreover, in case of notification data, it is assumed that everybody is immune from a certain age on. These assumptions are unrealistic in the present context (see also [21]). Here we present a method to estimate the age-dependent force of infection that is consistent with the model presented in the main text. This method allows us to take into account waning of immunity and to study the impact of sub-clinical infection.

To obtain estimates for the age-dependent force of infection, we assume that the disease has reached the endemic steady state. Assuming type I mortality (everybody lives exactly $L$ yr), and dropping time dependencies in (1), we arrive at the following set of differential equations:

\[
\begin{align*}
\frac{dS_1(a)}{da} &= -\lambda(a)S_1(a) - v(a)S_1(a) \\
S_1(0) &= B, \\
\frac{dI_1(a)}{da} &= \lambda(a)S_1(a) - \rho_1I_1(a) \\
I_1(0) &= 0, \\
\frac{dR_1(a)}{da} &= \rho_1I_1(a) - \sigma_1R_1(a) \\
R_1(0) &= 0, \\
\frac{dR_3(a)}{da} &= v(a)S_1(a) - \sigma_3R_3(a) \\
R_3(0) &= 0, \\
\frac{dS_2(a)}{da} &= \sigma_1R_1(a) + \sigma_2R_2(a) + \sigma_3R_3(a) - \lambda(a)S_2(a), \\
S_2(0) &= 0, \\
\frac{dI_2(a)}{da} &= \lambda(a)S_2(a) - \rho_2I_2(a), \\
I_2(0) &= 0, \\
\frac{dR_2(a)}{da} &= \rho_2I_2(a) - \sigma_2R_2(a), \\
R_2(0) &= 0.
\end{align*}
\]

We simplify (A.1) by assuming that the processes of infection and recovery occur at a much faster time-scale than the process of loss of immunity. In this case we may put $dI_1/da = dI_2/da := 0$, and reduce the number of equations by two. The prevalence of primary and secondary infection is now directly related to the prevalence of susceptibles $S_1$ and $S_2$ through (e.g. [18 p. 676]).
\[ I_1(a) = \frac{\lambda(a)}{\rho_1} S_1(a), \]  
\[ I_2(a) = \frac{\lambda(a)}{\rho_2} S_2(a). \]  

Now we subdivide the total age-range into a number of age-classes. Within each age-class we assume that the force of infection is constant. Vaccination is assumed to occur between consecutive age-classes. As a result, (A.1) reduces to a set of autonomous differential equations in each age-class that can be solved explicitly. The solutions of these equations are used to estimate the force of infection from age-specific incidence data.

We introduce the following notation. The age interval \([0, L]\) is subdivided into \(L\) age-classes of 1 yr, \(A_i(0) = [i, i+1); \ i = 0, ..., L - 1\). Throughout we use superscripts to denote age-classes. Hence \(S_1(i)(s)\) denotes the fraction of susceptibles \(S_1\) in the \(i\)th age-class, \(0 \leq s < 1\). The constant force of infection in age-class \(A_i\) is given by \(\lambda(i)\), and the fraction of \(S_1\) individuals vaccinated at the beginning of age-class \(A_i\) is given by \(\nu(i)\). Now the dynamics within age-class \(A_i\) are given by

\[ \frac{dS_1(i)(s)}{ds} = -\lambda(i) S_1(i)(s), \]
\[ \frac{dR_1(i)(s)}{ds} = \lambda(i) S_1(i)(s) - \sigma_1 R_1(i)(s), \]
\[ \frac{dR_3(i)(s)}{ds} = -\sigma_3 R_3(i)(s), \]
\[ \frac{dS_2(i)(s)}{ds} = \sigma_1 R_1(i)(s) + \sigma_2 R_2(i)(s) + \sigma_3 R_3(i)(s) - \lambda(i) S_2(i)(s), \]
\[ \frac{dR_2(i)(s)}{ds} = N(i)(s) - \left( 1 + \frac{\lambda(i)}{\rho_1} \right) S_1(i)(s) - \left( 1 + \frac{\lambda(i)}{\rho_2} \right) S_2(i)(s) + R_1(i)(s) + R_3(i)(s) \right). \]

Note that, since population size is constant, one equation is redundant (here taken to be \(dR_2/ds\)). All individuals are born susceptible. Hence, \(S_1(0)(0) = 1\), and all other initial conditions of the zeroth age-class \(A_0\) are 0. The initial conditions \(S_1(i)(0), R_1(i)(0), R_3(i)(0), \) and \(S_2(i)(0)\) of other age-classes are given by

\[ S_1(i)(0) = (1 - \nu(i)) S_1^{(i-1)}(1), \]
\[ R_1(i)(0) = R_1^{(i-1)}(1), \]
\[ R_3(i)(0) = R_3^{(i-1)}(1) + \nu(i) S_1^{(i-1)}(1), \]
\[ S_2(i)(0) = S_2^{(i-1)}(1). \]  

(A.3a), (A.3b) can be solved explicitly. For instance, if we take \(\sigma = \sigma_i\) \((i = 1, 2, 3)\), the fractions of susceptibles \(S_1(i)(1)\) and \(S_2(i)(1)\), and recovereds \(R_1(i)(1)\) and \(R_3(i)(1)\) in age-class \(i\) are related to \(S_1(i)(0)\), \(S_2(i)(0)\), \(R_1(i)(0)\), and \(R_3(i)(0)\) through
We need one more ingredient to estimate the force of infection. Let us denote the observed incidence in age-class \(A_i\) by \(n_i\), and the fraction of primary and secondary infections that are notified by \(p_1\) and \(p_2\). We assume that the prevalence \(I_i\) at the start of a certain age-class reflects the incidence within that age-class. Hence, the prevalence of infection \(I_i\) equals the incidence \(n_i\) times the infectious period \((I_i = n_i \frac{1}{\lambda})\). Using (A.2), we find that the total incidence \(n_i\) is related to the fraction of susceptibles \(S_{1i}\) and \(S_{2i}\) through

\[
\begin{align*}
n_i &= n_1 + n_2, \\
&= p_1 p_1 I_1(0) + p_2 p_2 I_2(0), \\
&= \frac{\lambda (p_1 S_1(0) + p_2 S_2(0))}{n_i},
\end{align*}
\]

where \(p_1\) and \(p_2\) denote the fraction of primary and secondary infections that are notified.

Now we are in the position to estimate the age-dependent force of infection. Given the fraction of susceptible, recovered, and vaccinated individuals in the zeroth age-class, we may use the reported incidence \(n_0\) in age-class \(A_0\) to estimate the force of infection \(\lambda_0\). Using (A.4), the estimated force of infection in age-class \(A_0\) may in turn be used to estimate the fraction of susceptible, recovered, and vaccinated individuals at the start of the first age-class \(A_1\). Given these fractions, we may use the reported incidence in the first age-class \(n_1\) to estimate the force of infection in the first age-class \(\lambda_1\). This recursive procedure continues until the force of infection in the last age-class has been estimated.

In principle, it is also possible to obtain explicit formulas for the forces of infection and \(S_1, I_1, R_1\), etc. For instance, \(S_1(i)\) just before vaccination at age \(i\) is related to \(S_1(0), \lambda(i)\), and \(v(j)\) \((j = 0, \ldots, i - 1)\) through

\[
S_1(i) = S_1(0)e^{-\sum_{j=0}^{i-1} \lambda(j) \prod_{j=0}^{i-1} (1 - v(j))}.
\]

These formulas, however, do not provide additional insight.

References


