A stochastic model for the spread of infectious diseases
within households with intervening preventive treatment.

being a Thesis submitted for the degree of
Doctor of Philosophy
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by
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In Chapter 1 we describe the motivation for the development of a new model for the spread of infectious diseases, we define the statistical problem and briefly review some existing models.

In Chapter 2 we develop a general stochastic model for the spread of an infectious disease in households of two when there may be intervening preventive treatment. The distributions of the underlying epidemiological time periods are left arbitrary, while effectiveness of the treatment is considered to be measured both by the resulting modification to individual susceptibility, and by the speed with which it can be administered.

Chapter 3 is concerned with possible mathematical representations of the quantities required by the general model. A medically reasonable assumption is demonstrated to produce considerable simplification.

In Chapter 4 a simple form of the general model, in which the lengths of both incubation and latent periods are assumed to be constant between individuals, is applied to a detailed set of data for whooping cough. Maximum likelihood estimates of the model's parameters are obtained, the fit of the model is examined and simple medical implications are discussed.

Chapter 5 is concerned with fitting some forms of the model, in which the lengths of the incubation and latent periods are allowed to vary, to the whooping cough data. The fits and practicability of these forms are discussed, and compared with those of Chapter 4.

In Chapter 6 we suggest further investigations for the whooping cough data, compare our new model with more established ones, and consider how the general form may be simplified in order to apply it to some other infectious diseases. Results from an existing discrete time model which incorporates treatment effects are also examined.
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1.1: MOTIVATION FOR A NEW MODEL

In his analysis of morbidity due to smallpox in 1760 (see Gani, 1978), Daniel Bernoulli was one of the first to attempt a mathematical model for the spread of disease. Many subsequent attempts to explain the dissemination of infectious agents within communities of various sizes have been made, with varying degrees of success. In this thesis a model is proposed and investigated for the spread of such an agent within households when preventive treatment may be given to some household members.

The development of the new model was motivated by a set of data collected during a major epidemic of whooping cough in 1979/80, when vaccination against whooping cough was receiving considerable medical attention. The resulting analysis by Grob et al (1981) concentrated largely on this one aspect of the data, and was mentioned in the subsequent risks and benefits debate of Miller et al (1982).

However, the data contain a wealth of detailed information about families in which one or more cases of whooping cough were recorded. Appendix A gives full particulars of the variables recorded both for the family index who was the first member of the household to show symptoms, and for the remaining susceptible household members, termed the contacts.

Amongst the variables recorded for the contacts were two concerned with the administration of a preventive treatment, in this case the antibiotic erythromycin. A binary variable recorded whether or not this had been given to each contact. For each treated contact a second variable U represented the time, in this case measured in days, from the appearance of symptoms in the index to the contact's preventive treatment. In the multiway contingency table analysis
(Grob et al., 1981), the patients treated with erythromycin and those not given any antibiotics were analysed separately, but the observed values \( \{ u_i \} \) were ignored.

Since long-term vaccination and a more recently administered treatment are both concerned with the prevention of disease, it was desirable to attempt to model both factors together. For the present data, the efficacy of vaccine was in question, whilst erythromycin is accepted as an effective drug in widespread use, a fact which we would hope to see reflected by a realistic model. However, it is envisaged that the proposed model would also be used on data sets in which the effectiveness of a newly-developed preventive drug is to be measured against the background of a proven vaccination programme.

The usefulness of a treatment may be measured in two ways. Firstly, it ought to lower the individual's susceptibility to disease, so that infectious agents find it harder to gain a foothold. Secondly, the treatment must be given "in good time", so that the individual has only a small probability of becoming infected before the preventive measure can be taken. It is this second aspect which poses an interesting statistical problem, as well as an essential medical one.

1.2: THE STATISTICAL PROBLEM

We shall be considering diseases which are infectious in the sense of being capable of transmission from an individual suffering from the disease (the infective) to one not suffering (the susceptible) when there is sufficiently close contact between the two people. Individuals who are identified as being susceptibles (a discussion of the problems of such identification is found in Bailey (1975, Ch.14)), the contacts defined in §1.1, may be given preventive treatment.
A vector of covariates may be observed for each individual, whether an infective or a susceptible. These covariates may include the age of the individual, whether or not he was vaccinated, his socio-economic status, etc. - in fact, any information which may affect his general health and probability of resisting infection.

Further data may be collected concerning the appearance of symptoms and administration of preventive treatment. Two random variables record time periods observable during the passage of infection through a household:

$U = \text{time from the symptoms appearing in the index to preventive treatment being given to the contact,}$

$|S| = \text{time from the symptoms appearing in the index to those appearing in the contact.}$

NB. The second observable random variable is defined as $|S|$, rather than $S$, for reasons which become clear in Chapter 2.

However, $U$ and $|S|$ themselves depend on other unobservable variables, the basic epidemiological time periods associated with almost all infectious diseases. It will be useful to define these briefly:

$T = \text{the resistance time, the period elapsing between the contact's first exposure to infection and his becoming infected.}$

$X = \text{the latent period, during which the disease develops purely internally, and the contact is a "latent infective". At the end of the latent period, the contact becomes "actively infective".}$

$Y = \text{the infectious period, during which the infectious organism may be discharged to other susceptibles.}$

$Z = \text{the incubation period, the time from the receipt of infection to the appearance of symptoms.}$
Since the actual moments of infection, onset and cessation of infectiousness are not generally obvious, the values of these random variables are not observable. However we should like to make inferences about them, since the effectiveness of a preventive treatment depends on both their absolute and relative values in the index and the contact.

Suppose a contact has resistance time of length t, latent period of length x and incubation period of length z, assuming that he actually catches the disease.

Then

\[ t + z = \text{time elapsed between first exposure to infection and appearance of his symptoms.} \]

If preventive treatment is to be given to the contact, it will be administered before the end of this time period i.e. before it becomes evident that he already has the disease. If it is given before or during the resistance time t then the treatment may be considered to have been given early enough, but treatment during the incubation period z may be considered to be too late, as the infection has already begun. The values of X, Y and Z for the index are also important, as we shall see in the detailed examination of Chapter 2.

In conclusion, the data from which we wish to make inference about the effects of preventive treatment consist of a realization of observable random variables U and \(|S|\). The value of \(|S|\), in turn, depends on other unobservable random variables T, X and Z, whilst a useful quantity based on U (see later Definition 2.3) also involves X and Z. Before considering the exact nature of these relations, we shall briefly survey existing models for infectious diseases, and indicate, where appropriate, how these fundamental, but largely unobservable, time periods have been represented in the
literature. In Chapter 6 we shall investigate in some detail how our model relates to some of the models discussed below, and how it may be applied to infectious diseases other than whooping cough.

1.3: MATHEMATICAL MODELS FOR INFECTIOUS DISEASES

We shall not attempt to survey here all the mathematical models which have been developed to describe the spread of infectious diseases within communities of various sizes. Bailey (1975) presents a splendid review and bibliography of this work up to about 1973. However, it is interesting briefly to consider how some of the models proposed have dealt with the underlying time periods of infection, and with preventive measures such as vaccination.

The earliest epidemic models were largely deterministic in nature, being concerned with large populations of homogeneously mixing individuals. The work of Kermack and McKendrick (1927,1932,1933,1937,1939) and the celebrated Threshold Theorem largely dominated these early efforts.

However, as epidemiological data became more extensive, sometimes dealing with much smaller communities than before, the elements of chance involved in the spread of disease necessitated the development of stochastic models. These fell broadly into two categories.

Firstly, the "continuous infection" models envisage an individual being infectious from the instant he receives infection until he dies, recovers or is isolated (collectively referred to as "removal"). If such removal occurs as a Poisson process then we have effectively assumed a zero latent period and an exponentially distributed infectious period. Bailey (1950,1953a) obtains detailed large-scale results both for this general case and the simpler one involving no removal (i.e. an infinite infectious period), whilst parameter estimation
is considered by Ohlsen (1964), Morgan (1965), and Bailey and Thomas (1971). Hammond and Tyrrell (1971) use an alternative form of the general model, where the average duration of the infectious period is constant, in their empirical fits of common-cold epidemics on Tristan da Cunha.

The second class of models, the "chain binomial" models, assumes that the latent and incubation periods may be regarded as approximately constant, and the period of infectiousness is comparatively short (typically regarded as being reduced to an instant). Thus, new cases occur in a series of generations. Two different views of chain binomial theory were developed virtually simultaneously by Greenwood (1931) and by Reed and Frost (see Abbey, 1952). The models have been developed and extended by Greenwood (1949) and Bailey (1953b, 1956a), and have been applied reasonably successfully to household data on measles and the common cold (Lidwell and Sommerville (1951), Heasman and Reid (1961), Bailey (1975, Chapter 14)), and to the transmission of streptococci in families (Poku, 1979). Sugiyama (1961) extends the theory to allow for infection between, as well as within, households and applies his results to data on Asian influenza epidemics, whilst Gani (1969) and Gani and Jerwood (1971) demonstrate how Markov chain methods may be useful in the study of chain binomial models.

More recently, attempts have been made to unify the types of models discussed above in more generalized formulations. Becker (1980) proposes a general epidemic chain model which includes the stochastic version of the Kermack-McKendrick model as a special case and the Reed-Frost chain binomial model as a limiting case. He also proposes (Becker, 1981a) a general chain binomial model which contains the Greenwood and Reed-Frost models as particular cases. These approaches, together with a third (Becker, 1981b), concerned with the overall infective potential of individuals within households, are all applied
to the common cold data originally collected by Brimblecombe et al (1958) which were presented in a highly lumped form by Heasman and Reid (1961). Schenzle (1982) examines the diverse nature of some of the conclusions reached, and remarks that epidemic chain theory could yield a more satisfactory interpretation of the data if the complete information from the original survey were available.

Other models have been proposed which make different assumptions about the underlying time periods. Modified chain binomial models involving normally-distributed latent periods, and extended constant length infectious periods have been fitted to data on measles and infectious hepatitis (see Bailey 1956b,1956c and Bailey and Alff-Steinberger, 1970).

Anderson and Watson (1980) consider a general epidemic where the latent and infectious periods are each regarded as being composed of a number of independent stages, the lengths of which are exponentially distributed (the standard continuous infection model may be shown to be a special case). Thus the latent and infectious periods are independently gamma distributed. This model, and one similar proposed by Gough (1977) and based on interremoval times from households of two, may be regarded as stochastic variations on the deterministic model proposed by Bailey (1964) for small epidemics in large populations.

Attempts have also been made to model the effects of vaccination from various viewpoints. Large-scale population studies have included the design of immunization programs in order to minimize costs as discussed by Becker (1972), and the effects of a partial measles vaccination program studied by Griffiths (1973b). Optimal control theory methods are increasingly being emphasized (see, for example, Dayananda and Hogarth (1977,1978), Lefèvre (1981)), although these results appear to be mainly of theoretical interest rather than of great practical value.
The effects of vaccination or immunization at a more individual level have hitherto received rather less attention. Gart (1968) extends the simple deterministic epidemic model to the situation where the initial population of susceptibles may be divided into two groups having very different infection rates, and these groups might be chosen to correspond to the vaccinated and unvaccinated members of the community. In a later paper (Gart, 1972) he examines maximum likelihood techniques applied to Reed-Frost chain binomial models when the population may be divided into \( k \) kinds of susceptibles; thus again we may consider treated and untreated subgroups within the data set.

In their work on Markov chain methods applied to chain binomial models, Gani (1969) and Gani and Jerwood (1971) consider how the effects of inoculation on an epidemic may be represented. They obtain some theoretical numerical results for the Greenwood model: for a more detailed account, together with some reservations and comments, the reader is referred to §6.4. Elveback et al (1976) also consider modifications to individual susceptibility in response to vaccination in their highly structured simulation model for immunization studies.

However, all these approaches have been directed towards the effects of some type of treatment on the susceptibility of the individual. This is, of course, perfectly adequate when considering the effects of previous vaccinations, but no references have been found which consider the time element, seen to be so important when intervening preventive treatment may be administered.

An approach by Lagakos (1976), which was developed primarily for clinical trials and other investigations of survival times, deals with a situation very similar to our problem. He proposes a stochastic model which utilises a time-dependent auxiliary event (such as our preventive treatment) in the evaluation of survival time, and which
incorporates also censored observations and covariates. Higgins (1981) discusses a similar type of model where the underlying survival distributions follow Weibull forms. The approach taken to the effects of preventive treatment on resistance times in later chapters resembles these models.

Thus the model proposed in its most general form in the next chapter appears to be the first specifically designed to accommodate all the relevant factors of disease control simultaneously. During the development and application of the model in later chapters we have attempted to bear in mind some comments made by Becker (1979a): that new models should not be too restrictive in the assumptions made about the underlying time periods, that modelling attempts can only be taken seriously by epidemiologists if it is demonstrated that the epidemic models adequately describe the spread of disease, and that interest in epidemic models should be directed increasingly towards data-orientated mathematics in order to strive for more direct and immediate effects on the real problems of disease control.
2.1: PRELIMINARIES

2.1.1. The course of infection in families of two

The framework proposed is intended to model the course of infection in families with two initial susceptibles. One susceptible catches the disease and shows symptoms, becoming the family index referred to in §1.1. The other susceptible then becomes the contact, who may or may not be given preventive treatment after the appearance of the index' symptoms, and who may or may not subsequently show symptoms himself.

We shall assume that only one susceptible brings infection into the family, and refer to this as the primary; the second susceptible, who may or may not become infected by the primary, we shall call the secondary. It is usually apparent that the index is the primary family source of infection, but we will not necessarily assume that the primary and secondary are correctly identified (see §2.1.3). Correct identification is, of course, inevitable when the contact remains uninfected.

When applying the model to data, we shall be assuming that the secondary has been infected by the primary rather than from an external source of infection. This assumption has been made in previous models for household infection, and is recognised as occasionally being an unsatisfactory premise. Models have been developed to allow for community-acquired infection alongside household secondary infection (see, for example, Sugiyama (1961) and Longini and Koopman (1982)). In §2.4 we shall investigate our stochastic model when we assume that both infections are primary cases infected outside the household. Unfortunately it will be seen that such a situation can yield no
information about the aspects of preventive treatment in which we are interested, and it appears that the most satisfactory method of dealing with this problem may be to examine the data with this in mind before beginning any analysis.

**Assumption 2.1:**

The secondary, if infected, has been infected by adequate contact with the primary.

Assumption 2.1 is obviously more realistic for some infectious diseases than for others. For example, Christie (1980) remarks that the risk of catching whooping cough from someone in the same house is seven times higher than from someone living next door, whereas Longini and Koopman (1982) conclude that influenza seems to spread more easily in the community than within the household.

We define the following random variables that arise during the cycle of infection:

\[ T_1, T_2 \] : resistance times for primary and secondary respectively.

\[ X_1, X_2 \] : lengths of latent periods for primary and secondary respectively.

\[ Y_1, Y_2 \] : lengths of infectious periods for primary and secondary respectively.

\[ Z_1, Z_2 \] : lengths of incubation periods for primary and secondary respectively.

We denote the values of these variables by lower case letters.

The time origin \( t_0 \) for the measurement of observable time periods is the time of appearance of symptoms in the index.

Then the infection of a secondary by a primary may be represented diagrammatically as in Figure 2.1.
Fig 2.1: Time periods during the course of infection.
2.1.2. Relationships between the unobservable time periods.

We shall obviously have to make some assumptions about the distributions of \( T, X, Y \) and \( Z \) before the model can be put to any practical use. A discussion of possible distributions is deferred until Chapter 3, but it is useful at this point to discuss possible relationships between the random variables before proceeding with the development of the stochastic model.

Figure 2.1 shows the appearance of symptoms in both primary and secondary during their respective infectious periods, i.e. the actual values of the random variables defined in \( \S 2.1.1 \), satisfying
\[
\begin{align*}
    x_1 < z_1 < x_1 + y_1, \\
    x_2 < z_2 < x_2 + y_2.
\end{align*}
\]

Medical sources (for example Christie (1980), Krugman and Katz (1981)) infer that symptoms do most commonly occur during the infectious period of a disease. However, the proposed model is not affected by the relative values of these random variables, and we may define their distributions very generally, leaving specific relationships until the model is applied to some data.

One inequality which must always hold is
\[
t_2 \leq y_1
\] (2a)
since the secondary's resistance time cannot exceed the length of the primary's infectious period (unless he is not infected, in which case we may consider \( t_2 \) as infinite).

The relative magnitudes of \( x_1 \) and \( z_1 \) will also have a bearing on the course of infection in the secondary, and on the usefulness of preventive treatment:
Case I: $x_1 < z_1$. The primary becomes infectious before $t_0$, so the secondary is being exposed to infection before the primary's symptoms appear. Since treatment is not given until the index' symptoms appear, the length of the contact's pretreatment exposure time may be considerable. Also, if $t_2 + z_2$ is small, then the secondary may even show his symptoms before the primary: we shall return to this latter point in §2.1.3.

Case II: $x_1 \geq z_1$. The primary does not become infectious until after his symptoms have appeared. Thus the contact's treatment is likely to be administered more promptly, possibly even before he is under any infectious pressure.

So any expression obtained for the probability of infection in a secondary, whether treated or not, will be conditional on the primary's unobservable time periods $x_1, y_1$ and $z_1$.

2.1.3. The observable variable $|S|$  

The random variable $S$ is defined as  

$S = \text{the time from the primary's symptoms to the secondary's symptoms.}$

However, $S$ itself might not be observed, since substantial variation in the distribution of $Z$ may result in uncertainty about the identities of the primary and secondary cases. The index and contact can always be identified positively, but when the interval between symptoms is short, it is not always possible to be certain that the index is the true primary. The discussion of Case I in §2.1.2 and Figure 2.2 indicate how the uncertainty may occur. So the quantity observed is actually $|S|$, not $S$ itself.

Such doubts about the identity of the primary and secondary are most likely to be felt when the two sets of symptoms appear close together, in which case we may consider it more probable that we
First exposure $\rightarrow$ infected $\rightarrow$ becomes infectious $\rightarrow$ shows symptoms

**Primary**

$\leftarrow t_1 \rightarrow \leftarrow x_1 \rightarrow \leftarrow z_1 \rightarrow$

$1S_1 = S$

$\leftarrow t_2 \rightarrow \leftarrow x_2 \rightarrow$

$\leftarrow t_3 \rightarrow \leftarrow x_3 \rightarrow \leftarrow z_3 \rightarrow$

Secondary

$\rightarrow$ first exposure $\rightarrow$ infected $\rightarrow$ becomes infectious $\rightarrow$ shows symptoms

**Primary**

$\leftarrow t_1 \rightarrow \leftarrow x_1 \rightarrow \leftarrow z_1 \rightarrow$

$1S_1 = -S$

$\leftarrow t_2 \rightarrow \leftarrow x_2 \rightarrow \leftarrow z_2 \rightarrow$

Secondary

$\rightarrow$ first exposure $\rightarrow$ infected $\rightarrow$ becomes infectious $\rightarrow$ shows symptoms

---

*a. primary case becomes index case.*

*b. primary case becomes contact case.*

---

**Fig 2.2: Classifying primary and secondary cases.**
have two primary cases rather than a primary and a secondary case. Any discrepancies in the distributions of $S$ and $|S|$ are likely to be confined to values close to zero.

The distributions of $S$ and $|S|$ may be obtained from those assumed for the underlying random variables $T, X$ and $Z$. From Figure 2.2 it may be seen that

$$s = (t_2 + z_2) - (z_1 - x_1).$$

Luckily, however, it will not generally be necessary to find the form of the distribution of $S$, although in §2.4 the distribution of $T_2 + Z_2$ will be useful.

2.1.4. Individual susceptibility and preventive treatment.

Each secondary will have a "natural susceptibility" to the disease spread by his household's primary, and we define this as

$$p = P(\text{secondary is infected by the primary at some time in the future}).$$

It is improbable that all secondaries will be equally likely to contract the disease, even given identical home backgrounds; far more reasonable that factors such as age and previous vaccination, as well as household conditions, will affect an individual's resistance to disease. Thus we expect the value of $p$ to vary from one person to another.

An effective preventive treatment, if given in time, will modify this natural susceptibility to a value $q$ defined by

$$q = P(\text{secondary given preventive treatment is infected by the primary at some time in the future, after his treatment}).$$

Again, the value of $q$ will vary from one person to another, although for a given individual and an effective treatment, one would
expect to have:

\[ 0 \leq q \leq p \leq 1. \]

A treatment which gives complete protection against disease in all individuals would reduce all susceptibilities to zero, and in general a treatment's protective value may be measured by the magnitude of the effect it has in lowering the natural susceptibility \( p \).

2.1.5. Resistance time and preventive treatment.

The distribution of \( T \), or more specifically \( T_2 \), is also an important factor in determining the effectiveness of preventive treatment. Roughly speaking, if \( t_2 \) is small and \( x_1 < z_1 \) then treatment is almost useless, as we observed in §1.2. More precisely, even a treatment which is shown to be effective in considerably reducing the value of \( p \) may be quite ineffective in practice when, by the nature of the disease, it is unlikely to be given early enough. We are assuming here that preventive treatment may have some protective value for those not already infected, but has little effect on the course of an infection which has already begun.

Assumption 2.2:

Protective treatment can only have an effect on those not already infected.

Inspection of medical texts leads us to believe that Assumption 2.2 will be realistic for some infectious diseases. For example, Christie (1980) observes for measles that "antibiotics have no effect on the inflammatory changes caused by measles virus" and that in a carefully controlled study (Medical Research Council, 1953) into the effects of antibiotics on whooping cough, "even with early cases, the effect of the drugs was not dramatic".
It may be expected that distributions traditionally used to model survival times would also be useful to model $T$, if infection is viewed as "failure". In his original model, Farewell (1977) used an exponential distribution to model the time of resistance to infection, and we shall investigate this and other survival time distributions later. However we need to consider two aspects not previously taken into account:

(i) In proposing $P(T_2 \leq a \mid \text{secondary infected}) = 1 - e^{-\lambda a}$, $(a > 0, \lambda > 0)$, Farewell has implied that exposure to infection goes on forever, whereas condition (2a) requires $t_2 \leq y_1$ for an infected secondary.

If we define the event

$SI \equiv \text{secondary is eventually infected},$

then any distribution function proposed for $T$ must be conditional on $SI$ as well as on the primary's time periods $x_1$, $y_1$ and $z_1$ as discussed in §2.1.2.

For convenience, we define

$\phi = (x_1,y_1,z_1)$

and the distribution function for the resistance time $T$

$F_1(t) \equiv F_1(t \mid \phi, SI).$

Now we require

$F_1(t) = 1, \ t \geq y_1,$

and if $G(\cdot)$ is a distribution function we may satisfy this condition by defining

$F_1(t) = \begin{cases} 
0 & t < 0, \\
G(t)/G(y_1) & 0 \leq t \leq y_1, \\
1 & t > y_1.
\end{cases}$
If \( G(\cdot) \) is such that \( G(0) = 0 \), then we have

\[
F_1'(0) = 0
\]

and thus exclude the possibility of instantaneous infection i.e. there is no probability mass at \( t_2 = 0 \).

Of course, if the length of the infectious period \( y_1 \) is large, then \( G(y_1) \approx 1 \) and this extra complexity may not be worthwhile. However, the conditional form of \( F_1(\cdot) \) in terms of \( G(\cdot) \) may be a more realistic approximation for diseases with short infectious periods.

(ii) We may wish to take account of the effect that preventive treatment has on the resistance time distribution i.e. \( F_1(\cdot) \) may be modified to some d.f. \( F_T(\cdot) \) on the administration of treatment. For example, \( F_1(\cdot) \) and \( F_T(\cdot) \) may belong to the same family of distributions, the modifications being made to the parameters. Higgins (1981) considers a similar situation when he envisages an alteration in Weibull hazard function being caused by an intervening event.

We shall return to this aspect of the model in §2.2.2.

\[2.2: \text{THE CONDITIONAL DENSITY OF } T_2 + Z_2\]

In §2.1.3, we observed from Figure 2.2 that

\[
s = (t_2 + z_2) - (z_1 - x_1).
\]

Thus

\[
t_2 + z_2 = s + (z_1 - x_1)
\]

is the time from the secondary's first exposure to infection to the appearance of his symptoms, conditional on the event SI. Further, given \( \phi = (x_1, y_1, z_1) \), \( t_2 + z_2 \) is a known value with a well-defined epidemiological significance, and it will be useful to derive its density.
Assumption 2.3:

$T_2$ and $Z_2$ are independent random variables i.e., the length of the secondary's incubation period is independent of his resistance time.

Assumption 2.3 seems reasonable, as we can find no indications in medical sources that the length of an individual's incubation period is in any way affected by the time it took him to contract the disease. We shall use this assumption in the following development to derive the density of $T_2 + Z_2$ for both treated and untreated secondaries.

We shall denote the distribution function of $Z_2$ by

$$F_Z(z) = F_Z(z|\psi, \text{SI})$$

where $F_Z(z) = 0$ for $z < 0$, and we shall assume for the present that densities $f_1(\cdot)$ and $f_2(\cdot)$ exist, corresponding to distribution functions $F_1(\cdot)$ and $F_2(\cdot)$ respectively. Modifications to the model may, of course, be made when such densities do not exist, for example in the case of degeneracy of either $T_2$ or $Z_2$. We shall consider such a case in Chapter 3.

We shall now consider the density of $T_2 + Z_2$ separately for the cases of treated and untreated secondaries.

2.2.1. Density for an untreated secondary.

$T_2$ has density $f_1(\cdot)$ and $Z_2$ has density $f_2(\cdot)$ and both random variables are non-negative. Thus if we denote the density of $T_2 + Z_2$ for an untreated secondary by

$$f_3(w) = f_3(w|\psi, \text{SI})$$

then
Since \( f_1(t) = 0 \) for \( t > y_1 \), we could write this as

\[
 f_3(w) = \begin{cases} 
 m \
 \int_0^w f_1(t)f_2(w-t)dt \
 0 \
 0 \
 \end{cases} \quad w > 0, \quad \text{elsewhere,}
\]

where \( m = \min(y_1, w) \).

2.2.2. Density for a treated secondary.

We shall assume that preventive treatment administered to a secondary not already infected has two effects:

(i) The secondary's probability of becoming infected, \( p \), is modified to \( q \) (see §2.1.4).

(ii) The secondary's resistance time distribution is modified from \( F_I(t) \) to \( F_T(t) = F_I(t | \phi) \) with corresponding density \( f_T(t) \), and we require \( F_T(t) = 1 \) for \( t \geq y_1 \).

Before proceeding, we need to make two definitions:

**Definition 2.1**

\( P_{\phi}(A) \) denotes the probability of an event \( A \) given \( \phi = (x_1, y_1, z_1) \). i.e. \( P_{\phi}(A) = P(A | \phi) \).

**Definition 2.2**

The **infection curve** \( I(t) \) represents the probability that a secondary has become infected by time \( t \) after his initial exposure. i.e. \( I(t) = P_{\phi}(SI \cap \{T_2 \leq t\}) \).
Since treatment may now intervene during the secondary's resistance time, the density of $T_2$ will no longer be simply $f_1(\cdot)$, but may be derived using $I(t)$.

$I(t)$ for an untreated secondary:

Immediately, $I(t) = pF_1(t)$.

$I(t)$ for a secondary treated before exposure to infection:

$I(t) = qF_T(t)$,

as transitions $p \rightarrow q$ and $F_1(\cdot) \rightarrow F_T(\cdot)$ take place prior to exposure to infection.

Figure 2.3 illustrates how these two infection curves might appear.

$I(t)$ for a secondary treated during exposure to infection:

In order to derive an expression for $I(t)$, we need to consider both the early untreated part of the resistance time and the later treated period. $I(t)$ must be monotone increasing by definition, as the probability of infection by time $t$ cannot decrease as $t$ increases. We should also like it to be a continuous function of $t$, so that there is no concentration of probability mass at the time of treatment. Thus we envisage the treatment as being based on a transition from $pF_1(t)$ to $qF_T(t)$ which preserves continuity in $t$ at the time of treatment (see Figure 2.3b).

In order to find the time of this transition, we are interested in the length of time during which the secondary is exposed to infection before his preventive treatment. This is not generally the same as the observed value $u$, as may be seen from Figure 2.4.

Figure 2.4a shows a secondary who is treated after the primary's infectious period. His density is thus precisely the same as the untreated secondary considered in §2.2.1. Figure 2.4b shows a secondary
Fig 2.3: Infection curves
infected infectious symptoms

Primary

Secondary

Secondary treatment

a. Secondary treated after primary infectious period.

Secondary

Secondary treatment

b. Secondary treated during primary infectious period.

c. Secondary treated before primary becomes infectious

Fig 2.4: Times of preventive treatment.
who is treated during the primary's infectious period, and it may be seen that he is untreated whilst under infectious pressure for a time \( u + z_1 - x_1 \). This expression is independent of the relative lengths of the primary's latent and incubation periods i.e. it holds for \( z_1 \leq x_1 \) in addition to the illustrated \( z_1 > x_1 \).

Figure 2.4c shows a secondary who is treated before the primary's infectious period; this can only occur if \( z_1 < x_1 \) since treatment must follow the index' symptoms. Such a secondary remains treated throughout his period of exposure to infection, and has infection curve \( I(t) = qF_T(t) \) as above.

In order to derive a general expression for \( I(t) \) in the two latter cases above (the first is identical to the untreated case in §2.2.1), we define a new random variable:

**Definition 2.3**

\[ U_1 = \max(0, U + Z_1 - X_1). \]

Hence \( U_1 \) represents the time of untreated exposure to infection when the secondary is treated before the end of the primary's infectious period.

Then for a secondary who is treated before the end of the primary's infectious period, the infection curve is seen to be given by:

\[
I(t) = \begin{cases} 
    pF_1(t) & 0 < t \leq u_1, \\
    pF_1(u_1) + q(F_T(t) - F_T(u_1)) & u_1 < t \leq y_1, \\
    pF_1(u_1) + q(1 - F_T(u_1)) & t > y_1. 
\end{cases}
\]

If a treatment has been effective, then we should have

\[ pF_1(t) > pF_1(u_1) + q(F_T(t) - F_T(u_1)) \]

\[ \iff p(F_1(t) - F_1(u_1)) > q(F_T(t) - F_T(u_1)), \quad u_1 < t \leq y_1. \]
i.e. in Figure 2.3b, the solid line $I(t)$ should not exceed the dotted line $pF_1(t)$. A sufficient, but not necessary, condition for this is

$$\frac{dF_1}{dt} \geq q \frac{dF_T}{dt}, \ t > u_1.$$ 

The probability of secondary infection may now be found to be

$$P_\phi(SI) = I(\infty) = pF_1(u_1) + q(1-F_T(u_1)); \ (2.2)$$

and we may now deduce the distribution function of $T_2$ for a treated secondary, which we denote by

$$F_4(t) = F_4(t|\phi,SI),$$

and its corresponding density $f_4(\cdot)$:

$$F_4(t) = P(T_2 \leq t | \phi,SI)$$

$$= \frac{P_\phi(SI \cap T_2 \leq t)}{P_\phi(SI)} = \frac{I(t)}{P_\phi(SI)}, \ by \ Definition \ 2.2.$$ 

Hence

$$F_4(t) = \begin{cases} 
\frac{pF_1(t)}{pF_1(u_1) + q(1 - F_T(u_1))} & 0 < t \leq u_1, \\
\frac{pF_1(u_1) + q[F_T(t) - F_T(u_1)]}{pF_1(u_1) + q(1 - F_T(u_1))} & u_1 < t \leq y_1, \\
1 & t > y_1.
\end{cases}$$

and the density of $T_2$ is given by

$$f_4(t) = \begin{cases} 
\frac{pf_1(t)}{pF_1(u_1) + q(1 - F_T(u_1))} & 0 < t \leq u_1, \\
\frac{qF_T(t)}{pF_1(u_1) + q(1 - F_T(u_1))} & u_1 < t \leq y_1, \\
0 & \text{elsewhere}.
\end{cases}$$
If we denote the density of $T_2 + Z_2$ for a treated secondary by
$$f_5(w) = f_5(w|\phi,SI),$$
then we may use the density $f_2(\cdot)$ and Assumption 2.3 to obtain
$$f_5(w) = \begin{cases} 
\frac{1}{pF_1(u_1) + q(1-F_T(u_1))} \left[ p \int_0^w f_1(t)f_2(w-t)dt + q \int_w^w f_1(t)f_2(w-t)dt \right] & w > u_1, \\
0 & \text{elsewhere.}
\end{cases}$$

Expressions (2.3) and (2.4) reflect the different possible situations with secondary treatment:

(i) (2.3) applies for $T_2 + Z_2 \leq U_1$, i.e. a secondary whose symptoms appear before he is given preventive treatment. This form will therefore rarely arise in practice.

(ii) (2.4) applies for $T_2 + Z_2 > U_1$. The first integral in the expression will apply if $T_2 \leq U_1$, so that the secondary catches the disease before being given his treatment (i.e. "too late"), thus $f_4(t)$ has numerator $pf_1(t)$. The second integral applies for $T_2 > U_1$, when treatment is given "in time", and $f_4(t)$ has numerator $qf_T(t)$. Thus (2.4) allows for our uncertainty about whether treatment was really given early enough to an infected secondary.

By defining $w_u = \min(w,u_1)$, expressions (2.3) and (2.4) may be combined to produce
$$f_5(w) = \begin{cases} 
\frac{1}{pF_1(u_1) + q(1-F_T(u_1))} \left[ p \int_0^w f_1(t)f_2(w-t)dt + q \int_w^w f_1(t)f_2(w-t)dt \right] & w > 0, \\
0 & \text{elsewhere,}
\end{cases}$$
where the second integral is zero if \( w_1 = w < u_1 \).

It is interesting also to note the consequences of writing \( u_1 = 0 \) in (2.4). Then, assuming instantaneous infection is impossible so that \( F_1(0) = F_T(0) = 0 \),

\[
pF_1(u_1) + q(1-F_T(u_1)) = q,
\]

and \( f_5(w) \) becomes

\[
f_5(w) = \begin{cases} 1/q \left[ p \cdot 0 + q \int_0^w f_T(t)f_2(w-t)dt \right] - \int_0^w f_T(t)f_2(w-t)dt & w > 0, \\ 0 & \text{elsewhere}. \end{cases}
\]

This expression is of the same form as (2.1) for the untreated secondary. Replacement of \( f_1(t) \) by \( f_T(t) \) indicates that the secondary is fully treated throughout the primary's infectious period.

### 2.3: TOWARDS A LIKELIHOOD FUNCTION

Each record of the data contains information about a particular index-contact pair. Covariates relevant to susceptibility are observed for each individual, and depending on the course of infection and treatment in the contact, values for variables \(|S|\) and \( U \) may also be recorded. Table 2.1 illustrates the four possible sets of circumstances and the variables recorded.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>TREATMENT GIVEN</th>
<th>SYMPTOMS APPEAR</th>
<th>VARIABLES RECORDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NO</td>
<td>YES</td>
<td>(</td>
</tr>
<tr>
<td>II</td>
<td>YES</td>
<td>YES</td>
<td>(U,</td>
</tr>
<tr>
<td>III</td>
<td>NO</td>
<td>NO</td>
<td>None</td>
</tr>
<tr>
<td>IV</td>
<td>YES</td>
<td>NO</td>
<td>(U)</td>
</tr>
</tbody>
</table>

Table 2.1
In the following four sections we obtain mathematical expressions for the observed course of infection for each type of contact. For Types I and II these expressions are "mixed distributions", combining probabilities and densities: for Types III and IV actual probabilities can be found. Eventually, suitable parametric forms will be assumed for the distributions and susceptibilities (see Chapter 3 ff.), the expressions obtained will be combined to produce an overall likelihood for the data and we would hope to maximise this in order to obtain parameter estimates and make inferences about the quantities of interest.

The contributions to this likelihood obtained below will be conditional on the time periods \( \{x^1, y^1, z^1\} \) of the corresponding primaries, which cannot be observed. Unconditional expressions may be obtained by taking the expectation over the joint distribution of \( X_1, Y_1 \) and \( Z_1 \), denoted by the operator \( E_\phi \).

For contacts of Types III and IV, no symptoms of the disease are observed. In practice, of course, we can only monitor the progress of each contact for a finite period of time, thus we define a "follow-up" time \( V \) for each contact by

\[
V = \text{time from the symptoms appearing in the index to the end of the period recorded for the contact.}
\]

Thus for contacts of Types III and IV we have

\[
|S| > V
\]

whilst for Types I and II the inequality

\[
|S| \leq V
\]

applies.
2.3.1. Likelihood contribution for a Type I contact.

A Type I contact is an untreated contact who subsequently becomes infected and shows symptoms. Hence a value for $|S|$ is observed. However, as discussed in §2.1.3, we cannot be absolutely sure that the contact is the secondary, so we need to take into account two possible sets of circumstances.

(i) $|s| = s > 0$ i.e. the contact is the secondary. Then from Figure 2.2a,

$$|s| = s = t^2 + z^2 - (z_1 - x_i)$$

$$\Rightarrow t_2 + z_2 = z_1 - x_i + |s|$$

and the likelihood contribution (L.c.) is given by

$$p f_3(z_1 - x_i - |s|).$$

(ii) $|s| = -s > 0$ i.e. the contact is the primary. Then from Figure 2.2b,

$$-s = |s| = (z_1 - x_i) - (t_2 + z_2)$$

$$\Rightarrow t_2 + z_2 = z_1 - x_i - |s|$$

and the L.c. is

$$p f_3(z_1 - x_i - |s|).$$

Thus the combined L.c. for a Type I contact, conditional on $\phi$, is given by

$$L_{I|\phi} = p f_3(z_1 - x_i + |s|) + f_3(z_1 - x_i - |s|)$$

(2.5a)

and the unconditional likelihood contribution by

$$L_I = E_\phi[p f_3(z_1 - x_i + |s|) + f_3(z_1 - x_i - |s|)].$$

(2.5b)
One, neither or both of the arguments of \( f_3(\cdot) \) may be negative, depending on the relative magnitudes of \(|s|, x_1\) and \(z_1\), thus producing zero densities. In fact both arguments are actually equal to \(z_1 - x_1 + s\), but the value \(s\) cannot be observed.

2.3.2. Likelihood contribution for a Type II contact.

A Type II contact is a contact who is given preventive treatment but who nevertheless subsequently shows symptoms. Hence values for \(U\) and \(|S|\) are both observed. As in \(\S2.3.1\), we have two possibilities:

(i) \(|s| = s > 0\) i.e. the contact is the secondary. Thus the secondary has been given preventive treatment, and

\[ t_2 + z_2 = z_1 - x_1 + |s| . \]

So the \(\ell.c.\) is given by

\[ P(\Phi (SI)f_5(z_1-x_1+|s|)) = \{pF_1(u_1)+q(1-F_T(u_1))\}f_5(z_1-x_1+|s|) \text{ by (2.2)}. \]

Practical Note: Since treatment will only be given before the contact's symptoms appear, \(f_5(\cdot)\) will be of form (2.4), so the factor \(\{pF_1(u_1)+q(1-F_T(u_1))\}\) cancels and the \(\ell.c.\) is

\[ \frac{u_1}{0} f_1(t)f_2(z_1-x_1+|s|)-t)dt + q\int_{u_1} f_T(t)f_2(z_1-x_1+|s|-t)dt . \]

(ii) \(|s| = -s > 0\) i.e. the contact is the primary. Thus treatment given to the contact has in fact been given to the primary, leaving the true secondary untreated. (Incidentally, the treatment cannot have affected the primary, since he must have already been a latent infective at the time of his treatment). So we have the same situation as \(\S2.3.1\) and \(\ell.c.\) given by

\[ pf_3(z_1-x_1-|s|) . \]
Thus the combined \(\ell.c.\) for a Type II contact is given by

\[
L_{II\phi} = (pF_1(u_1) + q(1-F_T(u_1)))f_3(z_1-x_1 + |s|) + pf_3(z_1-x_1 - |s|) \]

(2.6a)

and the unconditional likelihood contribution by

\[
L_{II} = \mathbb{E}_\phi[(pF_1(u_1) + q(1-F_T(u_1)))f_3(z_1-x_1 + |s|) + pf_3(z_1-x_1 - |s|)]. \]

(2.6b)

2.3.3. Likelihood contribution for a Type III contact.

A Type III contact is an untreated contact whose symptoms have not appeared up to an observed follow-up time \(v\). His circumstances are therefore similar to those of a Type I contact, but now \(|S| > v\).

Thus the \(\ell.c.\) for a Type III contact is given by

\[
L_{III\phi} = 1 - \int_0^v L_{I\phi}d|s|
\]

\[
= 1 - \int_0^v p[f_3(z_1-x_1 + |s|) + f_3(z_1-x_1 - |s|)]d|s|
\]

\[
= 1 - \int_{z_1-x_1-v}^{z_1-x_1+v} f_3(w)dw
\]

(2.7a)

and the unconditional likelihood contribution by

\[
L_{III} = 1 - \mathbb{E}_\phi[p\int_{z_1-x_1-v}^{z_1-x_1+v} f_3(w)dw].
\]

(2.7b)

2.3.4. Likelihood contribution for a Type IV contact.

A Type IV contact is a treated contact whose symptoms have not appeared up to an observed follow-up time \(v\). The reasoning of §2.3.2 may be followed using the observed value of \(U\), but now with \(|S| > v\).
The $L_{IV}$ for a Type IV contact is given by

$$L_{IV} = 1 - \int_{0}^{v} L_{II} d|s|$$

$$= 1 - \int_{0}^{v} \left( \{pF_1(u_1) + q(1-F_T(u_1))\} f_5(z_1-x_1 + |s|) + p f_3(z_1-x_1 - |s|) \right) d|s|$$

$$= 1 - \{pF_1(u_1) + q(1-F_T(u_1))\} \int_{0}^{v} f_5(z_1-x_1 + |s|) d|s| - p \int_{0}^{v} f_3(z_1-x_1 - |s|) d|s|$$

$$= 1 - \{pF_1(u_1) + q(1-F_T(u_1))\} \int_{z_1-x_1}^{z_1-x_1+v} f_5(w) dw - p \int_{z_1-x_1}^{z_1-x_1-v} f_3(w) dw$$

(2.8a)

and the unconditional likelihood contribution by

$$L_{IV} = 1 - E \left[ \{pF_1(u_1) + q(1-F_T(u_1))\} \int_{z_1-x_1}^{z_1-x_1+v} f_5(w) dw \right] - E \left[ p \int_{z_1-x_1}^{z_1-x_1-v} f_3(w) dw \right].$$

(2.8b)

2.4 : FAMILIES WITH TWO PRIMARY CASES

The probabilities obtained in §2.3.1 and §2.3.2 reflect the assumption that when two sets of symptoms appear in a family we have a primary and a secondary i.e. that only one individual was infected by a source outside the household. However, it is possible that both infections stem from an external infectious source or sources, so that we have two primaries. In this section we investigate the contribution to the likelihood in such circumstances.

2.4.1. Notation and assumptions.

Since we do not wish to imply any ordering of the two primaries we shall use subscripts $A$ and $B$ to distinguish between them.
We define:

\[ P_A, P_B \] : the susceptibilities of primaries A and B respectively.

\[ T_A, T_B \] : resistance times for primaries A and B respectively.

\[ X_A, X_B \] : lengths of latent periods for primaries A and B respectively.

\[ Z_A, Z_B \] : lengths of incubation periods for primaries A and B respectively.

\[ Y_0 \] : the length of that part of the infectious period of the external source of infection during which A and B are in contact with him.

Thus the time periods defined above are not generally observable.

We define the observable time period by the random variable

\[ R = \text{time from the appearance of the first set of symptoms to the appearance of the second set of symptoms}. \]

Thus observed values of \( R \) are always positive, and we do not specify which of primaries A and B is the first to show symptoms (see Figure 2.5).

We define the event

\[ BI = \text{both primaries are eventually infected}. \]

**Assumption 2.4:**

\( T_A \) and \( T_B \) are i.i.d. with distribution function

\[ F_{1p}(t) \equiv F_{1p}(t | Y_0, BI) \]

and corresponding density \( f_{1p}(\cdot) \).

The conditional form of \( F_{1p}(\cdot) \) arises since inequalities

\[ \begin{align*}
    t_A &\leq y_0 \\
    t_B &\leq y_0
\end{align*} \]

(2b)
A
infected

\[ t_A \rightarrow z_A \]

first exposure
to external source of infection.

B
infected

\[ t_B \rightarrow z_B \]

\[ r \]

\[ r = (t_B + z_B) - (t_A + z_A) \]

A is the index:

b. B is the index:

\[ r = (t_A + z_A) - (t_B + z_B) \]

Fig 2.5: Two primary cases.
must always hold for the same reasons as condition (2a) of §2.1.2
in the primary and secondary framework. Thus \( F_{ip}(t) = 1 \) for \( t > y_0 \).

So the distribution of the exposure time \( Y_0 \) is of interest.

In order to make the model both realistic and mathematically tractable
we shall make one more assumption about the manner in which \( A \) and
\( B \) are exposed to the external infectious source:

Assumption 2.5:

Both family primaries are exposed to infection from the same
instant in time, and are always exposed at the same times.

Assumption 2.5 may, for instance, be a reflection of the rarity
of the disease in the community, so that two members of a family
are only likely to come into contact with a single infectious source
during an outbreak. In his investigations into the distributions
of incubation periods of infectious diseases, Sartwell (1950,1966)
discusses the effect that assumptions similar to 2.5 may have when
modelling such distributions. The assumption implies that \( Y_0 \) will
have the same value for both family susceptibles, but will have a
distribution over households.

The distribution of \( Y_0 \) over households is unlikely to be
the same as that for \( Y_1 \) when the primary and secondary framework
was considered, since \( A \) and \( B \) will rarely be in contact with
the external source throughout his infectious period. It is more
probable that values of \( Y_0 \) will be fairly small, thus there will
be a high probability that \( T_A \) and \( T_B \) are restricted to small
values, by condition (2b).

Figure 2.5 shows the course of disease when a household has
two primary cases. From Figure 2.5a, when \( A \) is the index, the
observable time between symptoms $r$ is given in terms of unobservable time periods by

$$r = (t_B + z_B) - (t_A + z_A).$$

Similarly from Figure 2.5b, with $B$ as the index we have

$$r = (t_A + z_A) - (t_B + z_B).$$

The symmetry of these two situations is clear, and in general we may write

$$r = |(t_A + z_A) - (t_B + z_B)|.$$

We have observed above that values $t_A$ and $t_B$ are likely to be small when the period of exposure to external infection is short, in which case $r$ reflects largely the variation in length of the two incubation periods,

i.e. $r = |z_A - z_B|.$

Thus for diseases whose incubation periods typically display little variability (see the comments on virus diseases in §6.3), the possibility of two primary cases is probably only worth consideration when the time between the appearance of symptoms in the two cases is short.

2.4.2. Likelihood contribution without preventive treatment.

We now investigate the contribution made to the overall likelihood for the data when no preventive treatment is given to either primary, and the inter-symptoms interval is of length $r$.

Definition 2.4

$P_0(C)$ denotes the probability of an event $C$, given $y_0$.

i.e., $P_0(C) = P(C|y_0)$. 
Then, assuming independence of the two primaries,

\[ P_0(BI) = P_A P_B. \]

**Assumption 2.6:**

\( Z_A \) and \( Z_B \) are i.i.d. with distribution function

\[ F_{2p}(z) \equiv F_{2p}(z|y_0, BI), \] where \( F_{2p}(z) = 0 \) for \( z < 0, \)

and corresponding density \( f_{2p}(\cdot). \)

Then using Assumptions 2.3 (§2.2) and 2.6, \( T_A + Z_A \) and \( T_B + Z_B \) will be i.i.d. with density

\[ f_{3p}(w) = f_{3p}(w|y_0, BI) \]

given by

\[
  f_{3p}(w) = \begin{cases} 
    \int_0^w f_{1p}(t)f_{2p}(w-t)dt & \text{for } w > 0, \\
    0 & \text{otherwise,} 
  \end{cases}
\]

and we require the densities of \( (T_A + Z_A) - (T_B + Z_B) \) and \( (T_B + Z_B) - (T_A + Z_A) \) at the observed value \( r. \)

Writing \( M = T_A + Z_A \) and \( N = T_B + Z_B, \) \( M \) and \( N \) are i.i.d. random variables with density \( f_{3p}(\cdot). \) Thus the density of \( M-N \) (or equivalently \( N-M \)) is given by

\[
  f_{M-N}(r|y_0, BI) \equiv f_{M-N}(r) = \begin{cases} 
    \int_0^\infty f_{3p}(t+r)f_{3p}(r)dt & \text{for } r > 0, \\
    0 & \text{otherwise,} 
  \end{cases}
\]

and the likelihood contribution for the double primary situation with no preventive treatment is
\[ L_{pY_0} = 2p_A p_B \int_0^\infty f_{3p}(t+r)f_{3p}(t)dt. \]

The corresponding unconditional likelihood contribution is obtained by taking the expectation over the distribution of \( Y_0 \), giving

\[ L_p = 2E_{Y_0} \left[ p_A p_B \int_0^\infty f_{3p}(t+r)f_{3p}(t)dt \right]. \]

2.4.3. The effect of treatment and some comments.

The contact will sometimes be given preventive treatment during the inter-symptoms period (i.e. before his own symptoms appear, but after those appearing in the index). The likelihood contribution, although complicated, may be determined in such circumstances. However, it is unlikely to be of much practical use owing to the restrictions placed on the distribution of random variable \( Y_0 \).

Since \( Y_0 \) is likely to be restricted to small values, condition (2b) implies that \( T_A \) and \( T_B \) will be similarly restricted. Therefore preventive treatment will rarely, if ever, be given in time under the assumptions we have made for households which contain two primaries. We shall thus not consider the form of the likelihood contribution for the treated double primary situation.

Indeed, if we recall the quantities of interest in the model, it is unlikely that even inclusion of the untreated contribution \( L_p \) will be worthwhile. We are especially concerned with the form of the distribution of resistance time \( T \) since this has implications for future administration of preventive treatment. Since the distribution of \( Y_0 \) (and thus also of \( T_A, T_B \)) is considerably restricted, little information may be gained about the distribution of \( T \) for a continuous extended period of exposure to infection. Hence the inclusion of households with two primaries is probably not worth the extra complications involved.
The mathematical model developed above has deliberately used only general assumptions which are hopefully applicable to a wide range of diseases. It is interesting to consider briefly how it could be adapted to incorporate more specific requirements.

We have assumed above that preventive treatment modifies an individual's susceptibility $p$ to $q$ as soon as it is administered. We may also consider this sudden drop in susceptibility to occur a time $\delta$ after administration, or envisage a gradual decline from $p$ to $q$ over a specified interval of time.

During the course of an epidemic, recognised infectives are sometimes isolated, usually after their symptoms have appeared. Therefore we may consider how isolation of the family index would affect our model. If the index is the primary, then isolation will reduce the secondary's exposure time from the original value $y_1$. Two cases require consideration:

(i) $z_1 \leq x_1$: effective isolation of the index on appearance of his symptoms will completely remove the household source of infection.

(ii) $x_1 < z_1$: isolation will effectively shorten the index' infectious period from $y_1$ to $z_1 - x_1$. This reduction will obviously affect the secondary's resistance time distribution.

If we are interested in the ratio of between-household to within-household infections, we may use the primary-secondary and double primary expressions for those households with two cases of disease. The two expressions may be combined with a mixing proportion in the overall likelihood for the data, and estimation of this proportion may then provide clues to the main mode of dissemination of the disease.
The general model is developed only for families with two susceptibles. Extensions to larger numbers of susceptibles are possible, but will soon become complicated, as the sources of infection for successive cases may become increasingly difficult to trace.

The model in its most general form is obviously not immediately applicable to any particular set of data. In the next chapter we show how a few additional simple but realistic assumptions will allow easy application for data analysis.
3.1: PRELIMINARIES

Bailey (1975, Chapter 3) observes that a sophisticated mathematical model for the spread of disease should use the joint probability distribution for the various epidemiological time periods, but that such a degree of generality may cause considerable analytical difficulties. We shall therefore first consider the form of our stochastic model when few simplifying assumptions are made. This is intended solely as an indication of the magnitude of any such problems, and as we shall discuss later some of these initial assumptions are rather unrealistic.

Since the exponential distribution (NED) is among the simplest of the traditional survival time distributions, let us assume that all the time periods are distributed exponentially and independently. Writing the exponential distribution with mean $\frac{1}{\mu}$ as NED($\mu$), let us assume

$$X_1 \sim \text{NED}(\lambda)$$
$$Y_1 \sim \text{NED}(\gamma)$$
$$Z_1, Z_2 \sim \text{NED}(\alpha)$$

where $\lambda > 0$, $\gamma > 0$, $\alpha > 0$ take different values.

Further, suppose that d.f. $G(t)$ (see §2.1.5) is given by

$$G(t) = 1 - e^{-\alpha t}, \ t > 0$$

for some $\beta > 0$, $(\beta \neq \lambda, \beta \neq \gamma, \beta \neq \alpha)$, so that the distribution function of $T_2$ is given by

$$F_1(t) = \begin{cases} 
\frac{1-e^{-\alpha t}}{1-e^{-\alpha y_1}}, & 0 < t < y_1, \\
1, & t \geq y_1, \\
0, & \text{elsewhere}.
\end{cases}$$
Then from (2.1a), the density of $T_2 + Z_2$ for an untreated secondary is given by

$$f_3(w) = \int_0^{m\beta e^{-\beta t} - \alpha(w-t)dt} e^{-\beta y} \; dt \quad w > 0,$$

where $m = \min(w, y)$, which becomes

$$f_3(w) = \begin{cases} 
\frac{\alpha \beta (e^{-aw} - e^{-\beta y})}{(1-e^{-\beta y})(\beta - \alpha)} & 0 < w < y, \\
\frac{\alpha \beta (1-e^{-(\beta - \alpha) y}) e^{-aw}}{(1-e^{-\beta y})(\beta - \alpha)} & w > y, \\
0 & \text{elsewhere}.
\end{cases}$$

Expressions for $f_3(w)$ may of course also be found when the exponential parameters do not all take different values.

From (2.5b) the likelihood contribution for a Type I contact involves a term $E[f_3(z_1 - x_1 + |s|)]$. Using the form of $f_3(\cdot)$ above and dropping subscripts we find

$$E[f_3(z_1 - x_1 + |s|)] = \frac{2 \alpha \beta \gamma}{(\beta - \alpha)} \left[ e^{-\alpha |s|} \int_{R_1} e^{2az - (\lambda - \alpha) x - \gamma y} dx dy dz \right]$$

$$- e^{-\beta |s|} \int_{R_1} e^{-(\lambda - \beta) x - \gamma y e^{-(\alpha + \beta) z}} dx dy dz$$

$$+ e^{-\alpha |s|} \int_{R_2} (1-e^{-(\beta - \alpha) y}) e^{-(\lambda - \alpha) x - \gamma y e^{-2az}} dx dy dz$$

where $R_1 = \{(x, y, z) : 0 < z-x+|s| < y\}$

$R_2 = \{(x, y, z) : z-x+|s| < y\}$.

Likelihood contribution $L_{\lambda}$ involves a similar second term; thus we begin to realise the relative mathematical intractability of the model in this general form, even using the computationally convenient NED.
On reflection, the assumption of independence of $X_1$ and $Z_1$ seems intuitively unreasonable. The latent and incubation periods begin simultaneously on the receipt of infection, and are both concerned with the internal biological development of infection in the individual. Hence it seems more reasonable that their lengths should somehow be related. The precise nature of this relation will depend on the characteristics of the particular disease studied. In the next section we propose a realistic method of linking the two periods and investigate the resulting mathematical simplification.

3.2: A RELATIONSHIP BETWEEN THE LATENT AND INCUBATION PERIODS

When describing the clinical manifestations of infectious diseases, most medical texts cite a "usual range" for the length of the incubation period and state that infectiousness begins somewhat earlier than the end of this period. Christie (1980) observes, for example, that for measles "parents may date their child's infection from the day of the rash in the infecting case instead of two or three days earlier in the incubation period".

Therefore it seems not unreasonable that we should propose a relationship between $X$ and $Z$ of the form

$$Z = X + \mu$$

for some constant $\mu$. In practice, $\mu$ may be regarded either as a known constant, or as a parameter to be estimated. We shall restrict attention to

$$\mu \geq 0$$

since this appears medically to be the most common occurrence. The special case $\mu = 0$ may indicate a disease which is only spread via its symptoms.
Inspection of the expressions obtained for the secondaries in Chapter 2, in particular the mode of their dependence on the primarys' time periods, \( \phi = (x_1, y_1, z_1) \), indicates that the proposed relationship may also be mathematically useful. The conditional \( \ell.c.'s \) depend on the distributions of \( X_1 \) and \( Z_1 \) solely through the actual value \( z_1 - x_1 \), now equal to \( \mu \).

Thus we have

\[
S = T_2 + Z_2 - \mu, \quad U_1 = U + \mu,
\]

and the unconditional \( \ell.c.'s \) may now be obtained by taking the expectations over the distribution of \( Y_1 \) only.

The assumption \( \mu \geq 0 \) also allows us positively to identify the contact as the secondary, for it is clear from inspection of Figure 2.2 that case (b) cannot arise if \( z_1 - x_1 = z_2 - x_2 = \mu \).

3.2.1. Likelihood contributions for the contacts.

We shall now investigate the forms of the \( \ell.c.'s \) for each of the four types of contacts assuming the relationship \( Z = X + \mu \), \( \mu \geq 0 \). Therefore we impose the conditions

\[
z_1 - x_1 = \mu \geq 0
\]

\[
s = |s|
\]
on the expressions obtained in §2.3.

For a Type I contact, expression (2.5b) becomes

\[
L_I = E_{Y_1} [p_f(s + \mu)] \tag{3.1}
\]

where the expectation is taken only over the distribution of \( Y_1 \), and the second term of (2.5b) disappears altogether since, as discussed above, the contact must be the secondary.
For a Type II contact, expression (2.6b) becomes

\[ L_{II} = E_{Y_1} [(pF_1(u+\mu)+q(1-F_T(u+\mu))]f_2(s+\mu) \]

\[ = E_{Y_1} \left[ \int_0^{u+\mu} f_1(t)f_2(s+\mu-t)dt + q \int_{u+\mu}^{s+\mu} f_T(t)f_2(s+\mu-t)dt \right] \]

\[ = E_{Y_1} \left[ \int_{u}^{s} f_1(t\mu)f_2(s-t)dt + q \int_{u}^{s} f_T(t\mu)f_2(s-t)dt \right], \quad (3.2) \]

where we have assumed form (2.4) for \( f_5(\cdot) \) and cancelled the factors \( \{pF_1(u+\mu)+q(1-F_T(u+\mu))\} \). Again, the expectation is taken only over the distribution of \( Y_1 \) and the second term of (2.6b) disappears.

For a Type III contact, using the notation for conditional l.c.'s followed in §2.3, we have

\[ L_{III} = 1 - \int_0^{v} L_{TY_1}ds \]

\[ = 1 - \int_0^{v} pf_3(s+\mu)ds \]

thus

\[ L_{III} = 1 - E_{Y_1} [p\int_{\mu}^{v+\mu} f_3(w)dw]. \quad (3.3a) \]

If we assume that distribution function \( F_3(\omega) \equiv F_3(\omega|\phi,S) \) is given by

\[ F_3(t) = \int_0^{t} f_3(w)dw, \quad t > 0 \]

then \( L_{III} \) may be written

\[ L_{III} = 1 - E_{Y_1} [p(F_3(v+\mu)-F_3(\mu))]. \quad (3.3b) \]

If the follow-up time may be regarded as virtually infinite, then we have \( v = \infty \), and

\[ L_{III} = 1 - E_{Y_1} [p(1-F_3(\mu))]. \]
Lastly, for a Type IV contact, we have

\[ L_{IVY_1} = 1 - \{pF_1(u+\mu)+q(1-F_T(u+\mu))\} \int_0^v f_5(s+\mu)ds \]  \hspace{1cm} (3.4a)

\[ = 1 - \int_0^v \left( p \int_0^u f_1(t+\mu)f_2(s-t)dt + q \int_0^s f_T(t+\mu)f_2(s-t)dt \right) ds. \]

Hence

\[ L_{IV} = 1 - E_Y \left[ p \int_0^v f_1(t+\mu)f_2(s-t)dt + q \int_0^v f_T(t+\mu)f_2(s-t)dt \right] \] \hspace{1cm} (3.4b)

3.2.2. The special case \( \mu = 0 \).

When symptoms and infectiousness begin together, we have the special case \( \mu = 0 \). Since this particular eventuality will be investigated further in later chapters, we reproduce here the expressions obtained above for \( \mu = 0 \):

\[ L_I = E_Y [pf_3(s)] \] \hspace{1cm} (3.5)

\[ L_{II} = E_Y \left[ p \int_0^u f_1(t)f_2(s-t)dt + q \int_0^s f_T(t)f_2(s-t)dt \right] \] \hspace{1cm} (3.6)

\[ L_{III} = 1 - E_Y \left[ p\{F_3(v)-F_3(0)\} \right] \]

\[ = 1 - E_Y [p] \text{ when } v = \infty, \text{ assuming } F_3(0) \equiv 0. \] \hspace{1cm} (3.7)

\[ L_{IV} = 1 - E_Y \left[ p \int_0^v f_1(t)f_2(s-t)dt + q \int_0^v f_T(t)f_2(s-t)dt \right] \] \hspace{1cm} (3.8)
3.3: THE DISTRIBUTIONS OF THE UNDERLYING TIME PERIODS

The unobservable time periods of the model fall neatly into two groups: the latent and incubation periods (random variables \( X \) and \( Z \) respectively), and the resistance time and infectious period (\( T \) and \( Y \) respectively). We shall consider briefly some distributions which may be used to model these periods.

3.3.1. The latent and incubation periods.

There is already a good deal of information available on incubation and latent periods, both from medical sources and existing mathematical models. For instance, the continuous infection type model discussed in §1.3 assumes

\[ X = 0 \]

whereas chain-binomial models assume

\[ Z = c \]

for some \( c > 0 \).

A modification of the strict chain-binomial model by Bailey and Alff-Steinberger (1970) assumes that \( X \) is normally distributed, thus allowing the unrealistic possibility \( X < 0 \).

In a more practical approach, Sartwell (1950, 1966) found that lognormal distributions adequately describe the variation in incubation periods for many common diseases. By considering the proposed birth-and-death process of an underlying virus or bacterium, and viewing \( Z \) as the time of first passage to a high population level, Williams (1965) supports Sartwell's observations of positively skew incubation period distributions.

An approach by Bailey (1964) for small epidemics in large populations, discussed by Morgan (1964), proposes a latent period which is proportional
to $X^2$ variates. He envisages a number of hypothetical independent stages during the latent period, the length of each stage being exponentially distributed. Gough (1977) develops this approach with some generalizations in order to estimate the latent period of measles, whilst Anderson and Watson (1980) investigate the progress of an epidemic when the latent period is assumed to have a gamma distribution.

Many of the models discussed above are concerned with epidemics in large populations where infectives are removed from circulation when their symptoms appear. Thus the infectious period is foreshortened by isolation, and we have effectively

$$Z = X + Y.$$

However, our model is concerned with the spread of infection in small family groups where infectives cannot be isolated effectively, and we assume a relation between $X$ and $Z$ of the form

$$Z = X + \mu$$

as proposed in §3.2.

Therefore we require a distribution for $Z$ which should ideally be both realistic and mathematically convenient. In later chapters we investigate some possibilities:

(i) Constant incubation period ($Z$ is degenerate).

(ii) Uniform distribution.

(iii) "Trapezium" distribution (See Chapter 4).

(iv) NED.

(v) Weibull distribution.

### 3.3.2. The resistance time and infectious period.

Existing models have tended to regard the end of the infectious period as the removal from circulation of an infective on appearance of his symptoms. They do not, therefore, envisage a natural decline
in infectivity, and as observed in §3.3.1 effectively assume
\[ Y = Z - X. \]

Chain-binomial models assume a very short infectious period which may be regarded as a single point. The modified model by Bailey and Alff-Steinberger (1970) extends the infectious period to a constant length, during which time infection is taken to be a Poisson process: this latter aspect may be viewed as equivalent to assuming a NED for resistance time T. Exponentially distributed resistance times are also considered by Farewell (1977).

The general continuous-infection model assumes that the infectious period up to removal is approximately exponential in distribution whereas Bailey's model (1964) for large populations allows for multi-stage removals so that the infectious period has a \( \chi^2 \) distribution. Gough (1977) uses this same type of approach but also considers the case of non-uniform infectiousness. Anderson and Watson (1980) similarly propose a gamma-distributed infectious period composed of the sum of a number of i.i.d. NED infectious "stages".

For our model, the form of the distribution of T is likely to be of more importance than that assumed for Y. As stated in §1.1, the shape of \( F_i(t) \) has implications for treatment effectiveness. Furthermore, the shape may accommodate variation in the infectiousness of the index over time, hence if the distribution tails off rapidly, then the value \( y_1 \) may be relatively unimportant. Medical texts (for example, Christie (1980)) infer that this rapid decline in infectiousness is a feature of many common infectious diseases (see the remarks on virus infections in §6.3). In later chapters we shall investigate the family of generalized gamma distributions as possible approximations to the unknown true distribution of T. This family has been used extensively in the modelling of failure times, and incorporates the
Weibull, gamma and exponential distributions as special cases, and the lognormal as a limiting case.

The model assumes that a transition from $F_1(\cdot)$ to $F_T(\cdot)$ occurs when preventive treatment is administered. Since the data analysed in later chapters contain few treated cases who subsequently became infected, there is little basis for investigating a different form for $F_T(\cdot)$. More generally, one might allow the parameters of $F_1(\cdot)$ to vary between defined subgroups in the data.

The simplest assumption we may make about the length of the infectious period is that the value $y_1$ is constant for all individuals. We may impose a reasonable fixed value for $y_1$ for any particular disease based on medical information, or may attempt to estimate the degenerate random variable $Y_1$. As we shall see in later chapters, this latter course may present problems related to the asymptotic properties of the resulting maximum likelihood estimate.

3.4: REPRESENTATION OF INDIVIDUAL SUSCEPTIBILITY

The concept of an individual's susceptibility to infection has been well established since the development of the first mathematical models for the spread of disease. Indeed Frost (1976), in a lecture delivered at Harvard University in 1928, observed that "...if it were possible to measure the susceptibility of all individuals and classify them accordingly, they would fall ... into many classes according to their different degrees and kinds of susceptibility".

We consider below how susceptibility may be represented within the framework of our model. One feature which is common to all the approaches suggested is that the contact's susceptibility is assumed to remain constant throughout his period of exposure to infection. If this is felt to be unreasonable, variation in the susceptibility may be accommodated in the shape of the distribution of resistance time $T$. 
3.4.1. Constant susceptibility.

We may assume that for all individuals,

\[ p = p_0 \]

for \( 0 \leq p_0 \leq 1 \).

The suggestion that all contacts should be equally susceptible to disease is quite obviously not realistic. However, this type of assumption was used in the first chain-binomial models (see Bailey (1975), Chapter 14). For a more detailed discussion of the similarities and dissimilarities between our model and existing models for infectious diseases, the reader is referred to Chapter 6.

3.4.2. The beta distribution.

We may assume that \( p \) varies between contacts according to the beta distribution with density

\[ f(p) = \frac{1}{\beta(\mu, \nu)} p^{\mu-1} (1-p)^{\nu-1} \quad 0 \leq p \leq 1, \]

where \( \beta(\mu, \nu) \) is the beta function given by

\[ \frac{\Gamma(\mu) \Gamma(\nu)}{\Gamma(\mu+\nu)}, \]

\( \mu > 0, \ \nu > 0. \)

This distribution for \( p \) was investigated for chain-binomial models by Bailey (1953b), where it was used to allow variation in susceptibility between households: this is clearly equivalent to allowing variation between individuals when attention is restricted to single-contact households.

The use of the beta distribution is also discussed by Griffiths (1973a) in models for the incidence in households of both infectious and noninfectious diseases.
3.4.3. The logistic form.

The logistic model (Cox (1970), Chapter 2) is frequently used in studies in which a dichotomous outcome variable (e.g. presence or absence of disease) is related to a number of independent variables. Therefore if we have relevant covariates recorded for the contacts in our data, we clearly should use this information in such a model to estimate their susceptibility.

So we may assume that for the contact in household \( i \) we have a susceptibility which may be expressed in the form

\[
p_i = \frac{\exp(\sum_{j=1}^{n} X_{ij} \beta_j)}{1 + \exp(\sum_{j=1}^{n} X_{ij} \beta_j)} = \frac{\exp(\sum_{j=1}^{n} X_{ij} \beta_j)}{1 + \exp(\sum_{j=1}^{n} X_{ij} \beta_j)}^{-1}
\]

where \( X_i = (X_{i1}, X_{i2}, \ldots, X_{in}) \) is a vector of covariates recorded for the contact, and \( \beta^t = (\beta_1, \beta_2, \ldots, \beta_n) \) is a vector of coefficients.

We may include in \( X_i \) such factors as the contact's age and sex, his previous vaccinations, the standard of his living conditions, the severity of disease in the household index, etc. Since \( \beta_1, \ldots, \beta_n \) will be parameters of our overall model we would wish to restrict their number relative to the sample size. Therefore when we use this logistic form for susceptibility in later chapters we shall use scores for some of the covariates rather than binary variables reflecting all categories. This means that we shall be looking for a linear effect, at most, of these covariates, and any further variation will be attributed to "error" (see §4.4.2).
3.5 : THE EFFECT OF TREATMENT ON SUSCEPTIBILITY.

During the development of the general model (see §2.1.4) we assumed that when preventive treatment is given to an individual his susceptibility is modified from $p$ to $q$. If such a treatment is effective in preventing infection, one would expect

$$0 \leq q < p \leq 1$$

for all contacts. We now consider some ways of relating $p$ and $q$ mathematically.

3.5.1. Constant difference between $p$ and $q$.

We may assume a relationship of the form

$$q = p - c$$

for constant $c$ ($c > 0$ if the treatment is effective).

This approach has one obvious drawback: if a contact has very low initial susceptibility, so that $p < c$, then $q \notin [0,1]$. Thus in order to use this approach, we require $p \geq c$.

3.5.2. $p$ and $q$ in constant ratio

A more useful relationship may be

$$q = \alpha p$$

for some $0 < \alpha < 1/p$.

Then generally we would hope to obtain estimates of $\alpha$ in the range $0 \leq \alpha \leq 1$, and would expect $\alpha \ll 1$ for a recognised effective treatment. The case $\alpha = 0$ indicates a treatment which achieves complete immunity for all individuals.
3.5.3. Treatment as a time-dependent covariate.

If we already have covariates recorded for the contacts, then it may be convenient to include the preventive treatment as a binary time-dependent covariate in the logistic form for $p_i$ proposed in §3.4.3. This is similar to the time-dependent event considered by Lagakos (1976).

Assuming that we already have $n$ covariates recorded for each contact, we propose a further binary variable $X_{n+1}(t)$ defined by

$$X_{n+1}(t) = \begin{cases} 0 & \text{if contact still untreated at time } t, \\ 1 & \text{if contact treated by time } t, \end{cases}$$

where the time origin is $t_0$ as defined in §2.1.1. Hence for a contact in household $i$ with preventive treatment recorded at time $u_i$ we have

$$X_{i,n+1}(t) = \begin{cases} 0 & t < u_i, \\ 1 & t \geq u_i. \end{cases}$$

So the susceptibility is expressed generally as

$$\sum_{i=1}^{n} \left[ 1 + \exp \left( - \sum_{j=1}^{n} \beta_{ij} X_{i,j,n+1}(t) \right) \right]^{-1}$$

and we have

$$p_i = \left[ 1 + \exp \left( - \sum_{j=1}^{n} \beta_{ij} \right) \right]^{-1}$$

$$q_i = \left[ 1 + \exp \left( - \sum_{j=1}^{n} \beta_{ij} \right) \right]^{-1}.$$

Now if the treatment is effective, we expect to have

$$\frac{q_i}{p_i} < 1 \quad \forall i.$$
\[
1 < \exp(- \sum_{j=1}^{n} X_{ij} \beta_j) \quad \text{implies} \quad 1 < e^{-\beta_{n+1}} \quad \text{implies} \quad \beta_{n+1} < 0.
\]

i.e. when the parameters of the model are estimated, an effective treatment should be indicated by a negative estimate of \( \beta_{n+1} \). (Note that this result also implies that \( p_i \) and \( q_i \) are both increasing functions of \( \beta_j \) (1\( \leq j \leq n+1 \)) when the covariates are all non-negative).

It should be noted that this approach is not equivalent to that considered in §3.5.2 since the value of ratio \( q_i/p_i \) depends on the value of \( p_i \), and is thus not constant over all contacts.

To illustrate, suppose \( \beta_{n+1} = -2 \), then

\[
p_i = 0.5 \Rightarrow \exp(- \sum_{j=1}^{n} X_{ij} \beta_j) = 1
\]

\[
\Rightarrow q_i = (1+1\exp^{-2})^{-1} = 0.119 \quad \text{and} \quad q_i/p_i = 0.238.
\]

The ratio \( q_i/p_i \) may be calculated for a range of values of \( p_i \): values of the ratio are given in Table 3.1 for \( \beta_{n+1} = -1 \) and \( \beta_{n+1} = -2 \).

<table>
<thead>
<tr>
<th>( p_i )</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
<th>0.7</th>
<th>0.8</th>
<th>0.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>( q_i/p_i; \beta_{n+1} = -1 )</td>
<td>0.393</td>
<td>0.421</td>
<td>0.454</td>
<td>0.492</td>
<td>0.538</td>
<td>0.593</td>
<td>0.660</td>
<td>0.744</td>
<td>0.853</td>
</tr>
<tr>
<td>( q_i/p_i; \beta_{n+1} = -2 )</td>
<td>0.148</td>
<td>0.164</td>
<td>0.183</td>
<td>0.207</td>
<td>0.238</td>
<td>0.281</td>
<td>0.343</td>
<td>0.439</td>
<td>0.610</td>
</tr>
</tbody>
</table>

**TABLE 3.1:** Ratio \( q_i/p_i \) for \( p_i = 0.1 \) (0.1)0.9.
From the table we can see that for both values of \( \beta_{n+1} \), 
\( q_i^*/p_i \) increases as \( p_i \) increases; hence large susceptibilities
are reduced by treatment proportionally less than smaller ones. Also,
as expected, a larger value of \( \beta_{n+1} \) in the negative sense indicates
a more effective treatment.

It is unclear which of the two approaches gives the more realistic
representation of the true effects of preventive treatment, since
no references to research in this area have been found. It is possibly
easier to interpret results from the constant ratio method, since
an estimate of \( \alpha \) together with its standard error have more immediate
meaning than those for \( \beta_{n+1} \). In the next chapter we shall compare
results using both relations for an extremely simple form of the
general model applied to whooping cough data.

3.6 : CONCLUDING REMARKS.

In this chapter we have suggested various ways in which susceptibility,
effect of preventive treatment and distributions of time periods
may be represented in our model. In the following chapters we shall
investigate some combinations of these possible representations when
applied to the whooping cough data described fully in Appendix A.

Although we have been concerned only with the effect of a single
preventive treatment during §3.5, the model may easily be extended
to investigate several such treatments simultaneously. For example,
the constant ratio approach may be modified to allow

\[
q_i = \alpha_j p_i
\]

for treatment \( j \) administered to contact \( i \), and several binary
covariates may be added to the logistic form of \( p_i \) in the approach
of §3.5.3.
4.1: DEFINITION OF THE SIMPLE MODEL

We shall now propose a very simple form of the general model which may be realistic for whooping cough. This form will be applied to the whooping cough data later in the chapter together with suitable distributions for $T$ and expressions for $q_i$ to produce parameter estimates and, hopefully, meaningful medical implications.

4.1.1. A set of assumptions.

The following assumptions are made throughout this chapter:

Assumptions 4

(i) Relation (3a) holds with $\mu = 0$.

(ii) $F_2(z) = \begin{cases} 0 & 0 < z < \ell, \\ 1 & z \geq \ell. \end{cases}$

(iii) $v = \infty$ for all secondaries.

(iv) $y_1 = \infty$ for all primaries.

(v) $F_1(t) = F_T(t)$ $\forall t$.

(vi) $p_i = \left[1 + \exp\left(-\sum_{j=1}^{n} \frac{X_{ij} \beta_j}{\ell}\right)\right]^{-1}.$

Conditions (i) and (ii) imply that infectiousness and symptoms begin simultaneously, and that for all cases of disease we have

$$X = Z = \ell,$$

and hence

$$S = T_2 + \ell.$$

So $X$ and $Z$ are degenerate random variables, and suitable values for $\ell$ will be discussed in §4.2.3. In support of these assumptions we quote Christie (1980) who states that the length of
the incubation period of whooping cough is fairly constant between cases when observation is accurate, and that a child is unlikely to be infectious before his symptoms have developed but becomes highly infectious once the illness is recognizable.

In support of (iii) we may quote Grob et al. (1981) who state that, for our particular data, "medical surveillance was maintained until there was no further evidence of clinical respiratory disease in the family". In a similar type of model, Farewell (1977) examines theoretically the effect of having \( \nu_1 < \infty \) rather than complete follow-up, or of wrongly assuming \( \nu_1 = \infty \), on the asymptotic distribution of the maximum likelihood estimates of coefficients \( \{\beta_1\} \) in the logistic form of the susceptibility proposed in §3.4.3 and assumption 4(vi). By the nature of the data, we have assumed that these effects may be ignored in the present case.

In (iv), we are in effect assuming that the shapes of the tails of \( F_1(t) \) and \( F_T(t) \) will accommodate the decline in infectiousness of the primary adequately. In §4.3.3 we shall consider briefly the case

\[ y_1 < \infty \]

where \( y_1 \), assumed constant for all primaries, requires estimation.

We assume in (v) that the resistance time distribution is not affected by an intervening preventive treatment, in this case the antibiotic erythromycin. This condition is largely imposed by the nature of the data, since we have few treated contacts for whom infection is subsequently recorded, thus little information on which to propose a different form for \( F_T(\cdot) \). Incidentally, this same aspect of the data may also imply that the treatment has been effective. This seems likely, as erythromycin is recognised as an effective preventive measure for whooping cough. Christie (1980), for example, recommends
its use to control household spread of disease, especially in the presence of very young children.

4.1.2. The form of the likelihood contributions.

The l.c.'s obtained for special case $\mu = 0$ in §3.2.2 may be simplified further by Assumptions 4. Dependence on the distribution of $Y_1$ is removed by assumption 4(iv) and we may simplify the expressions further by considering the form of $f_3(\cdot)$ under 4(ii).

From (2.1), we have

$$f_3(w) = \begin{cases} \int_0^w f_1(t)f_2(w-t)dt, & w > 0, \\ 0 & \text{elsewhere}, \end{cases}$$

but since $f_2(\cdot)$ is not defined we consider an alternative form

$$f_3(w) = \begin{cases} \int_0^w f_1(w-t)dF_2(t), & w > 0, \\ 0 & \text{elsewhere}, \end{cases}$$

whence

$$f_3(w) = f_1(w-\ell), \quad \forall w. \tag{4.1}$$

So we have $f_3(w) = 0, \ w < \ell,$

or $f_3(w) = 0, \ w \leq \ell$ if instantaneous infection is excluded.

The problem of instantaneous infection recurs in §4.2.3; for the moment, we shall assume that such infection is impossible.

We now consider the l.c.'s for the four different types of contacts in turn.

For Type I, from (3.5) and (4.1) we have

$$L_1 = p_1 f_1(s-\ell). \tag{4.2}$$
Thus households for which we have recorded

\[ s \leq \ell \]

are effectively excluded from the data which may be analysed, since by our assumptions the contact must have caught the disease from an external source (the double primary case considered in §2.4).

For Type II, from (3.6) we have

\[ L_{II} = p_{i} \int_{0}^{u} f_{1}(t)dF_{2}(s-t) + q_{i} \int_{u+}^{s} f_{1}(t)dF_{2}(s-t) \].

Thus \( s \in (\ell, \ell+u] \Rightarrow t \in (0,u] \) and \( L_{II} = p_{i} f_{1}(s-\ell) \) (4.3a)

whereas \( s > \ell+u \Rightarrow L_{II} = q_{i} f_{1}(s-\ell) \) (4.3b).

The form (4.3a) is appropriate for a secondary who caught the disease before being treated, whilst (4.3b) applies for post-treatment infection. It should be noted that the assumption of a constant incubation period makes it clear which expression is appropriate for each treated contact, removing the ambiguity "built in" to the expression for \( f_{5}(\cdot) \) obtained in §2.2.2.

For Type III, clearly from (3.7) we have

\[ L_{III} = 1 - p_{i} \].

(4.4)

For Type IV, from (3.4a) we have

\[ L_{IV} = 1 - \left( p_{i} F_{1}(u) + q_{i} (1-F_{1}(u)) \right) \int_{0}^{\infty} f_{5}(s)ds \]

\[ = 1 - p_{i} F_{1}(u) - q_{i} (1-F_{1}(u)) \) (4.5)

which may be interpreted intuitively as

\[ 1 - P(\text{pre-treatment infection}) - P(\text{post-treatment infection}). \]
4.1.3. The overall likelihood and parameter estimation.

The $\ell$ for the $i$th contact recorded in the data takes one of the four forms obtained in §4.1.2. Various parametric forms may be assumed for $p^i$, $q^i$ and $F^i(*)$ and the overall log-likelihood for the data is then

$$\ell = \Sigma \ln L_i$$

summed over all contacts. Maximisation of $\ell$ with respect to the parameter vector was achieved for our applications using a computer program based on the DFP algorithm (Fletcher and Powell, 1963), and the asymptotic covariance matrix of the maximum likelihood estimates (m.l.e.'s) was estimated by the inverse of the sample information matrix. More details of the computational aspects may be found in Appendix B.

In order to compare some of the fitted models using likelihood ratio tests, we shall assume asymptotic normality of the m.l.e.'s. An attempt to check a set of conditions for asymptotic normality for our independent, but not identically distributed, observations is made in Appendix D.

4.2 : THE WHOOPING COUGH DATA AND SOME PRELIMINARY INVESTIGATIONS

4.2.1. The data set.

The initial sample contained information on 343 index cases and their siblings. (Details of the variables recorded for each index-contact pair may be found in Appendix A). However some reduction was required before analysis:

(a) Only single-contact households were to be included.

(b) Records for contacts who were already immune following previous whooping cough attacks were excluded: Krugman and Katz (K&K, 1981)
report that such attacks confer protection against subsequent illness.

(c) A few adult contacts were recorded; since these were presumably included only on account of their subsequent infection they may have introduced bias into the results and hence were excluded.

NOTE: Condition (a) was relaxed a little for some of the preliminary work described in §4.2.2 and §4.2.3. In §4.6 we discuss whether such an extension of the data subset may be warranted or desirable more generally.

The final sample comprised 277 single-contact households. In 67 households the contact was given the antibiotic erythromycin as a preventive measure, and the treatment times \( \{u_i\} \) varied from 2 days to 76 days, although most of the values were less than 26 days. The highest concentrations of values were between 4 and 7 days and between 12 and 17 days.

In 99 households, the contact eventually became infected. The inter-symptoms times \( \{s_i\} \) are illustrated in Figure 4.1, although for convenience three outlying times (42, 47 and 58 days) are omitted from the graph. It is interesting to note the excess of observations for 7 days and, to a lesser extent, for 28 days, possibly owing to an unconscious bias towards "one week" or "one month" during the data collection. This situation is not uncommon, and may also be observed both in Hope Simpson's data on measles in households of two (see Bailey (1975), p.274), and in measles data collected by Chapin (1925) and used by Gough (1977). We may also suspect a compensating dearth of values for 6 days, and this irregularity will be seen to present problems for model fitting in this and later chapters.

Only 2 of the 67 treated contacts subsequently caught whooping cough, thus justifying assumption 4(v) in §4.1.1.
Fig 4.1: The inter-symptoms times \( \{ s_i \} \)

Fig 4.2: Distribution of index illness lengths.
4.2.2. Choice of covariates for logistic form of susceptibility.

In the data set we have five variables recorded for each household which we may wish to consider as covariates in the susceptibility of contact \( i \) (proposed in §3.4.3 and assumption 4(vi)). For the \( i \)th household they are

\[ p_i = [1+\exp(-\sum_{j=1}^{n} X_{ij} \beta_j)]^{-1} \]

of contact \( i \) (proposed in §3.4.3 and assumption 4(vi)). For the

\( X_{i1} \): the social status of the family, scored 1 to 7 on the usual socio-economic scale,

\( X_{i2} \): length of illness (in days) of the family index,

\( X_{i3} \): maximum daily number of coughing spasms of the family index,

\( X_{i4} \): age (in years) of the contact,

\( X_{i5} \): vaccination status of the contact; scored as 0 if unvaccinated,

\( 1 \) if partially vaccinated, 2 if fully vaccinated, 3 if fully vaccinated with a booster.

It is hoped that \( X_{i1} \) may indicate nutritional and general standards in the home. \( X_{i2} \) and \( X_{i3} \) are intended to reflect the severity of disease in the index, and were used as indicators in Grob et al (1981). The distribution of \{\( X_{i2} \)\} for the 277 index cases is illustrated in Figure 4.2. \( X_{i4} \) may be important in determining resistance to infection: K & K (1981) state that whooping cough has a predilection for infants and young children and that little or no immunity is transferred from the mother to the newborn infant. Clearly, we would hope that the contact's vaccination status, \( X_{i5} \), would also affect his resistance.

Medical texts (e.g. K & K (1981)) also report an interesting distribution of whooping cough according to sex. In contrast to other common infectious diseases of childhood, morbidity and mortality
are higher for females than for males. Unfortunately, information on the sex of contacts was not available.

However, the proposed covariates may not be independent, making the estimates of the coefficients \( \beta_j \) difficult to interpret. It is not unreasonable that some relation may link \( X_{i4} \) and \( X_{i5} \) (although the nature of the relation is unclear), or that \( X_{i2} \) and \( X_{i3} \) may be related.

Some of the covariates proposed above may well have little effect on contact susceptibility. Since we wish to restrict the number of parameters of the model, some preliminary investigations were performed to find a "best" subset. These investigations involved fitting to the whooping cough data the model with a Weibull resistance time distribution, constant ratio form for \( q_i \) and the \( 2^5 \) different combinations of covariates in \( p_i \). (More details of such fitting are found in later sections).

The "full" fit includes all five covariates, thus six coefficients \( \beta_0, \beta_1, \ldots, \beta_5 \) require estimation (\( \beta_0 \) being the constant term). In this fit, the estimates \( \hat{\beta}_1, \hat{\beta}_3 \) and \( \hat{\beta}_4 \) were not large relative to their standard errors (although their signs were intuitively reasonable, \( p_i \) being an increasing function of each \( \beta_j \)), but the estimated asymptotic covariance matrix showed considerable correlation between some parameter estimates. Fitting the model with the different combinations of covariates produced a fit, including only \( X_{i2} \) and \( X_{i5} \), which was almost as good as the full model; the difference in maximised log-likelihoods was only 1.74, producing a \( \chi^2 \) value of 3.48 in the likelihood ratio test. Also, the parameter estimates in this reduced model were very close to the corresponding values in the full model, and were virtually uncorrelated. Thus in fitting models to the whooping cough data in later work we include only contact
vaccination status and index illness length as covariates in the susceptibility.

The above results would appear to be corroborated by Grob et al (1981) who found that social class, contact age and the frequency of coughing spasms had little effect on the severity and dissemination of whooping cough.

4.2.3. The length of the incubation period.

By assumptions 4(i) and 4(ii) we have

\[ X = Z = \lambda \]

and the density of \( T_2 + Z_2 \) for an untreated contact is given by (4.1)

\[ f_3(w) = f_1(w-\lambda), \quad \forall w. \]

Thus to produce the distribution of \( T_2 + Z_2 \) from that of \( T_2 \) for an untreated contact, we effectively introduce a threshold parameter \( \lambda > 0 \), the length of the incubation period \( Z_2 \), into the resistance time distribution \( F_1(\cdot) \).

Attempts to estimate \( \lambda \) as a parameter of the model were abortive. Firstly, since \( \lambda \) is a threshold parameter, the likelihood function may not generally possess the required regularity to permit the use of standard asymptotic likelihood results for the estimation of \( \lambda \).

(The maximum product of spacings (MPS) estimation procedure proposed by Cheng and Amin (1983) may prove useful if \( \lambda \) is to be estimated). Secondly, applying the model for several values of \( \lambda \) and maximising the log likelihood in each case yields little information, since households having \( s_i \leq \lambda \) must be excluded from the sample. Hence the maximised log likelihoods are based on different numbers of observations and are difficult to compare.
The problem of threshold parameters is common in failure time modelling. However, as Kalbfleisch and Prentice (1980) observe, it is rare that such a parameter would be known to exist without its value being known.

In fact medical texts (e.g. Christie (1980), K & K (1981), Top and Wehrle (1976)) tend to agree that the incubation period for whooping cough is about 7 days, and rarely longer than 10 days. Thus we may propose a value for $\lambda$ in the interval $[6,7]$.

However, whilst the resistance time distribution itself is continuous, we have only discrete observations (in days) of the inter-symptoms intervals $\{s_i\}$. The assumptions $\lambda = 6$ or $\lambda = 7$ present problems of whether or not to include observations for which $s_i = \lambda$ i.e. whether or not to allow instantaneous infection. So an intermediate value appears more attractive, but the discrete nature of the data still presents problems for parameter estimation and these problems are to some extent escalated by the large number of observed values $s_i = 7$. For instance, the assumption $\lambda = 6.2$ would imply that we have 9 observed resistance times $t_2 = 0.8$, whereas if $\lambda = 6.8$ these same observations have values $t_2 = 0.2$. Estimates of some parameters of the assumed resistance time distribution may be affected considerably by different values of $\lambda$: in particular, the estimate of the shape parameter of the Weibull distribution is sensitive to the number of small values observed.

Finally, it was decided to use the interval mid-point

$$\lambda = 6.5$$

to represent the incubation period during investigation of the simple model. This may not be the optimal solution to the problem in any sense, but it represents a realistic compromise.
A better strategy may be to fit the model using a discretised form of the chosen resistance time distribution: careful grouping could be used to smooth out any irregularities in the observations.

4.3: FITTING THE SIMPLE MODEL

In addition to assumptions 4, we impose the condition

\[ \lambda = 6.5 \]

for the models fitted in this section. Also, following the investigations of §4.2.2, we have covariates in the logistic form of the susceptibility:

- \( x_{10}^* \equiv 1 \) (constant term),
- \( x_{11}^* \) : length of illness (in days) of the family index,
- \( x_{12}^* \) : vaccination status of the contact, scored 0 to 3 as defined in §4.2.2.

One of the purposes of the model-fitting is to explore possible distributions for \( T \); in particular we shall seek a parsimonious model within the family of generalised gamma distributions.

We say that a random variable has a generalised gamma distribution with parameters \((\lambda, c, k)\), hereafter abbreviated to \( \text{GG}(\lambda, c, k) \), if it has probability density function

\[
f(t) = \begin{cases} \frac{c}{\Gamma(k)} \frac{t^{c-1} e^{-\lambda t/(\lambda c)}}{\lambda c} & \text{if } t > 0, \\ 0 & \text{if } t \leq 0, \end{cases}
\]

for \( \lambda, c, k > 0 \).

This three-parameter model was introduced by Stacy (1962) and parameter estimation for the distribution is discussed in Johnson and Kotz (1970, Chapter 17). Special cases of the generalised gamma distribution include the gamma distribution \((c = 1)\); the Weibull...
distribution \((k = 1)\); and the NED\((c=k=1)\). The log-normal is also a limiting special case as \(k \to \infty\).

Model fitting with the generalised gamma and two-parameter gamma distributions is described in §4.3.2. We consider first the computationally more convenient Weibull and NED resistance time distributions, and compare also the constant ratio and time-dependent covariate approaches to treatment.

4.3.1. The Weibull and NED resistance time distributions.

Both models fitted below assume that \(T_2\) has a Weibull distribution

\[ i.e. \ T_2 \sim G(\lambda, c, 1). \]

Model A also assumes

\[ q_{Ai} = \alpha p_i \quad \text{for} \quad 0 \leq \alpha \leq 1 \]

for all contacts \(i\), whereas Model B proposes

\[ q_{Bi} = \left[1 + \exp(-\sum_{j=0}^{2} X_{ij}^* \beta_{j} - \beta_3)\right]^{-1} \]

\[ i.e. \ \text{Model A assumes the constant ratio approach to treatment whilst Model B introduces a binary variable } X_3(t) \text{ to represent treatment in the logistic form for } p_i. \]

So from §4.1.2 the likelihood contributions for Model A are given by

\[ L_1 = \left[1 + \exp(-\sum_{j=0}^{2} X_{ij}^* \beta_{j})\right]^{-1} \frac{ct^{c-1}e^{-(t/\lambda)^c}}{\lambda^c} \]

\[ L_{II} = \begin{cases} L_1 & \text{if } 0 < t \leq u \\ \alpha \left[1 + \exp(-\sum_{j=0}^{2} X_{ij}^* \beta_{j})\right]^{-1} \frac{ct^{c-1}e^{-(t/\lambda)^c}}{\lambda^c} & \text{if } t > u \end{cases} \]
\[ L_{III} = 1 - \left[ 1 + \exp \left( - \sum_{j=0}^{2} X_{ij} \beta_j \right) \right]^{-1} \]

\[ L_{IV} = 1 - \left[ 1 + \exp \left( - \sum_{j=0}^{2} X_{ij} \beta_j \right) \right]^{-1} \left[ 1 - e^{-u/\lambda} \right] - \alpha \left[ 1 + \exp \left( - \sum_{j=0}^{2} X_{ij} \beta_j \right) \right]^{-1} e^{-u/\lambda} \]

where \( t = s - \xi \) in \( L_I \) and \( L_{II} \).

For Model B we have \( L_I, L_{III} \) as above and

\[
L_{II} = \begin{cases} 
L_{I} & \text{if } 0 < t \leq u \\
\left[ 1 + \exp \left( - \sum_{j=0}^{2} X_{ij} \beta_j \right) \right]^{-1} \frac{c \lambda^{c-1} e^{-(t/\lambda)^c}}{\lambda^c} & \text{if } t > u 
\end{cases}
\]

\[ L_{IV} = 1 - \left[ 1 + \exp \left( - \sum_{j=0}^{2} X_{ij} \beta_j \right) \right]^{-1} \left[ 1 - e^{-u/\lambda} \right] - \left[ 1 + \exp \left( - \sum_{j=0}^{2} X_{ij} \beta_j \right) \right]^{-1} e^{-u/\lambda} . \]

First and second derivatives of these likelihood contributions are given in Appendix C.

So both models have six parameters. For Model A we have parameter vector

\[ \theta_A = (\beta_0, \beta_1, \beta_2, \alpha, \lambda, c) \]

and for Model B

\[ \theta_B = (\beta_0, \beta_1, \beta_2, \beta_3, \lambda, c) \].

Initial parameter estimates were required for the iterative computer program. Starting values for the Weibull shape and scale parameters \((c \text{ and } \lambda \text{ respectively})\) were found by regarding the observed resistance times \( \{ t_i \} = \{ s_i - \xi \} \) as a sample from a \( \text{GG}(\lambda, c, 1) \) distribution and finding the m.l.e.'s of the parameters based on this sample (see Johnson and Kotz, 1970, p.255). Also, since erythromycin is a recognised effective treatment, we would guess that \( \alpha \ll 1 \).

However, although reasonable signs for most of the \( \{ \beta_j \} \) were clear
\((\beta_1 > 0, \beta_2 < 0, \beta_3 < 0)\), their magnitude was difficult to predict.

Therefore several initial trial parameter vectors were adopted for both models. The iterative process proved to be happily free of snags in all cases, and for each model the same solution was reached, irrespective of the starting point. The reader is referred to Appendix B for more details of the convergence criteria and the number of iterative steps required throughout the model-fitting. In Table 4.1 we show the m.l.e.'s and their standard errors for Model A, and in Table 4.2 corresponding information for Model B. The correlations between the estimates \(\{\hat{\beta}_j\}\) and \(\hat{\alpha}\) were very small for both models: as expected, \(\text{corr}(\hat{\lambda}, \hat{c})\) was much larger, at 0.21.

From the two tables, the similarity between the estimates of the common parameters is clear.

The maximised log-likelihood for Model A was

\[ \ell_A = -355.46 \]

and for Model B

\[ \ell_B = -355.16. \]

Loosely speaking, vaccination of contacts would appear to be an important factor in lowering susceptibility, since \(\hat{\beta}_2\) is fairly large compared to its standard error. Although increasing index illness length would seem to raise contact susceptibility, the effect of this covariate is probably not as large. However the absolute values of \(\hat{\beta}_1\) and \(\hat{\beta}_2\) are clearly not directly comparable since the ranges of values of the corresponding covariates are markedly different. This aspect will be investigated more thoroughly in the medical implications of §4.5.

The fitted treatment parameters \(\hat{\alpha}\) and \(\hat{\beta}_3\) are compared in some detail in §4.4.4.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$ (constant term)</td>
<td>-0.433</td>
<td>0.326</td>
</tr>
<tr>
<td>$\beta_1$ (index illness length)</td>
<td>0.0088</td>
<td>0.0047</td>
</tr>
<tr>
<td>$\beta_2$ (contact vaccination)</td>
<td>-0.884</td>
<td>0.161</td>
</tr>
<tr>
<td>$\alpha$ (treatment)</td>
<td>0.113</td>
<td>0.113</td>
</tr>
<tr>
<td>$\lambda$ (Weibull scale)</td>
<td>11.135</td>
<td>1.365</td>
</tr>
<tr>
<td>$c$ (Weibull shape)</td>
<td>1.067</td>
<td>0.100</td>
</tr>
</tbody>
</table>

**Table 4.1. Parameter estimates for Model A.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$ (constant term)</td>
<td>-0.447</td>
<td>0.322</td>
</tr>
<tr>
<td>$\beta_1$ (index illness length)</td>
<td>0.0092</td>
<td>0.0046</td>
</tr>
<tr>
<td>$\beta_2$ (contact vaccination)</td>
<td>-0.887</td>
<td>0.161</td>
</tr>
<tr>
<td>$\beta_3$ (treatment)</td>
<td>-2.779</td>
<td>1.071</td>
</tr>
<tr>
<td>$\lambda$ (Weibull scale)</td>
<td>11.145</td>
<td>1.366</td>
</tr>
<tr>
<td>$c$ (Weibull shape)</td>
<td>1.067</td>
<td>0.100</td>
</tr>
</tbody>
</table>

**Table 4.2. Parameter estimates for Model B.**

Unfortunately $\hat{\alpha}$ is within one standard error of its zero lower limit. We know however, that for our data set the true value of $\alpha$ cannot be zero, since we have treated contacts who subsequently became infected. Since $\beta_3 \in (-\infty, \infty)$, Model B's approach to treatment would appear to be more convenient, and the time-dependent covariate form $q_{Bi}$ will be used in fitting most of the models hereafter.

The estimates of Weibull shape parameter $c$ are not markedly different from 1, indicating that the one-parameter NED may be as satisfactory for $T_2$ as the two-parameter Weibull distribution.
Both models were fitted with the constraint $c = 1$ since the NED is equivalent to $GG(\lambda, 1, 1)$. The maximised log-likelihoods were $-355.78$ for Model A and $-355.40$ for Model B, producing $\chi^2$ values of 0.64 and 0.48 respectively in the likelihood ratio tests. The fit is therefore not significantly worse.

Since the relatively large numbers of observed values $t_2 = 0.5$ may have had considerable influence on this result, the models were also fitted with the assumptions

$$\lambda = 4.5$$

and

$$\lambda = 5.5.$$

These assumptions are by no means unreasonable, since McInnes (1975) reports incubation periods occasionally as short as 5 days. The resulting estimates of $c$ were 1.22 and 1.24 respectively and in both cases the Weibull fit was significantly better than the corresponding NED fit ($\chi^2_1 = 4.58$ and 5.04 respectively). Thus it is probably generally worth retaining the Weibull distribution for $T_2$; it would be interesting also to compare the fit and estimates for a discretised Weibull distribution, as proposed in §4.2.3.

4.3.2. The Gamma and $GG(\lambda, c, k)$ resistance time distributions.

The model was fitted assuming $q_i = \alpha p_i$ and

$$T_2 \sim GG(\lambda, 1, k)$$

i.e. a two parameter gamma distribution for resistance time $T_2$. The estimates $\{\hat{\beta}_j\}$ and $\hat{\alpha}$ were practically identical to those for Model A, the shape of the resulting gamma distribution was also very much the same as the Weibull distribution previously obtained, and the maximised likelihood values differed only by 0.12. However, maximisation with the gamma distribution proved to be a much lengthier process than the previous fits, the required $\ell.c.'s$ and their derivatives...
requiring the calculation of gamma and incomplete gamma functions and their derivatives. The gamma function was calculated using an approximation (Abramowitz and Stegun (1972), 6.1.36) which has maximum absolute error $3 \times 10^{-7}$. The recursive algorithm of Lau (1980) was used to calculate the incomplete gamma function, with a user-specified accuracy of $10^{-12}$. The digamma and trigamma algorithms (Bernardo (1976), Schneider (1978)) were both based on relations found in Abramowitz and Stegun (1972, pp.258-260), the relative errors due to series truncation being less than $10^{-10}$ and $10^{-8}$ respectively. Therefore we may conclude that the Weibull distribution, being computationally more convenient, is the better choice of two-parameter resistance time distribution. It may also be regarded as being more flexible, as both positive and negative skew distributions can be produced by varying the shape parameter. As an extreme value distribution (see Galambos, 1978), we may regard it as the distribution of the time to "failure" of the weakest link in the body's defences.

An attempt was also made to fit the model assuming $q_i = \alpha p_i$ and

$$T_2 \sim GG(\lambda, c, k)$$

i.e. a three-parameter generalised gamma resistance time distribution.

Starting values for $(\lambda, c, k)$ were found in two ways:

(i) If the Weibull distribution is a reasonable fit for the \{t_i\}, then from Model A, a suitable starting point may be $(11.14, 1.07, 1)$.

(ii) The observed times \{t_i\} = \{s_i - \tilde{\lambda}\} may be regarded as a sample from a $GG(\lambda, c, k)$ distribution. The log likelihood was maximised for various values of $k$, producing $(\hat{\lambda}, \hat{c})$ for each value. This technique of maximising the likelihood function for several fixed $k$ values, and then zeroing in on the value of $\hat{k}$ is suggested
by Lawless (1980) in his discussion of the problems commonly associated with inference procedures for the generalised gamma distribution. However, plotting the maximised likelihood against \( k \) (\( k \) ranging from 0.4 to 16.0) produced no clear starting value, since the likelihood was rather flat. This suggested that the data contained no information about this third parameter, although reparameterisation (see Lawless, 1980) might have improved matters.

The iterative process was thus started at several trial values for \((\lambda, c, k)\). Whilst the estimates \(\hat{\beta}_i\) and \(\hat{\alpha}\) remained close to the m.l.e.'s obtained for Model A, the three generalised gamma parameters showed considerable instability. The gradients of the log likelihood with respect to these parameters were particularly difficult to reduce. Finally several fits were obtained, all producing maximum log likelihoods of about \(-355.33\) (Model A gave \(-355.46\), so \(\chi^2_1 = 0.26\)), for widely differing values of \((\lambda, c, k)\). In all the fits, the correlations between any two of these three estimates exceeded 0.97 in absolute value, although correlations between the remaining estimates remained low. We thus conclude that the data do not support such a three-parameter distribution for \(T_2\).

4.3.3. The Weibull resistance time distribution with finite infectious period.

In order to investigate how an infectious period of finite length might affect the m.l.e.'s, an attempt was made to fit Model A, but replacing assumption 4(iv) by

\[ y_1 = y^* < \infty \]

for all contacts, where \( y^* \) is regarded as a parameter to be estimated. Since \( \max\{s_i\} = 58 \), we have (assuming \( \lambda = 6.5 \))

\[ 51.5 \leq y^* < \infty. \]
The d.f. of \( T_2 \) is then given by
\[
F_1(t) = \begin{cases} 
0 & \text{if } t \leq 0, \\
1 - e^{-\frac{t}{\lambda}} & \text{if } 0 < t < y^*, \\
1 - e^{-\frac{y^*}{\lambda}} & \text{if } t \geq y^*.
\end{cases}
\]

However, the iterative maximisation process was not successful: the log likelihood was maximised progressively further as \( y^* \) approached its theoretical minimum value 51.5 from above. Thus we have the same type of problem as that discussed during the choice of threshold parameter \( \beta \) in §4.2.3. It may be possible generally to use the recent approach of Cheng and Amin (1983) to overcome the problem.

However, it is doubtful whether this extra work would be worthwhile for our particular data set: the log likelihood was maximised with the value of \( y^* \) fixed at 51.5, producing maximum value -355.36. This is little different from the value -355.46 found for Model A when \( y_i = \infty \). The new approach might be worth investigation if \( \max(s_i - \lambda) \) were smaller.

4.4 : THE FIT OF THE MODEL.

The following tests of fit of the susceptibility and resistance time distribution are performed for Model B, where treatment is regarded as a time-dependent covariate and \( T_2 \) is assumed to have a Weibull distribution. Since the m.l.e.'s of the common parameters of Models A and B are virtually identical (see Tables 4.1 and 4.2), the conclusions are valid for both. In §4.4.4 we compare the two ways of expressing the effect of treatment.
4.4.1. The fit of the resistance time distribution.

We define $F_n(t)$ to be the empirical distribution function of the $\{s_i\}$ given by

$$F_n(t) = n^{-1} \sum_{i=1}^{n_s} I(0,t)(s_i)$$

where $I$ is the indicator function and $n_s$ is the number of untreated contacts who caught the disease, i.e. the number of Type I contacts.

We wish to compare $F_n(t)$ with

$$F_3(t) = \hat{F}_1(t-6.5)$$

where $\hat{F}_1(\cdot)$ is the fitted Weibull resistance time distribution function. Inspection of Figure 4.3 suggests a good fit: using a chi-squared test with nine subdivisions of the time range we obtain $\chi^2 = 7.14$.

4.4.2. The logistic form of the susceptibility.

Before using the logistic form for contact susceptibility we should first have checked the validity of such a model by suitable plots of the data. We may regard the susceptibility as a function of each covariate $X^*_i$ and $X^*_{i1}$ (see §4.3) in turn, and use graphical methods to check that the linear effects sought (referred to in §3.4.3) are not unreasonable.

A technique for graphically checking such validity was developed by Copas (1983), unfortunately a short time after the bulk of the present modelling work had been completed. However, we use the techniques perhaps belatedly, to investigate the effects due to the covariates. In doing so, we use only information on untreated contacts recorded in the data set, since treatment is assumed to modify susceptibility and may affect the proportions of infected individuals. The subsample of the data used includes 181 households.
Fig 4.3: Empirical (F(t)) and fitted (\hat{F}(t)) distributions of inter-symptoms intervals \{x_i\}. 

\begin{align*}
F(t) &= \text{Empirical distribution of inter-symptoms intervals} \\
\hat{F}(t) &= \text{Fitted distribution of inter-symptoms intervals}
\end{align*}
We may assess the effect of vaccination status $X_{i2}^*$ by estimating $\hat{p}_0, \hat{p}_1, \hat{p}_2, \hat{p}_3$ as the observed proportions of infections for the recorded $x_{i2}^* = 0, 1, 2, 3$ respectively and plotting the logits of these proportions against $X_{i2}^*$. We see the result in Figure 4.4, and a linear relation does not appear unreasonable, although the points at $X_{i2}^* = 1$ and $X_{i2}^* = 3$ are based on only 10 and 26 observations respectively. (Since we have effectively ignored $X_{i1}^*$ during this analysis, in Figure 4.5 we check that the distributions of $X_{i1}^*$ are similar for all four values of $X_{i2}^*$). We also note that the slope of any fitted line would be negative as required (since $\hat{\beta}_2 < 0$).

We now examine the effect of $X_{i1}^*$, the illness length of the household index. Since $X_{i1}^*$ is continuous, the $\{x_{i1}\}$ are essentially all distinct, and we must average over neighbouring values of $X_{i1}^*$ by dividing the sample into class intervals. Then class averages $\{x\}$ may be plotted against the logits of the observed proportions $\{\hat{p}_x\}$ to investigate linearity.

Copas (1983) suggests the use of a kernel function, giving

$$\hat{p}_x = \frac{\sum y_i \psi(h^{-1}(x-x_{i1}^*)))}{\sum \psi(h^{-1}(x-x_{i1}^*)))}$$

where $y_i = \begin{cases} 0 & \text{if contact } i \text{ not infected,} \\ 1 & \text{if contact } i \text{ infected;} \end{cases}$

$\psi(u) = \exp(-u^2/2)$, a standard Normal kernel function;

$h$ = bandwidth (to control the amount of smoothing);

$x$ = point for class interval.

A rough idea of the standard error of $\hat{p}_x$ at any value of $x$ is given by the square root of

$$\frac{(\sum y_i \psi(h^{-1}(x-x_{i1}^*)))}{\sum \psi(h^{-1}(x-x_{i1}^*)))^2} \cdot \frac{\hat{p}_x(1-\hat{p}_x)}{\hat{p}_x(1-\hat{p}_x)}.$$
Fig 4.4: The effect of $X_{i2}^*$

Fig 4.5: The distributions of $X_{ii}^*$. 
Given sufficient data, we could produce four such plots corresponding to the subsets of the data with contact vaccination status $X^*_1 = 0, 1, 2$ and 3. Ideally we would hope to obtain four parallel lines. However, only 10 contacts have $X^*_1 = 1$ and only 26 have $X^*_1 = 3$, making plots for these values uninformative.

The plots for $X^*_1 = 0$ (87 contacts) and $X^*_1 = 2$ (58 contacts) use class points $x = 10(20)110$. Copas suggests that a suitable starting value for bandwidth $h$ may be ten times the average spacing of the $\{x_i\}$. For our data this was 11 and, although various $h$ values were tried, the value $h = 10$ seemed to strike the best balance between the wild fluctuations produced by small $h$ values and the oversmoothing produced by larger ones.

The $\hat{p}_x$, their standard errors and the number of observations on which they were based are given in Table 4.3, and the logit plots are shown in Figure 4.6.

<table>
<thead>
<tr>
<th>class point x</th>
<th>$X^*_1 = 0$</th>
<th>$X^*_1 = 2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\hat{p}_x$</td>
<td>s.e.($\hat{p}_x$)</td>
</tr>
<tr>
<td>10</td>
<td>0.178</td>
<td>0.100</td>
</tr>
<tr>
<td>30</td>
<td>0.432</td>
<td>0.079</td>
</tr>
<tr>
<td>50</td>
<td>0.709</td>
<td>0.072</td>
</tr>
<tr>
<td>70</td>
<td>0.669</td>
<td>0.096</td>
</tr>
<tr>
<td>90</td>
<td>0.707</td>
<td>0.115</td>
</tr>
<tr>
<td>110</td>
<td>0.839</td>
<td>0.109</td>
</tr>
</tbody>
</table>

Table 4.3. $\hat{p}_x$ for bandwidth $h = 10$
(a) $X_{i2}^* = 0$. (Bandwidth = 10).

(b) $X_{i2}^* = 2$. (Bandwidth = 10).

**Fig 4.6:** The effect of $X_u^*$. 
Linearity is seen to be not unreasonable when $X_{12}^* = 0$, and the gradient would appear to be positive, supporting $\hat{\beta}_1 > 0$. Unfortunately Figure 4.6b is not so nicely behaved. However, as we see from Table 4.3, the points plotted for class points $x = 90$ and $x = 110$ are based on comparatively small numbers of observations and have relatively large standard errors. Removal of these two points could conceivably leave us with two linear parallel plots.

On the other hand, we may believe that these two points can be validated medically. When discussing distributions for $Y_1$ in §3.3.2 we noted that many infectious diseases display a rapid decline in infectiousness following an initial rampant period. Thus the relation between the length of index illness $X_{11}^*$ and the logit of contact susceptibility may not be linear for large values of $X_{11}^*$.

However, the logistic form of the susceptibility with the two proposed covariates would not seem to be too unreasonable for our model.

4.4.3. The fitted susceptibilities.

Having justified the use of the logistic form, we now investigate how well the estimated (or fitted) susceptibilities fit the data. The fitted susceptibility of contact $i$ is given by

$$
\hat{p}_i = \frac{1}{[1+\exp(-\sum_{j=0}^{2} X_{ij}^* \hat{\beta}_j)]^{-1}}.
$$

We have already remarked that the signs of $\hat{\beta}_1$ and $\hat{\beta}_2$ are reasonable. Further, the average susceptibility, estimated roughly from the data as the proportion of exposed contacts who caught whooping cough, was 0.285 which compares well with

$$
\bar{p} = 0.317, \quad \text{s.d.}(\hat{p}_i) = 0.197.
$$
The distribution of the \( \{ p^*_i \} \) is shown in Figure 4.7a, and is partitioned into infected and uninfected contacts in Figure 4.7b. Although this partition does not explain the bimodality as we may have hoped, it does suggest different distributions for the fitted susceptibilities of infected and uninfected contacts, with higher proportions of infected contacts in the higher \( \{ p^*_i \} \) categories. The difference between these distributions was explored using a 2x6 contingency table which yielded \( \chi^2 = 41.11 \). However the number of degrees of freedom is unclear (although the maximum number must be 5), and indeed the validity of the test is doubtful since the \( \{ p^*_i \} \) are not independent, being based on the same \( \{ \beta_j \} \).

The bimodality of the distribution of \( \{ p^*_i \} \) may be attributed in some part to the effect of vaccination status on susceptibility. This is clear from Table 4.4, where \( X_{12}^* = 0 \) is seen to account for nearly all the \( \hat{p}_i \in [0.4,0.7] \) and \( X_{12}^* = 2, \ X_{12}^* = 3 \) for the lower fitted susceptibilities.

<table>
<thead>
<tr>
<th>Range</th>
<th>Frequency of ( \hat{p}_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( X_{12}^* = 0 )</td>
</tr>
<tr>
<td>0.0-0.1</td>
<td>-</td>
</tr>
<tr>
<td>0.1-0.2</td>
<td>-</td>
</tr>
<tr>
<td>0.2-0.3</td>
<td>-</td>
</tr>
<tr>
<td>0.3-0.4</td>
<td>-</td>
</tr>
<tr>
<td>0.4-0.5</td>
<td>63</td>
</tr>
<tr>
<td>0.5-0.6</td>
<td>35</td>
</tr>
<tr>
<td>0.6-0.7</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 4.4 \( \{ p^*_i \} \) classified by vaccination status
a. The overall distribution.

b. Infected and uninfected contacts.

Fig 4.7: The distribution of \{\hat{p}_i\}.
The effect of index illness length $X^*_i$ may be similarly tabulated, although the pattern is found to be much less clear.

The fit of the susceptibilities may also be investigated in an ad-hoc manner by splitting the $\{\hat{p}_i\}$ into categories $0.0-0.1, \ldots, 0.6-0.7$ and calculating the proportion of contacts within each category who became infected. We would hope that the proportions obtained would lie within their respective categories. Table 4.5 shows that this is generally the case, allowing for the small numbers of observations in some categories.

In their review of goodness-of-fit tests for logistic models, Lemeshow and Hosmer (1982) propose and compare several statistics for assessment of fit. They consider the logistic model with $p$ covariates and propose three statistics which can easily be calculated for our data (where $p = 2$).

We let $Y_i$ be a binary infection variable i.e.

$$Y_i = \begin{cases} 
0 & \text{if contact } i \text{ is uninfected,} \\
1 & \text{if contact } i \text{ is infected,}
\end{cases}$$

<table>
<thead>
<tr>
<th>Range</th>
<th>No. of contacts</th>
<th>Number infected</th>
<th>Proportion infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-0.1</td>
<td>28</td>
<td>3</td>
<td>0.107</td>
</tr>
<tr>
<td>0.1-0.2</td>
<td>83</td>
<td>10</td>
<td>0.120</td>
</tr>
<tr>
<td>0.2-0.3</td>
<td>17</td>
<td>4</td>
<td>0.235</td>
</tr>
<tr>
<td>0.3-0.4</td>
<td>4</td>
<td>1</td>
<td>0.250</td>
</tr>
<tr>
<td>0.4-0.5</td>
<td>63</td>
<td>22</td>
<td>0.349</td>
</tr>
<tr>
<td>0.5-0.6</td>
<td>37</td>
<td>19</td>
<td>0.514</td>
</tr>
<tr>
<td>0.6-0.7</td>
<td>17</td>
<td>12</td>
<td>0.706</td>
</tr>
</tbody>
</table>

Table 4.5. Proportions of infected contacts
and \( \{D_k\} \) be the deciles of the fitted susceptibilities \( \{\hat{p}_i\} \) \((D_1 \) contains the smallest \( \frac{n}{10} \) values of \( \hat{p}_i \), etc).

Then the first statistic proposed is

\[
X^2 = \frac{10}{\sum_{k=1}^{10} \frac{(0_{ik} - e_{ik})^2}{e_{ik}}}
\]

where \( 0_{ik} = \sum_{i \in D_k} y_i \), \( e_{ik} = \sum_{i \in D_k} \hat{p}_i \).

Although the distribution of \( X^2 \) has not been studied, it is often compared to \( \chi^2_{10-(p+1)} \) (see Lemeshow and Hosmer (1982)). Our results yield \( X^2 = 11.53 \), which we may tentatively compare with \( \chi^2_7 \) to imply that the fit is reasonable.

However \( X^2 \) uses only observed data on infected contacts, and the next statistic compares observed and expected frequencies for all available contacts. We have

\[
\hat{C}^{*} = \frac{1}{\sum_{k=0}^{10} \sum_{l=1}^{10} \frac{(0_{0kl} - e_{0kl})^2}{e_{0kl}}}
\]

where \( 0_{0kl} = \sum_{i \in D_k} y_i \), \( 0_{k} = \sum_{i \in D_k} (1-y_i) \), \( e_{0kl} = \sum_{i \in D_k} \hat{p}_i \).

An earlier paper (Hosmer and Lemeshow, 1980) shows by simulation that, if \( p+1 < g \), then \( \hat{C}^{*} \) will be distributed approximately as \( \chi^2_{g-2} \). However, in the same paper, simulations have also shown that a third statistic, also distributed as \( \chi^2_{g-2} \), is more powerful than \( \hat{C}^{*} \).

This is

\[
\hat{H}^{*} = \frac{1}{\sum_{k=0}^{g} \sum_{l=1}^{g} \frac{(0'_{kl} - e'_{kl})^2}{e'_{kl}}}
\]
where the \{0'k\} and \{e'k\} are defined as \{0k\} and \{ek\} above, but summations are carried out within \(g\) categories of the \(\{p_i\}\) with fixed cutpoints. Using 9 categories for our results we obtain \(\hat{H}_9 = 11.17\) which is not significant as \(\chi^2_7\).

A further statistic (\(\hat{H}_g\); Hosmer and Lemeshow (1980)) has demonstrated even greater power against reasonably competitive models to the logistic. However, the expected values for this statistic are calculated by assuming that the covariates have multivariate normal distributions within the subpopulations (\(Y_i = 0, Y_i = 1\)), and simulations have suggested sensitivity to these assumptions when some of the covariates are discrete. By the nature of \(X_{i2}^*\), we are unable to use this statistic, and we conclude from the tests above that the susceptibilities for our model appear to fit reasonably well.

More recently, Landwehr, Pregibon and Shoemaker (1984) have developed graphical techniques for assessing logistic regression models. It would be interesting to compare results from these new methods with the conclusions reached above for our data.

4.4.4. The effects of preventive treatment.

It is difficult to assess the fit of the estimated treatment parameters, especially for Model B. For Model A, the value of parameter \(\alpha\) may be estimated roughly from the data: the proportion of treated contacts who caught whooping cough, and that of untreated contacts who caught it, may be computed. Their ratio gives a crude estimate of \(\alpha\), uncorrected for other variables. The value found, 0.079, is rather lower than the m.l.e. \(\hat{\alpha} = 0.113\) but is within one standard error. Also, both estimated parameters confirm the medically accepted effectiveness of the antibiotic erythromycin, since \(\hat{\alpha} << 1\) and \(\hat{\beta}_2 << 0\).
In order to compare results from the two fitted treatment parameters, in Figure 4.8 we plot both
\[ q_{Ai} = \hat{\alpha} \hat{p}_i \]
and
\[ q_{Bi} = \left[ 1 + \exp\left( -\sum_{j=0}^{2} X_j \beta_j - \beta_3 \right) \right]^{-1} \]
against \( \hat{p}_i \). \( q_{Ai} \) is thus seen as a straight line of gradient \( \hat{\alpha} \)
and the curve of \( q_{Bi} \) makes a D-shape with the untreated line \( \hat{p}_i = q_i \). The effectiveness of treatment is thus indicated by the
shallowness of the line for \( q_{Ai} \) and by the "fatness" of the D-shape for \( q_{Bi} \), and we see for \( q_{Bi} \) the proportionately smaller reductions in the larger \( \{\hat{p}_i\} \) discussed in §3.5.3. In fact a hypothetical "perfectly susceptible" individual, for whom \( p_i = 1 \), would be
totally unaffected by treatment using the approach of Model B. However,
since \( e^x > 0 \), \( \forall x \), we always have \( \hat{p}_i < 1 \) and this eventuality
cannot arise. For \( \hat{p}_i \in (0.8,1.0) \), \( q_{Bi} \) decreases much more quickly
than \( \hat{p}_i \) (for example, \( q_{Bi} = 0.53 \) when \( \hat{p}_i = 0.95 \)), thus effective
treatment is still seen to have an appreciable effect in this high
susceptibility range.

Indeed, \( q_{Ai} \) and \( q_{Bi} \) are very different for \( \hat{p}_i > 0.8 \), and
we may be surprised that this discrepancy was not reflected more
in the fits of Models A and B. A glance at Figure 4.7a solves the
mystery: all the \( \{\hat{p}_i\} \) are less than 0.7, and in this lower susceptibility
range \( q_{Ai} \) and \( q_{Bi} \) are very close.

Thus we conclude that, for our data, both treatment parameters
are indicating similar effectiveness of the preventive treatment
erthromycin. It would be interesting to compare fits and estimates
for the two models for more virulent diseases where higher susceptibilities
are common.
Fig 4.8: Comparison of treatment effects.
4.5.1. The resistance time distribution.

We have stressed throughout that knowledge of the resistance time distribution has important implications for treatment strategy. For instance, suppose that it were known that 90 per cent of all contacts who become infected at all do so in less than 7 days. Then this would contribute to a clinical judgement on whether to treat a contact when the index symptoms were reported to have appeared more than a week earlier, since any possible effect of treatment would be already reduced by a factor of more than 10. This would be particularly relevant when there are other treatment considerations such as cost and undesirable side-effects.

Such guidance may be conveyed in the form of the doctors' wallcharts of Figure 4.9 which may be constructed as follows. The probability of a contact's becoming infected eventually is \( p_i \) if untreated (from (4.4)), and \( p_i F_1(u) + q_i [1-F_1(u)] \) if treated at time \( u \) (from (4.5)). The ratio of these, which expresses the effectiveness of giving treatment at time \( u \), is

\[
F_1(u) + \frac{q_i}{p_i} [1-F_1(u)]. \quad \text{(4.6)}
\]

Therefore for Model A \( (q_i = ap_i) \), the effectiveness is measured by

\[
F_1(u) + a[1-F_1(u)]
\]

which is independent of the covariates i.e. the same for all contacts. This quantity is plotted against \( u \) in Figure 4.9a using estimates \( \lambda, \hat{c}, \hat{a} \) from Table 4.1.
Fig 4.9: Effectiveness of treatment: Medical "Wallcharts."
For Model B, (4.6) cannot be simplified and the effectiveness of treatment depends on the susceptibility \( p_i \), and therefore on the covariates. The ratio is plotted against \( u \), using estimated parameters from Table 4.2, in Figure 4.9b for \( p_i = 0.1 \) and \( p_i = 0.7 \), these being roughly the smallest and largest fitted susceptibilities.

The curves differ little: possibly a wallchart could display an intermediate curve (maybe that for \( p_i = 0.5 \)) with a note that individual susceptibility may alter the values a little. By inspection, such an intermediate curve would appear to differ little from that for Model A.

It is intended then that doctors may read off from such a chart that, for instance, treatment after 10 days will only reduce the chance of being infected to 64 per cent, whereas treatment after 4 days will reduce it to 36 per cent. The steeper this curve is initially, the more important it is to give treatment early: a shallow curve could indicate a long period during which treatment would be worthwhile.

4.5.2. The susceptibilities and covariates.

From the logistic model, all contacts may be assumed to have the same "baseline" susceptibility before their covariates are considered, an estimate of which is given by
\[
\hat{p}_0 = (1 + e^{-\hat{\beta}_0})^{-1} = 0.390
\]
for Model B.

This basic value is modified for each contact by the values of his covariates. Increasing the value of covariate \( x_{11}^* \) (the index illness length) will tend to increase fitted susceptibility (since \( \hat{\beta}_1 > 0 \)), whilst increasing \( x_{12}^* \) (contact vaccination status)
will lower it \( \hat{\beta}_2 < 0 \). The magnitudes of these two opposing modifications are, however, not independent, as may be seen in Figure 4.10.

If we consider an unvaccinated contact whose susceptibility has been raised from the baseline value to 0.6 by the length of illness of his family index, then from Figure 4.10a, partial vaccination will lower this figure to 0.37, whilst full vaccination and a subsequent booster will theoretically lower it further to 0.09 (a drop in susceptibility of 0.51 overall). However, for an unvaccinated contact with initial susceptibility 0.5, the overall decrease in susceptibility produced by a complete course of vaccination is only 0.43. A similar phenomenon is observed when considering the effect on susceptibility of different index illness lengths for a contact with a given constant vaccination status (see Figure 4.10b).

The above are direct consequences of the logistic form assumed for the susceptibility. This form was shown to be reasonable at least for \( X_{12}^* \) in §4.4.2. Therefore a chart such as Figure 4.10a may be of use in determining the effect of a partial or full vaccination program on an individual whose unvaccinated susceptibility may somehow be assessed.

**4.6 : CONCLUDING REMARKS**

In this chapter we have fitted a simple form of the general model to a set of data for whooping cough, one of the assumptions being that the incubation and latent periods of the disease may be assumed to have constant duration among the infected contacts. The goodness-of-fit tests of §4.4 suggest that the fit of the model is reasonable, no matter which approach to treatment we adopt. On this basis we have been able to illustrate results which hopefully are both medically informative and easy to use.
Fig 4.10: Effects of the covariates.
In fact the above results were based only on information recorded for single-contact households in the data set. In the interests of increasing the number of observations, especially in view of the small numbers of treated, infected contacts, we may feel that some of the data from larger households could also justifiably be included in the sample for analysis. For example, in a household of three where both contacts remained uninfected, we may consider it reasonable to include both as separate secondaries, or just to include one contact chosen randomly. Similarly, when one of two contacts became infected, the infected contact could be regarded as behaving like a single secondary and might be included.

Using rules such as these our data sample was expanded from 277 to 377 index-contact pairs. Models A and B were fitted and gave similar results to those obtained in §4.3, although the m.e.'s had smaller standard errors. This stability is encouraging, even though the expansion of the data set may not be well justified.

In the next chapter we investigate the fit of models which allow variation in the lengths of the incubation and latent periods, using the data from single-contact households only.
We now fit some forms of the general model which allow variation in the length of the incubation period to the whooping cough data for single-contact households. These fits will be compared with that of Model B (Chapter 4) in order to investigate whether or not the additional generality can produce a fit which is significantly better than that of the simple model.

The following assumptions are made throughout the chapter unless otherwise stated:

Assumptions 5

(i) Relation (3a) holds with \( \mu = 0 \).

(ii) \( v = \infty \) for all secondaries.

(iii) \( y_j = \infty \) for all primaries.

(iv) \( F_1(t) = F_T(t) \) \( \forall t \).

(v) \( p_i = \left[1 + \exp\left(-\sum_{j=0}^{2} x_{ij}^* \beta_j\right)\right]^{-1} \) where \( x_{i0}^*, x_{i1}^*, x_{i2}^* \) are as defined in §4.3.

(vi) \( q_i = \left[1 + \exp\left(-\sum_{j=0}^{2} x_{ij}^* \beta_j - \beta_3 \right)\right]^{-1} \).

Conditions (i) to (v) have already been justified for the whooping cough data (see §4.1.1) and the choice of covariates for the simple model was discussed in §4.2.2. We shall consider later the validity of retaining this combination of covariates for the models in this chapter. In (vi) we specify that treatment is to be regarded as a time-dependent binary covariate.
5.1 : THE "UNIFORM MODEL".

For this model we assume that the length of the incubation period is uniformly distributed on \([a,b]\) i.e. \(Z_2 \sim U[a,b]\) for \(0 < a < b\).

Thus
\[
F_2(z) = \begin{cases} 
0 & \text{if } z < a, \\
\frac{z-a}{b-a} & \text{if } a \leq z \leq b, \\
1 & \text{if } z > b.
\end{cases}
\]

Values for \(a\) and \(b\), to be chosen on medical grounds, will be discussed in §5.1.2.

We retain the Weibull distribution as an approximation to the resistance time distribution i.e.
\[
F_1(t) = \begin{cases} 
0 & \text{if } t \leq 0, \\
1-e^{-(t/\lambda)c} & \text{if } t > 0
\end{cases}
\]
for \(\lambda, c > 0\).

From the above, we may derive the density of the length of the inter-symptoms interval \(S = T_2 + Z_2\) which is given by
\[
f_3(s) = \begin{cases} 
\int_{0}^{s} f_1(t)f_2(s-t)dt & \text{if } s > 0, \\
0 & \text{elsewhere},
\end{cases}
\]
by (2.1).

Since \(f_2(z) = \frac{1}{b-a}\) for \(z \in [a,b]\), we obtain
\[
f_3(s) = \begin{cases} 
\frac{1}{b-a} F_1(s-a) & \text{if } a < s \leq b, \\
\frac{1}{b-a} [F_1(s-a)-F_1(s-b)] & \text{if } s > b, \\
0 & \text{elsewhere}
\end{cases}
\]
and we note that households for which we have recorded 
\[ s \leq a \]
are effectively excluded from the data set to be analysed. Also, for an observed value \( s \), we note that
\[ Z_2 \in [a, b] \Rightarrow T_2 \in [s-b, s-a]. \]

5.1.1. The contributions to the likelihood.

We simplify the \( \ell.c.'s \) obtained for the special case \( \mu = 0 \) in §3.2.2 using Assumptions 5 and the forms of \( F_1(\cdot) \) and \( F_2(\cdot) \) above.

Then for a Type I (untreated, infected) contact, from (3.5) and (5.3) we have
\[ L_I = p_i f_3(s) = \begin{cases} \frac{p_i}{b-a} F_1(s-a) & \text{if } a < s \leq b, \\ \frac{p_i}{b-a} [F_1(s-a) - F_1(s-b)] & \text{if } s > b. \end{cases} \]

The \( \ell.c.'s \) for uninfected contacts (Type III and Type IV) remain as for the simple model. So for uninfected, untreated contacts we have
\[ L_{III} = 1 - p_i, \tag{5.4a} \]
and for uninfected contacts treated at time \( u \),
\[ L_{IV} = 1 - p_i F_1(u) - q_i [1 - F_1(u)]. \tag{5.4b} \]

However, the \( \ell.c.'s \) for Type II (treated, infected) contacts are rather more difficult to derive than those for the simple model. We have again the basic expression
\[ L_{II} = p_i \int_0^u f_1(t) f_2(s-t) dt + q_i \int_u^s f_1(t) f_2(s-t) dt. \tag{5.5} \]
and by allowing $Z_2$ to vary we reintroduce the uncertainty, missing from the simple model, about whether or not treatment was given "in time" i.e. before or after the end of the resistance time. We are thus interested in the relative magnitudes of the (fixed) observed treatment time $u$ and the unobservable random variable $T_2$.

Therefore, not only must we investigate the form of $L_{II}$ for $s > b$ and $a < s \leq b$ (as for $L_I$ above), but also for different relative values of treatment time $u$, inter-symptoms time $s$ and incubation period limits $a$ and $b$. For if we have

$$a \leq Z_2 \leq b$$

then $S = T_2 + Z_2$ implies

$$s - b \leq T_2 \leq s - a$$

for observed inter-symptoms interval $s$.

Hence

$$u < s - b \Rightarrow u < T_2 \Rightarrow \text{treatment given "in time"},$$

$$u > s - a \Rightarrow u > T_2 \Rightarrow \text{treatment given "too late"},$$

but if

$$s - b \leq u \leq s - a \text{ then we are uncertain about the order of treatment and infection.}$$

These comments are reflected in the forms of the $L_{I}$'s obtained from the above basic expression for $L_{II}$. To see how these are derived, we consider the case

$$s > b, \ u < s - b$$

in basic expression (5.5).

Since $f_2(s-t)$ is only non-zero when $s - b < t < s - a$, and we have $u < s - b$, the first integral is zero, and the limits of the second integral become effectively $s - b$ (since $u < s - b$) and $s - a$ (since $s - a < s$).
Therefore we have

\[ L_{II} = \frac{q_i}{b-a} \int_{s-b}^{s-a} f_1(t) dt = \frac{q_i}{b-a} [F_1(s-a) - F_1(s-b)]. \]

for \( s > b, u < s-b. \)

Similarly, we may derive expressions for \( L_{II} \) for other values of \( s \) and \( u \), and we obtain

\[
L_{II} =
\begin{cases}
\frac{q_i}{b-a} [F_1(s-a) - F_1(s-b)] & \text{if } s>b, u<s-b; \\
\frac{p_i}{b-a} [F_1(u) - F_1(s-b)] + \frac{q_i}{b-a} [F_1(s-a) - F_1(u)] & \text{if } s>b, s-b \leq u \leq s-a; \\
\frac{p_i}{b-a} F_1(u) + \frac{q_i}{b-a} [F_1(s-a) - F_1(u)] & \text{if } s \leq b, s-b \leq u \leq s-a; \\
\frac{p_i}{b-a} F_1(s-a) & \text{if } s \leq b, u > s-a.
\end{cases}
\]

We note that the \( \lambda.c.'s \) are continuous in \( s \) and \( u \), assuming \( F_1(0) = 0 \) i.e. no instantaneous infection.

The first and second derivatives of these \( \lambda.c.'s \) may be found in Appendix C.

5.1.2. Fitting the model for various uniform intervals.

Given values for \( a \) and \( b \), the model now has six parameters to be estimated:

\( \beta_0, \beta_1, \beta_2 \) in logistic form for \( p_i \) (assumption 5(v)),
\( \beta_3 \) the treatment parameter in \( q_i \) (assumption 5(vi)),
\( \lambda, c \) the Weibull scale and shape respectively in expression (5.1) for \( F_1(.) \).

As for the simple model (see §4.1.3), the individual \( \lambda.c.'s \) may be combined into an overall log-likelihood which hopefully may be maximised using the available computer program.
Since Christie (1980) and other medical texts agree that the incubation period for whooping cough is about 7 days, and rarely longer than 10 days, reasonable choices for the end points of the uniform interval may be given by

\[ a = 6.5, \ b = 10.5. \]

Then households for which \( s \leq 6.5 \) will not be included in the data set for analysis i.e. our m.l.e.'s will be based on exactly the same subsample as that which produced the simple Model B results of Table 4.2. In fact reducing the value of \( b \) whilst retaining \( a = 6.5 \) should produce results increasingly similar to those for Model B. We recall from §4.3.1 that for Model B the maximised log-likelihood values obtained were \( L_W = -355.16 \) and \( L_E = -355.40 \) for Weibull and NED resistance time distributions respectively.

Models were fitted for \( b = 10.5(-1)7.5 \) and the resulting m.l.e.'s, standard errors and maximised log-likelihoods are shown in Tables 5.1.1 to 5.1.4. Comparison with Table 4.2 reveals that the estimates \( \hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3 \) and their standard errors differ little from the values obtained for the simple model, hence we may infer that the particular choice of distribution for \( Z_2 \) does not greatly affect the estimated susceptibility or treatment effect. We may also suspect that retention of the two significant covariates from the simple model is justified, and that the other covariates considered in §4.2.2 would similarly prove unhelpful.

Quite reasonably, \( \hat{\lambda} \) and \( \hat{c} \) are affected by the distribution of \( Z_2 \). As \( b \) increases, allowing \( Z_2 \) more variability, the estimate of scale parameter \( \hat{\lambda} \) decreases, signifying that less of the variation among the \( \{s_i\} \) is required to originate from the Weibull distribution. Also, the estimate of shape parameter \( \hat{c} \) decreases as \( b \) increases.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>m.l.e.</th>
<th>s.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$</td>
<td>-0.500</td>
<td>0.319</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>0.0094</td>
<td>0.0046</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>-0.881</td>
<td>0.160</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>-2.549</td>
<td>1.090</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>7.932</td>
<td>1.416</td>
</tr>
<tr>
<td>c</td>
<td>0.756</td>
<td>0.088</td>
</tr>
</tbody>
</table>

$L_W = -363.90$

$L_E = -367.25$

$\chi^2_1 = 6.7^{**}$

Table 5.1.1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>m.l.e.</th>
<th>s.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$</td>
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<td>0.320</td>
</tr>
<tr>
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<td>0.0046</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>-0.883</td>
<td>0.160</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>-2.609</td>
<td>1.085</td>
</tr>
<tr>
<td>$\lambda$</td>
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<td>1.430</td>
</tr>
<tr>
<td>c</td>
<td>0.811</td>
<td>0.090</td>
</tr>
</tbody>
</table>

$L_W = -363.05$

$L_E = -365.05$

$\chi^2_1 = 4.0^*$

Table 5.1.2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>m.l.e.</th>
<th>s.e.</th>
</tr>
</thead>
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<tr>
<td>$\beta_0$</td>
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<td>0.322</td>
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<tr>
<td>$\beta_1$</td>
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<td>0.0047</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>-0.886</td>
<td>0.161</td>
</tr>
<tr>
<td>$\beta_3$</td>
<td>-2.721</td>
<td>1.076</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>10.197</td>
<td>1.440</td>
</tr>
<tr>
<td>c</td>
<td>0.929</td>
<td>0.095</td>
</tr>
</tbody>
</table>

$L_W = -358.23$

$L_E = -358.50$

$\chi^2_1 = 0.54$

Table 5.1.3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>m.l.e.</th>
<th>s.e.</th>
</tr>
</thead>
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<tr>
<td>$\beta_0$</td>
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<td>0.322</td>
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<td>$\beta_1$</td>
<td>0.0094</td>
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<td>10.197</td>
<td>1.440</td>
</tr>
<tr>
<td>c</td>
<td>0.929</td>
<td>0.095</td>
</tr>
</tbody>
</table>

$L_W = -358.23$

$L_E = -358.50$

$\chi^2_1 = 0.54$

Table 5.1.4
In fact all the models with uniformly distributed incubation period have \( c < 1 \), indicating that the Weibull distribution for \( T_2 \) has a reverse J-shape. This may be reflecting a tendency of the model to consider the \( \{s_i\} \) in the range \([a,b]\) as almost wholly composed of incubation periods, thereby inferring a relatively large number of very small resistance times in the data set. The previously remarked excess of observations for \( s_i = 7 \) may also have contributed towards this result.

The maximised log-likelihood values are the \( \{L_W\} \) recorded in Tables 5.1.1 to 5.1.4. Clearly, further maximisation occurs as the uniform interval is narrowed, and the simple model, which represents the limit of this contraction, shows the greatest maximisation with \( L_W = -355.16 \). We recall also that the constraint \( c = 1 \) (i.e. \( T_2 \sim \text{NED} \)) did not significantly worsen the fit of the simple model (maximised log-likelihood \( L_E = -355.40 \) produced \( \chi^2_1 = 0.48 \)). To investigate whether a similar result holds for \( Z_2 \sim \text{U}[a,b] \) the uniform models were fitted with this same constraint, yielding the \( \{L_E\} \) in the tables. It may be seen that the Weibull distribution for \( T_2 \) becomes increasingly superior to the NED as the uniform interval for \( Z_2 \) widens, a result also indicated by the increasing value of \( 1 - c \).

Fits were also carried out with \( a = 4.5 \) and \( b = 10.5(1)12.5 \) to see whether the large number of observations with \( s_i = 7 \) was affecting the results. Generally, very similar estimates were obtained; the \( \{\hat{\beta}_j\} \) were virtually identical to those of Tables 5.1.1 to 5.1.4, and again both \( \hat{\lambda} \) and \( \hat{c} \) decreased as the uniform range \((b-a)\) increased. Also, comparison of the Weibull and exponential distributions for \( T_2 \) showed a similar pattern to that above. Values for \( b \) of 12.5 and 11.5 gave likelihood ratio values \( L_W - L_E \) of 3.93 and 2.80 respectively, yielding significant \( \chi^2_1 \) values 7.86 and 5.60.
When \( b \) was reduced to 10.5 a non-significant value 3.86 resulted. Thus again as the uniform interval narrows, the Weibull resistance time distribution is not significantly better than the NED. However, the simple model with \( \xi = 4.5 \) showed the Weibull distribution to be a definite improvement on the NED. This discrepancy in pattern between the families of models for \( a = 4.5 \) and \( a = 6.5 \) may well be explained by the surfeit of 7-day intervals recorded.

5.1.3. The fit of the model and discussion.

Since the \( \{ \hat{\beta}_j \} \) are very similar to those obtained for Model B we shall not re-examine the fit of the contact susceptibilities and treatment effects, and conclude that, by the tests of §4.4.2 - §4.4.4, these would appear to be adequate. However the fitted distribution of the \( \{ s_i \} \) requires investigation, and we wish to compare the empirical d.f. of the \( \{ s_i \} \), \( F_n(t) \), with the fitted d.f. \( F_3(t) \) which we now derive:

From (5.3) we have

\[
f_3(s) = \begin{cases} \frac{1}{b-a} F_1(s-a) & \text{if } a < s \leq b, \\ \frac{1}{b-a} [F_1(s-a)-F_1(s-b)] & \text{if } s > b, \\ 0 & \text{elsewhere.} \end{cases}
\]

where \( F_1(t) = 1-e^{-\left(\frac{t}{\lambda}\right)^c} \).

Thus for \( a < s \leq b \),

\[
F_3(s) = \int_a^s f_3(t)dt = \frac{1}{b-a} \int_a^s [1-e^{-\left(\frac{t-a}{\lambda}\right)^c}]dt
\]

\[
= \frac{s-a}{b-a} - \frac{\lambda}{c(b-a)} \int_0^\infty \left[ \left(\frac{s-a}{\lambda}\right)^c - 1 \right] e^{-y} dy
\]

\[
= \frac{s-a}{b-a} - \frac{\lambda \Gamma(\frac{1}{c})}{c(b-a)} \left(\frac{s-a}{\lambda}\right)^{\frac{1}{c}}
\]
where $\Gamma_x(k)$ is the incomplete gamma function defined by

$$
\Gamma_x(k) = \int_0^x y^{k-1}e^{-y}dy.
$$

Similarly, we obtain an expression for $F_3(s)$ when $s > b$, and we have

$$
\hat{F}_3(s) = \begin{cases} 
0 & \text{if } s \leq a, \\
\frac{s-a}{b-a} - \frac{\lambda}{c(b-a)} \hat{\Gamma}_a \left(\frac{1}{c}\right) & \text{if } a < s \leq b, \\
1 - \frac{\lambda}{c(b-a)} \left[\hat{\Gamma}_a \left(\frac{1}{c}\right) - \hat{\Gamma}_b \left(\frac{1}{c}\right)\right] & \text{if } s > b.
\end{cases}
$$

where $\hat{s}_a = \left(\frac{s-a}{\lambda}\right)^c$ and $\hat{s}_b = \left(\frac{s-b}{\lambda}\right)^c$.

$\hat{F}_3(s)$ was calculated for the fit shown in Table 5.1.1 with uniform interval $[6.5,10.5]$ since, medically speaking, this appears to be the most reasonable range for $Z_2$. The incomplete gamma functions were calculated using a recursive algorithm of Lau (1980). $\hat{F}_3(t)$ and $F_n(t)$ are plotted together in Figure 5.1. A chi-squared test with nine subdivisions of the time range produced $\chi^2 = 16.57$ which is almost significant at the 1% level.

The fit of the distribution of the $\{s_i\}$ would therefore appear to be unsatisfactory. Comparison with Figure 4.3, where a satisfactory fit for Model B was indicated, would suggest that when $Z_2 \sim U[6.5,10.5]$, $\hat{F}_3(t)$ has insufficient mass for small values of $t$.

Thus generally we conclude that the simple model appears to display a better fit to the whooping cough data than this uniform model. Not only is the fit of the $\{s_i\}$ distribution superior for Model B, but the log-likelihood maximises further for the simple
Fig. 5.1: $F_n(t)$ and $\hat{F}_3(t)$ for $U[65,10.5]$ incubation period.
model for both Weibull and NED resistance time distributions. As the variability in \( Z_2 \) increases, the maximised log-likelihood value decreases and the Weibull distribution for \( T_2 \) becomes a significant improvement on the NED.

From Figure 5.1 and the estimates \( \{ \hat{c} \} \) (all <1) we may suspect that a positively skewed distribution for \( Z_2 \) may improve on the fit of this uniform model: Sartwell (1950, 1966) has shown that the variation in observed incubation periods for many common diseases may be adequately described by the positively skewed lognormal distribution. In the next section we consider a "trapezium" distribution for \( Z_2 \) which allows us to investigate the effect of different skewness of the distribution of \( Z_2 \) on the fit of the model, whilst keeping the expressions for the \( c.c.'s \) simple.

5.2: THE "TRAPEZIUM MODEL"

We now assume that incubation period \( Z_2 \) has a "trapezium distribution" with parameters \( a_2, a_1, b_1, b_2 \), hereafter abbreviated to \( Z_2 \sim \text{Trap}(a_2, a_1, b_1, b_2) \), where \( 0 < a_2 \leq a_1 \leq b_1 \leq b_2 \), \( a_2 < b_2 \).

The density of this distribution is given by

\[
f_2(z) = \begin{cases} 
\frac{2(z-a_2)}{(a_1-a_2)(b_1+b_2-a_1-a_2)} & \text{if } a_2 \leq z < a_1, \\
\frac{2}{b_1+b_2-a_1-a_2} & \text{if } a_1 \leq z \leq b_1, \\
\frac{2(b_2-z)}{(b_2-b_1)(b_1+b_2-a_1-a_2)} & \text{if } b_1 < z \leq b_2, \\
0 & \text{elsewhere},
\end{cases}
\]

and the form of the density is illustrated in Figure 5.2.
The family of trapezium distributions includes the uniform $(a_1 = a_2, b_1 = b_2)$ and triangular $(a_1 = b_1)$ distributions as special cases. However, the most general form proposed above allows for considerable flexibility in investigating different types of distributions for $Z_2$, simply by altering the parameter values. For example,

$$a_1 - a_2 = b_2 - b_1 > 0, \quad a_1 \neq b_1$$

indicates a trapezium, symmetric about $\frac{a_1 + b_1}{2}$, with a uniform portion on $[a_1, b_1]$ and linear tails. Holding $(a_2, a_1, b_2)$ constant whilst lowering $b_1$ towards $a_1$ produces distributions with increasing positive skewness, and holding $(a_2, b_1, b_2)$ constant whilst increasing $a_1$ towards $b_1$ simulates distributions with increasing negative skewness.

The density $f_3(\cdot)$ of $S = T_2 + Z_2$ is then given by (5.2), and will have different forms depending on the relative magnitude.
of the observed $s$ and parameters $a_2, a_1, b_1, b_2$.

We consider first a Weibull resistance time distribution i.e. $F_1(t)$ given by (5.1). By the form of $f_2(\cdot)$ above, the complexity of expressions obtained for $f_3(\cdot)$ increases as $s$ increases. When we have $s > b_2$ for example, we obtain direct from (5.2)

$$
f_2(s) = \int_{s-a_2}^{s-a_1} \frac{f_1(t)2(s-t-a_2)}{(a_1-a_2)(b_1+b_2-a_1-a_2)} dt + \int_{s-b_1}^{s-b_2} \frac{f_1(t)2}{(b_1+b_2-a_1-a_2)} dt
$$

which becomes

$$
f_3(s) = \frac{2}{(a_1-a_2)(b_2-b_1)(b_1+b_2-a_1-a_2)} \left[ (b_2-b_1)(s-a_2)(1-e^{-s_1})-(b_2-b_1)(s-a_1)(1-e^{-s_2}) 
- (a_1-a_2)(s-b_1)(1-e^{-s_3})+(a_1-a_2)(s-b_2)(1-e^{-s_4})-\lambda(b_2-b_1)\left\{ \Gamma_{s_1} \left( \frac{c+1}{c} \right) - \Gamma_{s_2} \left( \frac{c+1}{c} \right) \right\} 
+ \lambda(a_1-a_2)\left\{ \Gamma_{s_3} \left( \frac{c+1}{c} \right) - \Gamma_{s_4} \left( \frac{c+1}{c} \right) \right\} \right]
$$

where $s_1 = \left( \frac{s-a_2}{\lambda} \right)^c$,
$s_2 = \left( \frac{s-a_1}{\lambda} \right)^c$,
$s_3 = \left( \frac{s-b_1}{\lambda} \right)^c$,
$s_4 = \left( \frac{s-b_2}{\lambda} \right)^c$.

Expressions for $f_3(\cdot)$ assuming a two-parameter gamma distribution for $T_2$ i.e. $T_2 \sim GG(\lambda, 1, k)$, prove to be even more complicated.

Since our primary intention at present is to compare different forms for the distribution of $Z_2$, we may feel that the assumption

$$
T_2 \sim NED(1/\lambda)
$$
will produce a reasonable simplification of the expressions. Previous results for the simple and uniform models suggest that any conclusions thus reached about the distribution of \( Z_2 \) will also hold for Weibull resistance time distributions.

Then assuming

\[
 f_1(t) = \begin{cases} 
 0 & \text{if } t \leq 0, \\
 \frac{t}{\lambda} & \text{if } t > 0, \\
 \frac{1}{\lambda} e^{-\frac{t}{\lambda}} & \text{if } t > 0,
\end{cases}
\]

\( \lambda > 0 \), in (5.2) we obtain

\[
 f_3(s) = \begin{cases} 
 0 & \text{if } s < a_2, \\
 \frac{2}{(a_1-a_2)(b_1+b_2-a_1-a_2)}[(s-a_2-\lambda)+\lambda e^{-s_1}] & \text{if } a_2 \leq s < a_1, \\
 \frac{2}{(a_1-a_2)(b_1+b_2-a_1-a_2)}[(a_1-a_2)+\lambda(e^{-s_1}-e^{-s_2})] & \text{if } a_1 \leq s \leq b_1, \\
 \frac{2}{(a_1-a_2)(b_1+b_2-a_1-a_2)}[(b_2-s+\lambda)(a_1-a_2)+\lambda((b_2-b_1)(e^{-s_1}-e^{-s_2})-(a_1-a_2)e^{-s_3})] & \text{if } b_1 < s < b_2, \\
 \frac{2\lambda[(b_2-b_1)(e^{-s_1}-e^{-s_2})+(a_1-a_2)(e^{-s_4}-e^{-s_3})]}{(a_1-a_2)(b_1+b_2-a_1-a_2)} & \text{if } s > b_2
\end{cases}
\]

(5.7)

where \( s_1 = \frac{s-a_2}{\lambda} \), \( s_2 = \frac{s-a_1}{\lambda} \), \( s_3 = \frac{s-b_1}{\lambda} \), \( s_4 = \frac{s-b_2}{\lambda} \),

and households for which we have recorded

\[ s \leq a_2 \]

are effectively excluded from the data set to be analysed.
5.2.1. The contributions to the likelihood.

The \( f_i \)'s \( L_{III} \) and \( L_{IV} \) for uninfected contacts are identical to those for the simple and uniform models (see (5.4a) and (5.4b)).

For a Type I (untreated, infected) contact we have

\[
L_I = p_I f_3(s)
\]

where the appropriate expression for \( f_3(s) \) is chosen from (5.7).

The \( f_i \)'s for Type II contacts can take many forms, depending on the observed values \((u,s)\). Firstly, the expression for \( f_3(s) \) is chosen from (5.7), depending on the value \( s \). Then similar partitioning of the range of \( u \) values (remembering \( u < s \)) produces many different expressions for \( L_{II} \). However, inspection of the data set reveals that only 5 of these are likely to be useful for our particular analysis. The observed pairs \([[u,s]]\) have relatively large \( s \) values, much larger than any value for \( b_2 \) which we are likely to consider medically reasonable. Hence we only consider the form of \( f_3(s) \) for \( s > b_2 \) above, which was the result of substituting

\[
f_1(t) = \frac{1}{\lambda} e^{-\frac{t}{\lambda}}
\]

into the basic form (5.6).

Having fixed \( s > b_2 \), and therefore the form of \( f_3(s) \), we now consider the \( L_{II} \) for different values of \( u \).

We recall

\[
Z_2 \in [a_2, b_2] \Rightarrow T_2 \in [s-b_2, s-a_2], \text{ since } S = T_2 + Z_2.
\]

Now

\[
\begin{align*}
u < s-b_2 & \Rightarrow u < T_2 \Rightarrow \text{treatment given "in time", so } L_{II} = p_1 f_3(s), \\
u > s-a_2 & \Rightarrow u > T_2 \Rightarrow \text{treatment given "too late", so } L_{II} = p_1 f_3(s),
\end{align*}
\]
but \( s-b_2 \leq u \leq s-a_2 \) reflects uncertainty about the timeliness of treatment. Expressions for \( L_{II} \) for this range of \( u \) values may be obtained by considering the basic form (5.6) of \( f_3(s) \), multiplying integrals for which \( T_2 \leq u \) by \( p_i \) and those for which \( T_2 > u \) by \( q_i \) (c.f. expression (5.5) for earlier models). For example, if \( u \in [s-b_1,s-a_1] \) we obtain the l.c.

\[
L_{II} = p_i \int_{s-b_2}^{s-b_1} \frac{f_1(t) \cdot 2(b_2-s+t)dt}{(b_2-b_1)(b_1+b_2-a_1-a_2)} + p_i \int_{s-b_1}^{u} \frac{f_1(t) \cdot 2dt}{(b_1+b_2-a_1-a_2)} +
q_i \int_{u}^{s-a_1} \frac{f_1(t) \cdot 2dt}{(b_1+b_2-a_1-a_2)} + q_i \int_{s-a_1}^{s-a_2} \frac{f_1(t) \cdot 2(s-t-a_2) \cdot dt}{(a_1-a_2)(b_1+b_2-a_1-a_2)}
\]

and we write \( f_1(t) = \frac{1}{\lambda}e^{-\frac{t}{\lambda}} \) and simplify.

Hence, for the case \( s > b_2 \), we obtain l.c.'s for Type II (treated, infected) contacts:

\[
L_{II} = \begin{cases} 
2\lambda q_i \left[ (b_2-b_1)(e^{-s_1}-e^{-s_2})+(a_1-a_2)(e^{-s_4}-e^{-s_3}) \right] / d & \text{if } u < s-b_2, \\
2[\lambda q_i (b_2-b_1)(e^{-s_1}-e^{-s_2})+\lambda(a_1-a_2)(p_i e^{-s_4}-q_i e^{-s_3}) \\
+(a_1-a_2)(b_2-s+u+\lambda)(q_i-p_i) e^{-u/\lambda}] / d & \text{if } s-b_2 \leq u < s-b_1, \\
2[\lambda q_i (b_2-b_1)(e^{-s_1}-e^{-s_2})+\lambda p_i (a_1-a_2)(e^{-s_4}-e^{-s_3}) \\
+(a_1-a_2)(b_2-b_1)(q_i-p_i) e^{-u/\lambda}] / d & \text{if } s-b_1 \leq u \leq s-a_1, \\
2[\lambda (b_2-b_1)(q_i e^{-s_1}-p_i e^{-s_2})+\lambda p_i (a_1-a_2)(e^{-s_4}-e^{-s_3}) \\
+(p_i-q_i)(b_2-b_1)(a_2-s+u+\lambda) e^{-u/\lambda}] / d & \text{if } s-a_1 \leq u \leq s-a_2, \\
2\lambda p_i \left[ (b_2-b_1)(e^{-s_1}-e^{-s_2})+(a_1-a_2)(e^{-s_4}-e^{-s_3}) \right] / d & \text{if } u > s-a_2,
\end{cases}
\]
where $s_1, s_2, s_3, s_4$ are as defined for (5.7) and 
\[ d = (a_1 - a_2)(b_2 - b_1)(b_1 + b_2 - a_1 - a_2). \]

We note that these log-likelihoods are continuous in $u$.

Again, the individual log-likelihoods are combined into an overall log-likelihood for the data which is to be maximised using the same iterative computer program.

The first and second derivatives of the log-likelihoods used in the fits may be found in Appendix C.

5.2.2. Investigating distributions for $Z_2$

From the tests of fit of the uniform model in §5.1.3, we inferred that a positively skewed distribution for $Z_2$ might be more reasonable than the uniform distribution. By fitting the trapezium model with suitably chosen parameters we now investigate this proposition.

End points
\[ a_2 = 4.5, \quad b_2 = 10.5 \]

were chosen in the first instance. When fitting the simple model with $Z_2 = 4.5$ we stated that a few medical texts report incubation periods for whooping cough occasionally as short as 5 days (see §4.3.1.) whilst Christie (1980) and others agree that, for well-documented outbreaks, periods longer than 10 days are rare.

Once the trapezium parameters have been fixed the model has five parameters to be estimated: $\beta_0, \beta_1, \beta_2, \beta_3$ as defined for the uniform model in §5.1.2, and the NED scale parameter $\lambda$.

We note immediately that the households with recorded inter-symptoms intervals less than 4.5 days are excluded from the data which may be analysed, as the contacts must have been infected under conditions not covered by our model. Since both simple and uniform models have been fitted previously to this same subsample of the
data we record here some results useful for comparison.

**Result 1 (Simple Model B)**

(i) When \( Z_2 = 4.5 \) and \( T_2 \sim \text{NED}(1/\lambda) \), the maximised log-likelihood was \( L_E = -388.24 \).

(ii) When \( Z_2 = 4.5 \) and \( T_2 \sim \text{Weibull}(\lambda, c) \), the maximised log-likelihood was \( L_W = -385.95 \).

**Result 2 (Uniform Model)**

When \( Z_2 \sim \text{U}[4.5, 10.5] \) and \( T_2 \sim \text{NED}(1/\lambda) \), the maximised log-likelihood was \( L_E = -394.31 \).

We begin by assuming

\[ a_1 = 5.5, \ b_1 = 9.5 \]

i.e. fitting a symmetric trapezium distribution for \( Z_2 \). The value of parameter \( b_1 \) is then gradually decreased in successive fits until a triangular distribution results when \( a_1 = b_1 = 5.5 \), the distribution meanwhile becoming increasingly positively skewed. This trend is continued by retaining \( a_1 = b_1 \) whilst decreasing their common value further towards \( a_2 = 4.5 \).

The results of fitting the model are displayed in Table 5.2.1. For each fit performed we have recorded

(i) the values of \( a_1 \) and \( b_1 \),

(ii) the shape of the distribution,

(iii) parameter estimates \( \hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2, \hat{\beta}_3, \hat{\lambda} \),

(iv) the maximised log-likelihood value \( L_E \).

The median standard errors of the parameter estimates are also indicated at the foot of the table. The standard errors of the \( \{ \hat{\lambda} \} \)
<table>
<thead>
<tr>
<th>$a_1$</th>
<th>$b_1$</th>
<th>Density shape</th>
<th>$\hat{\beta}_0$</th>
<th>$\hat{\beta}_1$</th>
<th>$\hat{\beta}_2$</th>
<th>$\hat{\beta}_3$</th>
<th>$\lambda$</th>
<th>$L_E$</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td>-0.434</td>
<td>0.0096</td>
<td>-0.870</td>
<td>-2.671</td>
<td>9.069</td>
<td>-399.97</td>
</tr>
<tr>
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<td></td>
<td>-0.430</td>
<td>0.0096</td>
<td>-0.871</td>
<td>-2.697</td>
<td>9.284</td>
<td>-399.08</td>
</tr>
<tr>
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<td>-0.426</td>
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<td>-0.872</td>
<td>-2.719</td>
<td>9.471</td>
<td>-398.08</td>
</tr>
<tr>
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<td>6.5</td>
<td></td>
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<td>0.0096</td>
<td>-0.872</td>
<td>-2.736</td>
<td>9.620</td>
<td>-397.00</td>
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<tr>
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<td>5.5</td>
<td></td>
<td>-0.422</td>
<td>0.0097</td>
<td>-0.873</td>
<td>-2.747</td>
<td>9.714</td>
<td>-396.20</td>
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<td></td>
<td>-0.418</td>
<td>0.0097</td>
<td>-0.873</td>
<td>-2.747</td>
<td>9.879</td>
<td>-393.05</td>
</tr>
<tr>
<td>4.8</td>
<td>4.8</td>
<td></td>
<td>-0.417</td>
<td>0.0097</td>
<td>-0.874</td>
<td>-2.772</td>
<td>9.946</td>
<td>-391.60</td>
</tr>
<tr>
<td>4.6</td>
<td>4.6</td>
<td></td>
<td>-0.416</td>
<td>0.0097</td>
<td>-0.874</td>
<td>-2.779</td>
<td>10.015</td>
<td>-390.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median standard errors</td>
<td>0.315</td>
<td>0.0046</td>
<td>0.155</td>
<td>0.835</td>
<td>1.24</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.2.1. Fitted trapezium model; $a_2 = 4.5$, $b_2 = 10.5$; increasing positive skewness.
were by far the most variable, ranging from 1.17 when $\hat{\lambda} = 9.069$ to 1.28 when $\hat{\lambda} = 10.015$.

We note immediately that the estimates $\{\hat{\beta}_i\}$ are little affected by changing the distribution of $Z_2$. Reference to Table 4.2 and Tables 5.1.1. to 5.1.4. reveals that they are also remarkably similar to the corresponding estimates for the simple and uniform models, even though these previous results were based on a slightly smaller subsample of the data (excluding $s_i$ values less than 6.5, rather than 4.5). The correlations between these estimates remain very small for all the fits. The value of $\hat{\lambda}$ is seen to increase as the variability in the distribution of $Z_2$ decreases, a result similar to that already discussed for the Weibull scale parameter in the fits of the uniform model (see §5.1.2).

As the distribution of $Z_2$ becomes more positively skewed we see that the value of $L_E$ increases. The very skewed triangular distributions lower in the table show further maximisation than the uniform model on the same range (result 2), although the value $L_E = -388.24$ for the simple model (result 1) is never quite reached. Since all these models have the same number of parameters to be estimated we cannot use formal likelihood ratio methods to compare the fits. Nevertheless, the degree of maximisation of $L_E$ may still provide useful information for ad hoc comparisons of the fitted models.

It is not clear from these results whether the improvement in $L_E$ stems from the increasing positive skewness of the distribution of $Z_2$, or from the reduced variability in the distribution. We recall that the latter was found to be important when fitting the uniform model. Thus, retaining the end-points $a_2 = 4.5$, $b_2 = 10.5$ two more sets of fitted trapezium models were investigated:
(a) beginning with $a_1 = 5.5$, $b_1 = 9.5$, the value of $a_1$ was gradually increased to represent more negative skewness,

(b) from the same starting point, the central uniform portion was narrowed progressively, producing a set of distributions symmetric about $\frac{a_2 + b_2}{2}$ with decreasing variability.

The results of the (a) fits are shown in Table 5.2.2, and of the (b) fits in Table 5.2.3. Since the estimates of the parameters are very similar to those previously obtained, they are not included. Inspection reveals that decreasing variability in the distribution of $Z_2$ does not appear generally to increase the value of $L_E$, and we conclude that the increasing positive skewness in the previous fits was an important factor.

Fits were also carried out with end-points

$$a_2 = 6.5, \quad b_2 = 10.5$$

in order to compare results directly with those investigated in detail in Chapter 4 for Model B, and with the uniform fits of §5.1.2. We recall the results for these models:

Result 3 (Simple Model B).

When $Z_2 = 6.5$, the maximised log-likelihoods were

$$L_W = -355.16; \quad L_E = -355.40.$$  

Result 4 (Uniform Model).

When $Z_2 \sim U[6.5,10.5]$ the maximised log-likelihoods were

$$L_W = -363.90; \quad L_E = -367.25,$$

using the obvious notation.
Table 5.2.2. Fitted trapezium model; $a_2 = 4.5$, $b_2 = 10.5$; increasing negative skewness.

<table>
<thead>
<tr>
<th>$a_1$</th>
<th>$b_1$</th>
<th>Density shape</th>
<th>$L_E$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5</td>
<td>9.5</td>
<td></td>
<td>-399.97</td>
</tr>
<tr>
<td>6.5</td>
<td>9.5</td>
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</tr>
<tr>
<td>9.5</td>
<td>9.5</td>
<td></td>
<td>-409.70</td>
</tr>
</tbody>
</table>

Table 5.2.3. Fitted trapezium model; $a_2 = 4.5$, $b_2 = 10.5$; symmetric densities.

<table>
<thead>
<tr>
<th>$a_1$</th>
<th>$b_1$</th>
<th>Density shape</th>
<th>$L_E$</th>
</tr>
</thead>
<tbody>
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<td>-397.05</td>
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<tr>
<td>5.5</td>
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<tr>
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<td>-403.81</td>
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</table>
The results of fitting increasingly positively skewed distributions for $Z_2$ on this range are shown in Table 5.2.4. Similar comments to those made on results for the previous range of values (Table 5.2.1) are seen to apply: the $\{\hat{\beta}_j\}$ differ little from previous fits, and both $\hat{\lambda}$ and $L_E$ increase as the positive skewness increases. Eventually, further maximisation occurs than that displayed by the uniform model on the same range (result 4), and this despite using the NED rather than the Weibull distribution for $T_2$. However, the values obtained for the simple model (result 3) are never reached.

Reducing variability in the distribution of $Z_2$, by considering negatively skewed and symmetric distributions on this new range, gives similar results to those already discussed for Tables 5.2.2 and 5.2.3. Increasing the range of values of $Z_2$ (keeping $a_2$ constant whilst gradually increasing $b_2$), also results in progressively less maximisation of $L_E$, a phenomenon already observed in Tables 5.1.1 to 5.1.4 for the uniform model.

5.2.3. The fit of the model and discussion.

Since the $\{\hat{\beta}_j\}$ are almost identical to those obtained in previous fits, we conclude that the fit of the susceptibilities and treatment effects are again probably adequate. We wish now to compare the empirical d.f. of the $\{s_i\}$, $F_n(t)$, with the fitted d.f. $\hat{F}_3(t)$, which we obtain using the forms (5.7) of $f_3(t)$.

For example, when $a_2 \leq s < a_1$ we have

$$F_3(s) = \int_0^s f_3(t) dt = \frac{2}{(a_1-a_2)(b_1+b_2-a_1-a_2)} \int_{a_2}^s \left( \frac{t-a_2}{-\lambda} \right) dt$$
<table>
<thead>
<tr>
<th>$a_1$</th>
<th>$b_1$</th>
<th>Density shape</th>
<th>$\hat{\beta}_0$</th>
<th>$\hat{\beta}_1$</th>
<th>$\hat{\beta}_2$</th>
<th>$\hat{\beta}_3$</th>
<th>$\lambda$</th>
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</tr>
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<td>0.0092</td>
<td>-0.881</td>
<td>-2.606</td>
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<td>0.0092</td>
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<td>0.0092</td>
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<td>-363.77</td>
</tr>
<tr>
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<td>6.6</td>
<td><img src="image" alt="Shape" /></td>
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<td>0.0092</td>
<td>-0.881</td>
<td>-2.622</td>
<td>9.485</td>
<td>-363.02</td>
</tr>
</tbody>
</table>

Median standard errors: 0.318 0.0046 0.160 0.839 1.247

Table 5.2.4. Fitted trapezium model; $a_2 = 6.5$, $b_2 = 10.5$; increasing positive skewness
whence

\[ F_3(s) = \frac{2 \left( \frac{(s-a_2)^2}{2} - \lambda (s-a_2) + \lambda^2 (1-e^{-s}) \right) - s-a_2}{(a_1-a_2)(b_1+a_2-a_1-a_2)} \]

and substituting \( \hat{\lambda} \) for \( \lambda \) gives \( \hat{F}_3(s) \).

Thus we obtain

\[ \hat{F}_3(s) = \begin{cases} 
0 & \text{if } s < a_2, \\
\frac{(s-a_2)^2}{2} - \lambda (s-a_2) + \lambda^2 (1-e^{-s}) & \text{if } a_2 \leq s < a_1, \\
\frac{(a_1-a_2)^2}{2} + (a_1-a_2)(s-a_2) & \text{if } a_1 \leq s \leq b_1, \\
\frac{(a_1-a_2)^2}{2} + (a_1-a_2)(b_1-a_1) & \text{if } b_1 \leq s < b_2, \\
2 \left[ \frac{(b_1-b_2)^2}{2} + \lambda (b_1-b_2) \right] & \text{if } s > b_2,
\end{cases} \]

where \( s_1, s_2, s_3, s_4 \) are as defined for (5.7), with \( \hat{\lambda} \) substituted for \( \lambda \).

\( \hat{F}_3(t) \) and \( F_n(t) \) are plotted together for the particular fit in which

\[ Z_2 \sim \text{Trap}(6.5,7.0,7.0,10.5) \]

in Figure 5.3. A chi-squared test with nine time subdivisions produces
Fig 5.3: $\hat{F}_n(t)$ and $\hat{F}_3(t)$ for $\text{Trap}(6.5,7.0,7.0,10.5)$ incubation period.
\( \chi^2 = 17.21 \), a value almost significant at the 1% level. This result is just about as extreme as that obtained when \( Z_2 \sim U[6.5,10.5] \) in §5.1.3: comparison of the maximised log-likelihood values for these two fitted models reveals that we might have expected such a result. Inspection of Figure 5.3 also reveals that

\[ \hat{F}_3(t) < F_n(t) \text{ for } t \in [6.5,38], \]

so the lack of fit is hardly surprising.

Similar plots drawn for the trapezium model with

\[ Z_2 \sim \text{Trap}(6.5,6.6,6.6,10.5) \]

and with

\[ Z_2 \sim \text{Trap}(6.5,6.6,6.6,12.5) \]

appeared virtually identical to Figure 5.3. The former produced a \( \chi^2 \) value of 14.17 which, although significant at the 5% level, shows some improvement on the previous value of 17.21, presumably owing to the increase in positive skewness. However, extension of the range by increasing \( b_2 \) to 12.5 produced \( \chi^2 = 20.73 \) indicating a considerably worse fit.

The results above suggest that the trapezium model is sufficiently flexible to produce a better fit to the whooping cough data than the uniform model, even restricting the distribution of \( Z_2 \) to the single-parameter NED. Generally speaking, the fit appears to be improved both by increasing the positive skewness and decreasing the range of the distribution of \( Z_2 \). The limit of these two operations, the simple model, still appears to give the best fit.

In the next section we consider a model in which both \( Z_2 \) and \( T_2 \) are exponentially distributed. For \( Z_2 \), this may be viewed as an extension of the sequence of positively skewed trapezium distributions, for which we have

\[ a_2 = a_1 = b_1, \quad b_2 = \infty, \]

and exponential, rather than linear, decay in the right-hand tail.
5.3: THE "EXPONENTIAL MODEL"

We assume now that both $Z_2$ and $T_2$ are exponentially distributed. Thus, as for the trapezium model, we have

$$F_1(t) = \begin{cases} 
0 & \text{if } t < 0, \\
-\frac{t}{\lambda} & \text{if } t \geq 0,
\end{cases} \quad (5.8)$$

for $\lambda > 0$, i.e. $T_2 \sim \text{NED}(1/\lambda)$.

It is obviously unreasonable to allow very small values for $Z_2$, so we introduce a location parameter $\delta > 0$ into the incubation period distribution, so that we have

$$F_2(z) = \begin{cases} 
0 & \text{if } z \leq \delta, \\
1 - e^{-\frac{(z-\delta)}{\gamma}} & \text{if } z > \delta,
\end{cases}$$

for $\gamma > 0$, i.e. $Z_2 - \delta \sim \text{NED}(1/\gamma)$.

Clearly, the value of $\delta$ represents the shortest permitted incubation period, and households for which we have recorded $s \leq \delta$

will be excluded from the data set to be analysed. As previously discussed for the simple model (see §4.2.3), such threshold parameters present problems for estimation, and we shall choose fixed values for $\delta$ which appear to be medically reasonable.

From (5.2), the density of $S = T_2 + Z_2$ may then be written

$$f_3(s) = \int_0^{s'} f_1(t)f_2(s-t)dt$$

where $s' = s - \delta$,

since $Z_2 > \delta \Rightarrow T_2 < s - \delta$. 
Substituting for $f_1(\cdot)$, $f_2(\cdot)$ this becomes

$$f_3(s) = \begin{cases} 
\frac{1}{\gamma - \lambda} \left( e^{-\frac{s'}{\gamma}} - e^{-\frac{s'}{\lambda}} \right) & \text{if } s > \delta, \\
0 & \text{if } s \leq \delta. 
\end{cases} \quad (5.9)$$

We are obviously assuming throughout the discussion that $\lambda$ and $\gamma$ are distinct: if $\lambda = \gamma$, then $S' \sim \text{GG}(\lambda,1,2)$ i.e. a Gamma distribution with scale parameter $\lambda$ and shape parameter 2.

5.3.1. The contributions to the likelihood.

The l.c.'s $L_{III}$ and $L_{IV}$ for uninfected contacts are again identical to those for previous models, where $F_1(\cdot)$ is given by (5.8).

For Type I contacts, from (5.9), we have

$$L_I = \frac{p_i}{\gamma - \lambda} \left( e^{-\frac{s'}{\gamma}} - e^{-\frac{s'}{\lambda}} \right),$$

and for Type II contacts

$$L_{II} = \begin{cases} 
p_i \int_0^{s'} f_1(t)f_2(s-t)dt & \text{if } u \geq s', \\
p_i \int_0^u f_1(t)f_2(s-t)dt + q_i \int_u^{s'} f_1(t)f_2(s-t)dt & \text{if } u < s'. 
\end{cases}$$

The expression for $L_{II}$ when $u \geq s'$ is clearly identical to $L_I$ for the untreated infected contacts, since we have $T_2 < s - \delta = s'$.

Thus $T_2 < u$, and the contact must have been infected before he was treated. Substituting for $f_1(\cdot)$ and $f_2(\cdot)$ when $u < s'$, we have

$$L_{II} = \left[ e^{-\frac{u}{A}} p_i \left( 1 - e^{-\frac{u}{A}} \right) + q_i \left( e^{-\frac{u}{A}} - e^{-\frac{s'}{A}} \right) \right].$$
The first and second derivatives of the l.c.'s may be found in Appendix C.

5.3.2. Fitting the exponential model.

In order to facilitate comparisons with previous models, values for \( \delta \) of 4.5 and 6.5 days would seem to be both convenient and reasonable. The exponential model may then be considered as intermediate between the trapezium and simple models. To explain this statement, we consider the case \( \delta = 6.5 \). In Table 5.2.4 we investigated trapezium models with \( a_2 = 6.5 \) which became progressively more positively skewed. We may consider the exponential model then as an extension of this sequence for which

\[
a_2 = a_1 = b_1 = 6.5, \quad b_2 = \infty,
\]

the decay between \( b_1 \) and \( b_2 \) being exponential, rather than linear. Then, as \( \gamma \to 0 \), we approach the simple model with \( \lambda = 6.5 \).

We have thus six parameters to be estimated:

\[ \beta_0, \beta_1, \beta_2, \beta_3, \] as defined for previous models;
\[ \lambda, \] the scale parameter of the distribution of \( T_2 \);
\[ \gamma, \] the scale parameter of the distribution of \( Z_2 \).

The iterative computer program ran smoothly for both values of \( \delta \), and the parameter estimates and maximised log-likelihoods are shown in Tables 5.3.1 and 5.3.2. Values of \( L_E \) and \( L_W \) for the simple model with the corresponding location parameters are also included for comparison. We see that for both values of \( \delta \), the exponential model produces further maximisation than the simple model when we restrict attention to \( T_2 \sim \text{NED}(1/\lambda) \). When \( \delta = 6.5 \) even the value \( L_W \) for the simple model with Weibull resistance time distribution is exceeded. The \{\hat{\beta}_j\} are meanwhile very similar to values obtained from previous fits.
5.3.3. The fit of the model and discussion

Since the \( \{ \hat{\beta}_j \} \) are so similar to previous estimates, we again assume that the fit of contact susceptibilities and treatment effects are adequate, as they were for the simple model. We compare the empirical d.f. of the \( \{ s^i \} \), \( F_n(t) \), with the fitted d.f. \( \hat{F}_3(t) \).

From (5.9) we obtain

\[
\hat{F}_3(s) = \int_0^s \hat{f}_3(t) dt = \int_0^s \frac{1}{\gamma - \lambda} \left[ e^{-(t/\lambda)} - e^{-(s/\gamma)} \right] dt
\]

\[
= 1 + \frac{\lambda e^{-s/\lambda} - \gamma e^{-s/\gamma}}{\gamma - \lambda},
\]

and thus

\[
\hat{F}_3(s) = \begin{cases} 
0 & \text{if } s \leq \delta, \\
1 + \frac{\lambda e^{-s/\lambda} - \gamma e^{-s/\gamma}}{\gamma - \lambda} & \text{if } s > \delta.
\end{cases}
\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>s.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_0 )</td>
<td>-0.384</td>
<td>0.323</td>
</tr>
<tr>
<td>( \beta_1 )</td>
<td>0.0098</td>
<td>0.0047</td>
</tr>
<tr>
<td>( \beta_2 )</td>
<td>-0.881</td>
<td>0.156</td>
</tr>
<tr>
<td>( \beta_3 )</td>
<td>-2.962</td>
<td>1.067</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>11.99</td>
<td>1.51</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>0.241</td>
<td>0.304</td>
</tr>
</tbody>
</table>

Exponential Model: \( L_E = -387.40 \)
Simple Model: \( L_E = -388.24 \)
\( L_W = -385.95 \)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>s.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_0 )</td>
<td>-0.454</td>
<td>0.322</td>
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<tr>
<td>( \beta_1 )</td>
<td>0.0093</td>
<td>0.0047</td>
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<tr>
<td>( \beta_2 )</td>
<td>-0.886</td>
<td>0.161</td>
</tr>
<tr>
<td>( \beta_3 )</td>
<td>-2.761</td>
<td>1.073</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>10.80</td>
<td>1.39</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>0.136</td>
<td>0.108</td>
</tr>
</tbody>
</table>

Exponential Model: \( L_E = -354.75 \)
Simple Model: \( L_E = -355.40 \)
\( L_W = -355.16 \)

Table 5.3.1: Exponential Model, \( \delta = 4.5 \)  
Table 5.3.2: Exponential Model, \( \delta = 6.5 \)
\( F_3(t) \) and \( F_n(t) \) are plotted together for \( \delta = 6.5 \) in Figure 5.4, and immediately, comparison with Figures 5.1 and 5.3 suggests an improvement in fit on the uniform and trapezium models for small values of \( s \). A non-significant \( \chi^2 \) value of 7.80 confirms this.

Thus the simple and exponential models both appear to fit the whooping cough data adequately, and if a "best" model is required the choice may be difficult. Since both have the same number of parameters to be estimated we cannot distinguish between them on these grounds. In fact, since the estimates of \( \gamma \) are small, the fits are virtually identical and the choice between models is probably unimportant. The simple model however may be more flexible when investigating new sets of data, as different resistance time distributions may be incorporated more easily.

5.4: THE "WEIBULL MODEL"

The models of previous sections which have displayed reasonable fits to the data have assumed the incubation period to be constant, or almost constant, between contacts. Medical texts infer that there is actually more variation in the distribution of \( Z_2 \) than these models suggest: for example K & K (1981) state that the incubation period of whooping cough is about 7 days, and that onset in most cases falls within 10 days. Christie (1980) quotes recorded periods of 3 to 21 days, although he sheds doubt on the validity of the more extreme values and infers that 5 to 12 days is a more usual outside range.

Thus it was decided to attempt to fit a model for which the distribution of \( Z_2 \) was fixed, based on medical information. After some searching, the Weibull distribution with scale parameter 8.5 and shape parameter 7.0 (abbreviated to Weib\((8.5,7.0)\)) was felt to
Fig 5.4: $F_n(t)$ and $\hat{F}_3(t)$ for Exponential Model, $\delta = 6.5$. 
be a suitable candidate. If \( Z_2 \sim \text{Weib}(8.5,7.0) \), then we have

\[
F_2(5) = 0.02, \quad F_2(12) = 1.00 \quad \text{and} \quad F_2(10) - F_2(7) = 0.73,
\]

all of which agree well with the observed information on whooping cough.

For the Weibull model we retain (i), (ii), (iv) and (v) from Assumptions 5, and assume further:

(a) \( q_i = \alpha p_i \).

(b) \( y_1 < \infty \), the same for all households.

(c) \( G(t) = \begin{cases} 0 & \text{if } t \leq 0, \\ 1 - e^{-\left(\frac{t}{\lambda}\right)^c} & \text{if } t > 0. \end{cases} \)

(d) \( Z_2 \sim \text{Weib}(8.5,7.0) \).

In (a) we specify the constant multiplier approach to treatment, previously used in Model A of Chapter 4. We assume in (b) that the length of the infectious period of whooping cough is both finite and constant over all index cases. Initially we shall regard \( y_1 \) as a parameter to be estimated.

In (c) and (d) we consider Weibull distributions for both the incubation periods \( \{Z_2\} \) and the resistance times \( \{T_2\} \). The parameters of the distribution of \( Z_2 \) are fixed, whereas those of \( T_2 \) require estimation. The distribution of \( T_2 \) is also right-censored at \( y_1 \), and

\[
F_1(t) = \frac{G(t)}{G(y_1)} = \begin{cases} 0 & t < 0, \\ 1 - e^{-\left(\frac{t}{\lambda}\right)^c} & 0 \leq t \leq y_1, \\ 1 - e^{-\left(\frac{y_1}{\lambda}\right)^c} & t > y_1. \end{cases}
\]

Then, from assumptions (c) and (d) above, the density of \( S = T_2 + Z_2 \) is given by
\[ f_3(s) = \int_0^s f_1(t)f_2(s-t)dt \]

\[ = \frac{7c}{\lambda^c(8.5)} \left[ \int_0^m \frac{t^{c-1}(s-t)^6\exp\left(-\frac{t^c}{\lambda}+\frac{(s-t)^7}{8.5}\right)}{1-e^{-\frac{t}{\lambda}}} \right] \]

where \( m = \min(s,y_1) \).

5.4.1. The contributions to the likelihood.

For Type I contacts, we have likelihood contributions of the form

\[ L_I = p_i f_3(s) \]

which, from (5.10), becomes

\[ L_I = \frac{7c p_i}{\lambda^c(8.5)} \left[ \int_0^m i(s,t)dt \right] \]

where \( i(s,t) = t^{c-1}(s-t)^6\exp\left(-\frac{t^c}{\lambda}+\frac{(s-t)^7}{8.5}\right) \),

and \( m \) is defined above.

\[ L_{II} \]

may be found by substituting expressions for \( f_1(\cdot) \) and \( f_2(\cdot) \) into (3.6), and we obtain

\[ L_{II} = \frac{7c p_i}{\lambda^c(8.5)} \left[ \int_0^m \left\{ \int_0^{u(s,t)+a} i(s,t)dt \right\} \right] \]

We note that this reduces to \( L_I \) if \( m \leq u \) i.e. if \( T_2 \leq y_1 \leq u \) (remember that we are assuming \( u < s \)).

As for all previous models, we have

\[ L_{III} = 1 - p_i \]
for untreated, uninfected contacts. Meanwhile for treated, uninfected contacts we have from (4.5)

\[ L_{IV} = 1 - p_i F_1(u) - \alpha p_i (1-F_1(u)) \]

which becomes

\[ L_{IV} = \begin{cases} 
1 - \frac{p_i}{1 - e^{-\frac{y_1}{\lambda}}} \left( 1 - e^{-\frac{u}{\lambda}} + \alpha \left( e^{-\frac{u}{\lambda}} - e^{-\frac{y_1}{\lambda}} \right) \right) & \text{if } u < y_1, \\
1 - p_i & \text{if } u \geq y_1.
\] 

The forms of \( L_{II} \) and \( L_{IV} \), when \( u \geq y_1 \), reflect the fact that treatment given to a contact after the end of the index' infectious period can have no effect.

First and second derivatives of the likelihood contributions were found, for use in the fitting process. However, their forms are rather cumbersome and of little interest, and are thus not reproduced in Appendix C.

5.4.2. Fitting the Weibull model.

Although the Weibull model can accommodate small values of \( S \) in the form of \( f_3(\cdot) \), it is clearly nevertheless undesirable to include such households in the data set to be analysed, since it is more likely that these families had two externally-infected primaries. Therefore households for which

\[ S \leq 4.5 \]

were excluded from the data sample before the fitting began. Unfortunately, this means that we have zero observed frequency, but positive density \( f_3(s) \), in this region, which will certainly not improve the fit of the model (see the comment on the choice of incubation period distribution at the end of this section).
Preliminary fits allowing \( y_1 \) to vary were unsuccessful. From §4.2.1 we recall that  \( \max\{s_i\} = 58 \), and this provides a lower limit for the value of parameter \( y_1 \). Since the likelihood is not differentiable with respect to \( y_1 \) at the end-point, the estimation procedure used is not suitable for this type of censoring parameter.

Therefore we fix

\[
y_1 = 58
\]

and wish to estimate the other six parameters of the model:

- \( \beta_0, \beta_1, \beta_2 \) as for the previous models,
- \( \lambda, c \) the scale and shape parameters of the Weibull resistance time distribution,
- \( \alpha \) the treatment parameter.

The form of the integrand \( i(s,t) \) in the l.c.'s, and its derivatives, required numerical integration techniques. Routines from the NAG library for Gauss-Legendre and Gauss-Laguerre quadrature were used. Since these made the computations for the iterative maximisation program rather lengthy, the likelihood surface was explored first with small numbers of abscissae for the numerical integration, to find a reasonable starting point. However, even during these preliminary investigations there were some computational problems. For example, the term

\[
\text{exp} - \left( \frac{s-t}{8.5} \right)^7
\]

becomes very small when the observed time \( s \) is "large" (>35 in our calculations), and the l.c.'s and derivatives from such observations had to be set to zero in order to avoid underflow on the computer.

Eventually, however, a suitable starting point was found, the number of abscissae in the numerical routines were increased, and the iterative procedure ran smoothly, if rather slowly. The estimates of the parameters and the maximised log-likelihood \( L_W \) are shown in Table 5.4.1.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_0$ (constant)</td>
<td>-0.427</td>
</tr>
<tr>
<td>$\beta_1$ (ill. length)</td>
<td>0.0094</td>
</tr>
<tr>
<td>$\beta_2$ (vaccination)</td>
<td>-0.872</td>
</tr>
<tr>
<td>$\alpha$ (treatment)</td>
<td>0.130</td>
</tr>
<tr>
<td>$\lambda$ (Weibull scale)</td>
<td>8.75</td>
</tr>
<tr>
<td>$c$ (Weibull shape)</td>
<td>0.689</td>
</tr>
</tbody>
</table>

$L_W = -400.46.$

Table 5.4.1. Parameter estimates from the Weibull model.

Comparison with parameter estimates from previous models reveals a marked similarity. However, the standard errors of these new estimates were not obtained. The sample information matrix looked very similar to that for the simple Model A (Chapter 4) with $\lambda = 4.5$, apart from the entries representing derivatives of the log-likelihood with respect to shape parameter $c$. Attempts to invert this matrix using a NAG routine specially designed for positive definite matrices (Cholesky's method) were unsuccessful, the routine reporting that the matrix was "not positive definite, possibly due to rounding errors". (The matrix was later successfully inverted using a NAG routine based on Crout's method, and was thus non-singular). The large amount of numerical integration involved in the calculation of the required second derivatives may indeed have contributed towards a problem with rounding errors. On the other hand, expressions for the derivatives involved were lengthy and tedious to obtain, and may have contained an error.
These possibilities were not pursued: the log-likelihood did not maximise as far as the simple Model A with \( \lambda = 4.5 \) (for which \( L_W = -387.27 \) with the same number of parameters) and, as discussed earlier in this section, the fit of the model is unlikely to be very good.

However, the above investigations into the Weibull model do indicate how quickly the computations required can become unwieldy, even when an appreciable number of simplifying assumptions are applied to the general model.

On reflection, the choice of distribution for \( Z_2 \) may well have been unwise: it would probably have been more reasonable to have assumed a fixed Weibull distribution with a location parameter (as in the exponential model). We should then also have avoided the unrealistic assumption of a negatively skewed incubation period distribution.

5.5: CONCLUDING REMARKS

In this chapter we have fitted some forms of the general model which allow variation in the lengths of incubation periods between contacts to the set of data for whooping cough. These models are seen to allow for uncertainty about whether or not preventive treatment was administered "in time" to Type II contacts.

We have encountered models which, although easy to apply, gave unsatisfactory fits to the data (the uniform and trapezium models) and one which was computationally inconvenient (the Weibull model). The trapezium model, however, provided some useful insights into possible distributions for \( Z_2 \). The exponential model appears to be the only model considered which gives a reasonable fit whilst
retaining practical simplicity.

The fitted exponential model would appear to fit the data as well as the simple models of Chapter 4, although it would be more difficult to use generally for investigations into different resistance time distributions. These "good" models allow little or no variation in the lengths of incubation periods, which is perhaps surprising in view of the available medical information. One possible explanation for this anomaly may be that the variation between incubation periods for a single outbreak of whooping cough over a small area is considerably less than that reported for a whole series of epidemics of the disease which are distant both geographically and in time.

It is worth mentioning that the models of this chapter were also fitted to the augmented data set considered in §4.6. The results and estimates obtained were very similar to those which we have reported for the single-contact households.
6.1: REMARKS ON THE WHOOPING COUGH MODELS

Amongst the models fitted to the whooping cough data in Chapters 4 and 5, two (the simple and exponential models) have demonstrated satisfactory fits. The following general conclusions would appear to be valid for both of these models.

(i) The models suggest the efficacy of the antibiotic erythromycin as a preventive measure: this confirms information found in medical texts (e.g. Christie, 1980) and more recently in Kwantes et al (1983). For simple Model A we have $\hat{\alpha} \ll 1$ and for other models $\hat{\beta}_3 \ll 0$: in §4.4.4 the two approaches to treatment were seen to indicate very similar effects for the range of fitted susceptibilities, and the fitted resistance time distributions (also important in determining the effectiveness of preventive treatment) are almost identical for the simple and exponential models.

(ii) The vaccination status of the contact appears to be an important factor in determining susceptibility to whooping cough, since $\hat{\beta}_2 \ll 0$. Recent medical work (for example, see Vesselinova-Jenkins et al, 1978; Miller et al, 1982) indicates that modern vaccines are effective, although earlier prophylactic agents for the disease had more checkered careers.

In §4.4.2. we showed that the linear vaccination effect which we sought appeared to be reasonable. In his investigation into attack rates on "fully immunized" and "not fully immunized" children, Noah (1976) uses a coarser binary measure of vaccination status, regarding children as fully immunized only if they have received at least three doses of vaccine (our scores 2 and 3).
The estimates of the effects of vaccination status \(\hat{\beta}_2\) and preventive treatment \(\hat{\beta}_3\) or \(\hat{\alpha}\) on the susceptibility of contacts seem to be largely unaffected by the distributions assumed for the contact incubation periods \(\{z_2\}\). This is fortunate, since the choice of "best" distribution on medical grounds is by no means clear! The models fitted suggest that the assumption of constant length incubation periods produces a good fit for this particular data set, and indeed this may well prove to be reasonable more generally when dealing with localised epidemics.

Other investigations remain to be carried out for the available whooping cough data. It would be interesting to examine some further distributions for \(Z_2\), possibly, for example, the Weibull distribution with a threshold parameter suggested in §5.4.2. Discretized forms of distributions for \(T_2\) may also be informative: estimated parameters of a discretized Weibull distribution could be compared with the \((\lambda, c)\) obtained in previous chapters. This may prove to be particularly useful as a means of dealing with the excess of observations for 7 days in the data set, and judicious pooling of these observations could affect some of the problems we have encountered. Bailey (1956b) considers a similar "smoothing" technique to deal with this same problem when he carries out goodness-of-fit tests on a model applied to a set of data for measles in families with two susceptibles.

Since the data set contains a number of records on families with two or three contacts, it may be possible to extend the model to deal with larger households in order to use more of the information available. However, as we found in §2.4, households for which the observed \(\{s_i\}\) are small will still yield little or no information about the effectiveness of preventive treatment.

At a more theoretical level it may be possible to examine analytically the shape of the likelihood function of the model. In Appendix B
we indicate the pragmatic approach taken to the problem of checking whether we have found local or global maxima of the log-likelihoods when fitting the models, but it may be possible to use the forms of the l.c.'s and their derivatives to investigate this more generally. For instance, Olsen (1978) shows for the "Tobit" model used in economics that the likelihood function is globally concave and, hence, has a unique maximum, and Burridge (1982) considers the unimodality properties of likelihoods derived from grouped data.

The precision of the m.l.e.'s from the model fitting could be assessed using jackknife techniques rather than the sample information matrix. Miller (1974) reviews jackknife results up to the early 1970's and in particular Brillinger (1964) indicates how the methods may be applied to set approximate confidence limits for m.l.e.'s. The more recent bootstrap technique first proposed by Efron (1979) might also be used to assess the precision of the m.l.e.'s. Parr (1983) demonstrates that the jackknife and bootstrap are asymptotically equivalent, and Buckland (1983) investigates Monte Carlo methods for confidence interval estimation using the bootstrap. Both techniques typically involve much computation, but have the advantage that the variation in the estimates is assessed for the particular sample size of interest, and does not depend on asymptotic theory. It would be interesting to compare these confidence intervals with those obtained from the standard errors.

We may be tempted to feel disappointed at the apparent success of the simple model in view of the effort expended on the more complicated models of Chapter 5. However, we should perhaps keep in mind the observations of Becker (1979a), who comments that if a simple model does provide an adequate fit to some epidemic data, then it could easily prove to be more useful than a detailed, complex model which also provides an adequate fit, since the simplicity may help to clarify the important characteristics of the spread of disease.
6.2: RELATIONSHIP WITH PREVIOUS MODELS

The very general form of the model proposed in Chapter 2 makes no assumptions about the distributions of the underlying time periods, but we may investigate relations between this and the well-established stochastic models by proposing suitable sets of simplifying conditions. Since little work has hitherto appeared on models allowing for intervening preventive treatment, in practice we would only consider the expressions for the untreated Type I and Type III contacts. Alternatively, it may be possible to use the rough analogies drawn below to investigate how intervening treatment might be incorporated into existing models.

The simple "continuous-infection" type model (Bailey, 1950) assumes a zero latent period and an infectious period which is effectively infinite, since no removals are considered. Thus we have for all individuals

\[ X = 0, \quad Y = \infty \]

and, since all susceptibles eventually become infected, this would be equivalent to considering only Type I contacts.

The general "continuous-infection" model again assumes a zero latent period, but now removal is assumed to occur as a Poisson process, thus we have

\[ X = 0, \quad Y \sim \text{NED}(\lambda). \]

If removal may be interpreted as the isolation of infectives on the appearance of their recognisable symptoms, then we also have

\[ Z \sim \text{NED}(\lambda), \quad \text{since} \quad Z = X + Y \]

but otherwise no assumptions about the distribution of incubation periods are made. The distribution of resistance times is not explicitly considered.
The models of Gough (1977) and Anderson & Watson (1980) both envisage the latent and infectious periods as being composed of a number of independent exponentially distributed stages. Assuming $k$ such stages, each distributed as $\text{NED}(\alpha)$, for the latent period, and $m$ stages, each distributed as $\text{NED}(\gamma)$, for the infectious period, Anderson & Watson effectively consider

$$X \sim \text{GG}(k\alpha, 1, k),$$
$$Y \sim \text{GG}(m\gamma, 1, m),$$

using the notation of §4.3. The Markovian continuous time model discussed by Becker (1979a) is a rather simpler variation on the same theme, since it implicitly assumes that the durations of both the latent and infectious periods have independent exponential distributions.

All these models incorporate a "contact rate" or "infection rate". Conventionally, this is regarded as a constant value, which we may interpret as being equivalent to the assumption of equal susceptibilities of contacts (see §3.4.1). However Gart (1968, 1972) considers models where the susceptibles are divided into two or more groups having different infection rates, and Gough (1977) considers more general variation in the infection rate by assuming that the probability of infection of a given susceptible by a given infective in a given infectious "stage" has a beta distribution. We might also consider preventive treatment as producing a modification of the infection rate.

The chain binomial models assume a latent period of constant length and very short infectious period, i.e.

$$X = c, \quad Y = \delta$$

where $c > 0$, and $\delta > 0$ is very small.

Thus the concept of resistance time and the time element of treatment effectiveness are measured in discrete time for this type
of model: either the susceptible becomes infected almost immediately, or he remains uninfected until the next generation of infectives appears.

The Greenwood, Reed-Frost and Becker (1981a) chain binomial models are equivalent for households of two considered in our model. All of them are based on a quantity $p$, which measures the chance of contact between a susceptible and an infective sufficient to produce a new infection. Early modelling attempts (Greenwood, 1931) regarded $p$ as a constant value, which may be viewed as equivalent to the assumption of constant susceptibility of all contacts. However, later developments (Bailey 1953b, 1956a) allowed $p$ to vary according to a beta distribution between households; clearly this is similar to allowing variation between contacts when we restrict attention to single-contact households.

It would also be interesting to fit chain binomial models where $p$ is viewed as a function of covariates: that this has not previously been attempted suggests that suitable data have not been available.

A modified chain binomial model (Bailey 1956b, 1956c, Bailey & Alff-Steinberger, 1970) involves variable latent periods and extended infectious periods. More specifically, we have

$$X \sim N(\mu, \sigma^2),$$
$$Y = \alpha,$$

and, in households of two, we have a censored exponential resistance time distribution i.e. using the notation of §2.1.5,

$$G(t) = \begin{cases} 
1 - e^{-\lambda t} & \text{if } t > 0, \\
0 & \text{if } t \leq 0, 
\end{cases}$$

and the density of resistance time $T_2$ is given by

$$f_1(t) = \begin{cases} 
\frac{\lambda e^{-\lambda t}}{1 - e^{-\lambda \alpha}} & \text{if } t \geq 0, \\
0 & \text{if } t < 0.
\end{cases}$$
Since the probability of cross-infection, $p$, is given by

$$ p = 1 - e^{-\lambda a}, $$

the early attempts at fitting this type of model essentially assume equal susceptibilities for all contacts. Bailey (1975, p.281) suggests that this condition may be relaxed by investigating the consequences of variation in the value of $\lambda$ i.e. variation in the infection rate.

Sugiyama (1961) proposes a chain binomial model which allows for infections from outside the household i.e. the double primary situation considered in §2.4. The probability $p$ of adequate contact between two specified household members, and the probability $\pi$ of an external infection, are regarded as constants, thus returning to the assumption of equal contact susceptibilities.

Gani (1969) and Gani & Jerwood (1971) consider how chain binomial models may be represented as Markov chains, and in particular they show how inoculation of remaining susceptibles, after an initial outbreak of infectiousness, may be represented. This may be regarded as being similar to our concept of preventive treatment. However, their definitions contain some ambiguities which are investigated further in §6.4.

Other, more empirical, models display some similarities to our model, either in the assumptions made about contact susceptibilities or the distributions assumed for the time periods. For example, the structured simulation model for immunization programs in communities developed by Elveback et al (1976) assumes that for every individual we have

$$ X = Z $$

(c.f. our assumption $\mu = 0$), the incubation period distribution remaining arbitrary. Contact susceptibility is allowed to vary among individuals and change in time in response to immunization (similar to our modification
from $p_1$ to $q_1$). The investigations of Becker (1979b, 1981b) into the "infectious potential" of infected individuals assumes arbitrary distributions for the latent and infectious periods, allows infectivity to vary over time, and caters for different susceptibilities. However, these models are unsuitable for small households.

The model of Farewell (1977) may be regarded as a forerunner of our general model. He considers an exponential distribution for $T$, and a logistic form for the susceptibility. He does not, however, consider the effects of preventive treatment, finite periods of infectiousness or different incubation and latent period distributions.

6.3: MODELLING OTHER INFECTIOUS DISEASES

It would obviously be interesting to apply our model to infectious diseases other than whooping cough. In particular, given suitable data for some specific disease, we might wish to compare results (parameter estimates, quantities of interest, etc) obtained using our model with those from other, "established", models. The infectious diseases which we may wish to investigate will be mainly either bacterial or virus infections. The characteristics of these two types of diseases are quite different, and will influence the particular assumptions to be imposed on the general model.

Burnet and White (1972) observe that the slope indicating the disappearance of infectiousness is on the whole much steeper for virus diseases than for bacterial infections, the virus diseases probably compensating by liberating more infectious material during their brief infectious period. Sartwell (1966) also concludes that the variation in the length of incubation periods is much less for virus diseases than for bacterial infections.
It is therefore not surprising that chain binomial models, which assume a constant incubation period and very short period of infectivity, have been fitted with some success to household data on measles, which is a virus disease (Greenwood, 1931; Bailey, 1953b, 1956a). Abbey (1952) also fits the Reed-Frost chain binomial model to outbreaks of two other virus diseases, rubella and chickenpox.

Our model may also be applied to virus infections such as these. The assumption

\[ Z = \xi, \]

\[ \xi > 0, \] as for the simple model of Chapter 4, would seem to be appropriate (for measles we may have \( \xi = 10; \) chickenpox \( \xi = 14; \) rubella \( \xi = 17 \)), and we might also propose a small constant value for \( Y_1 \) and an exponential distribution for \( T_2 \). The assumptions of constant or beta-distributed susceptibilities (§3.4.1, §3.4.2) would facilitate comparisons of results with previous chain binomial fits, whilst covariates for the logistic form might include vaccination status and age of the contact. Since all these diseases are recognised as being highly infectious, we would hope to obtain fitted susceptibilities \( \{ \hat{p}_i \} \) rather closer to 1 than those illustrated for whooping cough in Figure 4.7.

The assumptions which may be made about the distribution of the latent period \( X \) depend on how we define the symptoms of these diseases: all begin with a common cold-like catarrhal period, the typical rash and spots appearing one or two days later. The onset of infectiousness occurs during this prodromal period, hence if by "symptoms" we refer to these earlier signs of malaise, it would not be unreasonable to assume

\[ Z = X, \]

exactly as we did for whooping cough.
Influenza and the common cold are also virus diseases, and we might wish to model these in a similar manner ($Z = 2$ days). Attempts to explain the spread of these infections using various models have been made by Lidwell & Sommerville (1951), Heasman & Reid (1961), Sugiyama (1961), Hammond & Tyrrell (1971), Becker (1980, 1981a, 1981b) and Schenzle (1982), amongst others. In particular, the results from Longini & Koopman (1982) should perhaps cause us to be wary when applying a model for household spread of disease to influenza, since they infer that this particular virus probably spreads more easily in the community.

The high infectivity and short infectious period of these virus infections make our ability to deal with intervening preventive treatment of little interest. However, this facility may be rather more useful when dealing with bacterial infections, such as scarlet fever and, of course, whooping cough, when the period of infectiousness is more extended. Antibiotics such as penicillin and erythromycin are often administered as preventive measures, since they reduce the need for isolation in intimate household exposure. It would be interesting to see the model applied to such diseases, possibly using assumptions similar to those of Chapters 4 and 5, to test the effectiveness of new antibiotics.
6.4: The Chain Binomial Model and Inoculation

Markov chain methods were first applied to chain binomial models by Gani (1969), in order to obtain probabilities for the duration time and the total number of cases in an epidemic. The later development by Gani & Jerwood (1971) dealt with the effects on these quantities produced by inoculation of susceptibles, a rather similar notion to our concept of preventive treatment. The numerical results produced for the Greenwood chain binomial model looked interesting, and further investigations were suggested; in the course of these calculations an ambiguity in the model has become apparent.

6.4.1. Markov chain methods for the Greenwood model.

We consider an initial population (typically a household) of \( n \) susceptibles, of whom \( s_0 \) primaries \((1 \leq s_0 < n)\) become infective at time \( t = 0 \), thereby posing a threat to the \( r_0 \) susceptibles \((r_0 + s_0 = n)\). Taking the latent period of the disease as the discrete unit of time of the infection process, we define two random variables:

\[
S_t = \text{number of infected individuals just prior to time } t \text{ who become infectious at } t,
\]

\[
R_t = \text{number of susceptibles remaining just prior to time } t,
\]

for \( t = 0, 1, \ldots, n \).

If \( p \) is the probability of "adequate contact" between any two household members \((0 < p = 1-q < 1)\), then we have

\[
P(R_{t+1} = r_{t+1} | R_t, R_{t-1}, \ldots, R_0) = \frac{r_t!}{s_{t+1}!} \frac{r_{t+1}!}{r_t!} p^{r_{t+1}} q^{r_t},
\]

where \( s_{t+1} = r_t - r_{t+1} \),

and this clearly shows the Markovian nature of \( \{R_t\} \).
Then, if \( r_0 = k \), the transition probability matrix for the number of susceptibles may be shown to be

\[
\begin{bmatrix}
1 & 0 & 0 & \cdots & 0 \\
p & q & 0 & \cdots & 0 \\
p^2 & 2pq & q^2 & \cdots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
k & kp^k & q^{k-1} & (k) & p^{k-2} & q^2 & \cdots & q^k \\
\end{bmatrix}
\]

The process ends at time \( T \) when either \( R_T = R_T-1 \) (no infectives remain) or \( R_T = 0 \) (no susceptibles remain).

We write

\[
P = \begin{bmatrix}
0 & 0 & \cdots & \cdots & 0 \\
p & 0 & \cdots & \cdots & 0 \\
p^2 & 2pq & 0 & \cdots & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
k & kp^k & q^{k-1} & (k) & p^{k-2} & q^2 & \cdots & k & k & q & \cdots & q^k \\
\end{bmatrix}, \quad Q = \begin{bmatrix}
1 \\
q \\
q^2 \\
\vdots \\
k \\
\end{bmatrix}
\]

and \( M = [m_0, m_1, m_2, \ldots, m_k]^T \)

where \( m_{r0} \) = mean number of cases in the epidemic when there are \( r_0 \) initial susceptibles.

Then if

\[
X = \begin{bmatrix}
x_{10} \\
x_{20} \\
\vdots \\
x_{k0} \\
x_{k1} \\
\end{bmatrix} = P + P^2 + P^3 + \ldots + P^k
\]
we may obtain for this homogeneous case,

\[
M = \begin{bmatrix}
0 & 0 \\
2x_{20} & x_{21} \\
3x_{30} & 2x_{31} & x_{32} \\
\vdots & \vdots & \vdots \\
kx_{k0} & (k-1)x_{k1} & x_{k,k-1} & 0
\end{bmatrix}
\]

\[Q \] (6.1)

The expressions obtained are easy to check analytically for the cases \( k = 2 \) and \( k = 3 \).

We now consider an expression for the mean number of cases in an epidemic when remaining susceptibles are inoculated directly after an initial outbreak of infectiousness in the household: this is equivalent to preventive treatment being given to all susceptibles at the time of infection of the first household secondaries.

Gani & Jerwood (1971) consider inoculation as equivalent to an increase in \( q = P(\text{no contact with the infection}) \). This varies from \( q = q_0 \) at time \( t = 0 \), to some maximum value \( q_1 > q_0 \) after one latent period, and then there is a gradual decrease to \( q_\infty = q_0 \) again. To compare once more with our new model, the increase in \( q \) may be viewed as equivalent to our decrease in susceptibility caused by preventive treatment, although we have not considered the subsequent decline in effectiveness of the treatment.

Thus the Greenwood model is now characterised by a non-homogeneous Markov chain, for which Gani & Jerwood define

\[q_t = P(\text{no contact in } (t,t+1)), \] (6.2)

and matrices \( P \) and \( Q \) above are simply adjusted to \( P_t \) and \( Q_t \), obtained by substituting \( p_t \) and \( q_t \) for \( p \) and \( q \).
Then if we define
\[ R'_1 = P_0 = \{r'_{ij}(1)\}, \]
\[ R'_2 = P_0 P_1 = \{r'_{ij}(2)\}, \]
\[ \vdots \]
\[ R'_k = P_0 P_1 \ldots P_{k-1} = \{r'_{ij}(k)\}, \]
we obtain an expression for the vector of means:
\[
M^* = \begin{bmatrix}
  m^*_0 \\
  m^*_1 \\
  \vdots \\
  m^*_k
\end{bmatrix} = \begin{bmatrix}
  0 \\
  r'_{10}(i) & 0 \\
  2r'_{20}(i) & r'_{21}(i) & 0 \\
  \vdots \\
  kr'_{k0}(i) & (k-1)r'_{k1}(i) & \ldots & r'_{kk}(i) & 0
\end{bmatrix} \begin{bmatrix}
  1 \\
  q_i \\
  \vdots \\
  q_i
\end{bmatrix}
\]

which may be compared with the time-homogeneous result (6.1).

6.4.2. A comparison of results.

Gani and Jerwood present numerical results for the Greenwood model in which \( r'_0 = 20 \). They assume a gamma-type form for \( q_t \):
\[
q_t = q_0 + 2.71813(1-q_0)t e^{-t}, \quad t = 0, 1, 2, \ldots, 20,
\]
so that \( q_1 = 1 \), and inoculation is considered to provide almost total protection against disease during the interval (1,2).

Thus we fix \( k = 20 \). The mean number of cases was obtained, using (6.1) for the homogeneous untreated chain, for various values of \( q (\equiv q_0) \) between 0.01 and 0.99. The values obtained, shown in the second column of Table 6.1, are identical to those given by Gani and Jerwood, and they display the expected decline in the mean number of cases as the probability of no contact increases.
<table>
<thead>
<tr>
<th>$q_0$</th>
<th>No inoculation</th>
<th>With Inoculation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>our results</td>
<td>G&amp;J results</td>
</tr>
<tr>
<td>0.01</td>
<td>20.00</td>
<td>19.80</td>
</tr>
<tr>
<td>0.1</td>
<td>19.95</td>
<td>18.00</td>
</tr>
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<td>0.3</td>
<td>19.73</td>
<td>14.00</td>
</tr>
<tr>
<td>0.5</td>
<td>19.14</td>
<td>10.00</td>
</tr>
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<td>0.7</td>
<td>17.19</td>
<td>6.00</td>
</tr>
<tr>
<td>0.9</td>
<td>6.81</td>
<td>2.00</td>
</tr>
<tr>
<td>0.99</td>
<td>0.24</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Table 6.1: Mean number of cases

Calculations for the inoculated non-homogeneous chain were then carried out. Expression (6.4) for $q_t$ ($t = 0,1,\ldots,20$) was used to obtain $P_0, Q_0, \ldots, P_{20}, Q_{20}$, and the vector of means was then given by (6.3). The results for various values of $q_0$, shown in the third column of Table 6.1, were found to be very different from those originally quoted by Gani & Jerwood, which are reproduced for comparison in the fourth column.

The discrepancy is easily explained when one considers the definition of $q_t$ given in (6.2). We have

- $q_0 = P$(no contact in $(0,1)$),
- $q_1 = P$(no contact in $(1,2)$),
- etc.

However, the actual instant of infectiousness for the first generation of secondaries is at time $t = 1$, and it is not clear from the above definition whether we should consider $q_0$ or $q_1$ to be the appropriate probability of no contact at this time. Since $q_1 \approx 1$, whilst $q_0$ may be small, the vector of means may be considerably affected, and further calculations revealed that this ambiguity was in fact the cause of the different results obtained above.
If we assume that

\[ q_t = P(\text{no contact in } (t, t+1)), \] (6.5)

then we obtain the results of Gani & Jerwood, whereas the assumption

\[ q_t = P(\text{no contact in } [t, t+1)), \] (6.6)

yields our results. We note also that (6.6) suggests that, since 
\[ q_1 = 1, \] households will have only one generation of secondaries, so the mean number of cases is obtained directly as the binomial mean \( r_0 P_0 \). Incidentally, calculation of expression (6.3) with \( q_t \) given by (6.4), which is precisely the situation cited by Gani & Jerwood, yields our results and not those given in the original paper, and (6.6) is also intuitively more reasonable than (6.5) when the underlying continuous gamma curve is considered. For the simple cases \( k = 2, k = 3 \) the form of (6.3) may quite easily be verified analytically.

6.4.3. Some concluding comments.

We have seen above that some discrepancy in results may be explained by the ambiguity in (6.2), where the \( \{q_t\} \) are defined everywhere except for the discrete time points of interest. Gani & Jerwood also originally defined

\[ R_t = \text{number of susceptibles remaining at time } t. \]

This definition is difficult to interpret, since it is not clear whether or not the instantaneous infection at time \( t \) has taken place. In §6.4.1 we have therefore reverted to the standard chain binomial definition (see Bailey (1975), p.241), which supports the equation

\[ R_t = S_{t+1} + R_{t+1}. \]
These rather subjective interpretations of the quantities sometimes rather loosely defined by Gani & Jerwood make comparison of the two sets of results difficult, and underline the necessity for precise definition when formulating discrete time models for infectious diseases. If a more rigid framework were proposed, it would be interesting to consider different forms for $q_t$. The expression (6.4) effectively proposes a treatment which affords almost total protection against disease (since $q_1 \equiv 1$). One could also consider the theoretical effect on the mean number of cases of less effective treatments: for example, the relation

$$q_t = q_0 + \frac{2.71813}{2} (1-q_0) te^{-t}$$

yields a "half-effective" treatment, since $q_1 - q_0 = \frac{1}{2}(1-q_0)$. It may also be possible to represent treatments which attain their specified maximum effectiveness at different rates.
The data available were collected originally for a study into the effect of whooping cough vaccination on the severity and dissemination of the disease. This survey was carried out in general practice during the winter of 1979/80, after routine recording practices of the Royal College of General Practitioners indicated that a major epidemic of whooping cough was probable.

Sixty-eight general practitioners in the South-West Thames region participated, and the necessary bacteriological investigations were undertaken by the Public Health Laboratories at Tooting, Guildford and Epsom. Clinically-diagnosed whooping cough cases were bacteriologically confirmed whenever possible, especially in the milder cases of disease. Details of patient selection and medical surveillance, as well as the analyses and conclusions of this survey, are described in some detail in Grob et al (1981).

Each computer line of data records information about two individuals:

(i) the first child in the family with whooping cough, called the index,

(ii) a sibling of the index case, called the contact.

Fifteen lines from the data file are reproduced in Table A.

The following provides a key to the records:

**Columns 1-6**: an alphanumeric family code which identifies the particular household.

**Column 7**: the area code T, G or E, identifying the site of the bacteriological investigations.

**Columns 8-9**: a one- or two-letter doctor code which identifies the general practitioner.

**Columns 10-11**: a two-letter nurse code which identifies the nurse who visited the family during the period of surveillance.
COLUMN 13 : the social class of the family on the usual scale of 1 to 7.

COLUMN 18-19 : the age of the index at his/her last birthday, in years.

COLUMN 21 : the vaccination status of the index. The scale used was:

  0 for no vaccination,
  1 for partial vaccination (one or two injections),
  2 for full vaccination (three injections),
  3 for full vaccination with booster.

COLUMN 23 : medicinal treatment given to the index:

  0 indicates no treatment given,
  1 indicates the antibiotic erythromycin given.

COLUMNS 25-27 : the length of illness of the index, in days.

COLUMNS 29-30 : the maximum number of coughing spasms per day of the index.

COLUMNS 32-33 : the age of the contact and his/her last birthday, in years.

COLUMN 35 : the vaccination status of the contact, using the same scale as that of the index.

COLUMN 37 : previous record of whooping cough in the contact:

  0 indicates no previous record of whooping cough,
  1 indicates a contact who has previously suffered from whooping cough.

COLUMNS 39-40 : the number of days from the first appearance of symptoms in the index to preventive treatment being given to the contact, (default value 0 for untreated contacts).

COLUMNS 42-43 : the preventive treatment given to the contact:

  0 indicates no preventive treatment given,
  1 indicates the antibiotic erythromycin given.
COLUMN 45 : the whooping cough category for the contact:

  0 indicates no disease observed,
  1 indicates a bacteriologically confirmed case of disease.

COLUMNS 47-48 : the number of days from first appearance of symptoms in the index to first appearance of symptoms in the contact (default value 99 for uninfected contacts).

COLUMNS 50-52 : the length of illness of the contact, in days (default value -1).

COLUMNS 54-55 : the maximum number of coughing spasms per day of the contact (default value -1).

Thus any records containing identical information in columns 1 to 30 inclusive indicate that a given family index has more than one contact recorded.

The original data also contained "proximity indicators" for the index-contact pairs. The values of these indicators depended on whether the pairs slept in the same room, played together, etc. Since a number of the nurses misinterpreted the information which was required, these indicators were ignored.
<table>
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<tr>
<th>Code</th>
<th>8 2 1</th>
<th>35 6 11</th>
<th>2 0 26</th>
<th>1 0 99</th>
<th>-1</th>
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<td>1 0 99</td>
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<td>-1</td>
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<td>3 2 1</td>
<td>22 12 4</td>
<td>2 0</td>
<td>0 0 99</td>
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<td>-1</td>
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<tr>
<td>000002GSTGC 7</td>
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<td>85 12 11 3</td>
<td>0 76</td>
<td>1 0 99</td>
<td>-1</td>
<td>-1</td>
</tr>
</tbody>
</table>

**TABLE A**
When fitting a particular form of the general model, we obtain the likelihood contributions \( \{L_i\} \) of the contacts recorded in the data. Writing

\[
\lambda_i = \ln L_i,
\]

the overall log-likelihood for the data is then given by

\[
\lambda = \sum \lambda_i.
\]

The first and second derivatives of the \( \lambda \)'s reported in Appendix C may be combined to produce the derivatives of \( \lambda \) with respect to a parameter vector \( \theta \) using the relations

\[
\frac{d\lambda}{d\theta} = \sum \frac{1}{L_i} \frac{\partial L_i}{\partial \theta},
\]

\[
\frac{\partial^2 \lambda}{\partial \theta \partial \theta'} = \sum \left\{ \frac{1}{L_i} \frac{\partial^2 L_i}{\partial \theta \partial \theta'} - \frac{1}{L_i^2} \frac{\partial L_i}{\partial \theta} \frac{\partial L_i}{\partial \theta'} \right\}.
\]

For each particular model, a subroutine is written which returns this log-likelihood and its derivatives for the specific combination of parameters. This in turn is used to serve a program based on the DFP algorithm for function minimization (Fletcher and Powell, 1963) which was also used by Crowder and Grob (1975) to investigate a legit model for infectious diseases. The algorithm has been used successfully to find minima of general functions of large numbers of variables whose derivatives can be calculated quickly, and it has demonstrated acceptable speeds of convergence even when only poor approximations to the solution are known.

Thus, we choose to minimise \(-\lambda\). The procedure is split into two stages. The manual stage allows the parameters to be varied
individually, the log-likelihood and its gradients being returned each time. So using a grid of parameter values, the likelihood surface may be explored in order to find very rough approximations to the m.l.e.'s. We may also examine the surface for local and global minima. Investigations for the models fitted in Chapters 4 and 5 suggested that in all cases the global minima had been found, although this was not checked analytically. More generally, it may be possible to use an analytical approach similar to that of Olsen (1978) for the "Tobit" model (Tobin, 1958) in order to investigate whether the likelihood function has a single minimum.

The rough minimum from this manual fit is then used as a starting point for the iterative stage. Iterations cease when the gradients and step lengths are both less than a user-prescribed accuracy (values of $10^{-3}$ and $10^{-2}$ respectively were used in fitting the models of Chapters 4 and 5), and when at least $n$ (the number of parameters) iterations have been worked through. The sample information matrix is then calculated and inverted.

In earlier runs, the iterative stage was started with several initial trial parameter vectors, but each led to the same solution in every case. Convergence was generally smooth and fairly rapid, the solution being reached usually after about 15 iterations and 120 to 150 function evaluations.
APPENDIX C : DERIVATIVES OF THE
LIKELIHOOD CONTRIBUTIONS

Definitions
\[ p_i = [1 + \exp\left(-\Sigma_{j=0}^{2} x_i^* \beta_j \right)]^{-1}; \quad f_1(t) = \begin{cases} \frac{ct}{\lambda}e^{-\left(\frac{t}{\lambda}\right)^c} & t > 0; \\ 0 & t \leq 0. \end{cases} \]

\[ F_1(t) = 1 - e^{-\left(\frac{t}{\lambda}\right)^c}, \quad t > 0; \]

\[ p_{ij}^\prime = \frac{\partial p_i}{\partial \beta_j} = x_i^* p_i(1-p_i); \quad p_{ijk}^\prime = \frac{\partial^2 p_i}{\partial \beta_j \partial \beta_k} = x_i^* x_{ik}^* p_i(1-p_i)(1-2p_i); \]

\[ q_{ij}, q_{ijk}^{\prime\prime} \text{ as for } p_{ij}^\prime, p_{ijk}^\prime \text{ but substituting } q_i \text{ for } p_i. \]

\[ f_1(t) = \frac{\partial f_1(t)}{\partial \lambda} = \frac{c}{\lambda}\left(\frac{t}{\lambda}\right)^{c-1}f_1(t); \quad f_c(t) = \frac{\partial f_1(t)}{\partial c} = \frac{f_1(t)}{c}\left(1+c\log\left(\frac{t}{\lambda}\right)\right)\left(1-\left(\frac{t}{\lambda}\right)^c\right); \]

\[ f_2(t) = \frac{\partial^2 f_1(t)}{\partial \lambda^2} = \frac{-c}{\lambda^2}\left(\frac{t}{\lambda}\right)^{c-2}\left(c+1\right)\left(\frac{t}{\lambda}\right)^{c-1}f_1(t); \]

\[ f_{\lambda c}(t) = \frac{\partial^2 f_1(t)}{\partial \lambda \partial c} = \frac{1}{\lambda}\left[2+c\log\left(\frac{t}{\lambda}\right)\right]\left(\frac{t}{\lambda}\right)^{c-1}+c\log\left(\frac{t}{\lambda}\right)\left(\frac{t}{\lambda}\right)^{c-2+(-\left(\frac{t}{\lambda}\right)^c)\right]f_1(t); \]

\[ f_{cc}(t) = \frac{\partial^2 f_1(t)}{\partial c^2} = \frac{\log\left(\frac{t}{\lambda}\right)}{c}\left[\left(1-\left(\frac{t}{\lambda}\right)^c\right)\left(1+c\log\left(\frac{t}{\lambda}\right)\right)\right]f_1(t); \]

\[ F_{\lambda}(t) = \frac{\partial^2 f_1(t)}{\partial \lambda^2} = \frac{c}{\lambda^2}\left(c\left(1-\left(\frac{t}{\lambda}\right)^c\right)+1\right)f_1(t); \quad F_{\lambda c}(t) = \frac{\partial^2 f_1(t)}{\partial \lambda \partial c} = \frac{c}{\lambda\left[\log\left(\frac{t}{\lambda}\right)\right]}\left(\left(\frac{t}{\lambda}\right)^{c-1}\right) \quad \text{for } P^\prime = \left(\frac{t}{\lambda}\right)^{c-1}; \]

\[ F_{cc}(t) = \frac{\partial^2 f_1(t)}{\partial c^2} = \frac{c}{\lambda}\left[\log\left(\frac{t}{\lambda}\right)\right]f_1(t). \]

Chapter 4, Model A.

We have \( t = s - \lambda; \quad q_i = \alpha p_i \)

The first derivatives of the \( l.c.'s \) are:

\[ \frac{\partial L}{\partial \beta_j} = p_{ij}^\prime f_1(t), \quad j = 0, 1, 2; \quad \frac{\partial L}{\partial \lambda} = p_i f_\lambda(t); \quad \frac{\partial L}{\partial c} = p_i f_c(t); \quad \frac{\partial L}{\partial \alpha} = 0. \]
The second derivatives of the \(L_i\)'s are

\[
\frac{\partial^2 L_i}{\partial \beta_j \partial \beta_k} = p_{ijk}^L f_1(t), \quad j, k = 0, 1, 2; \quad \frac{\partial^2 L_i}{\partial \beta_j \partial \lambda} = p_{ij}^L f_\lambda(t); \quad \frac{\partial^2 L_i}{\partial \beta_j \partial c} = p_{ij}^L f_c(t); \quad \frac{\partial^2 L_i}{\partial \alpha} = p_i f_L(t).
\]

For \(t > \alpha\),

\[
\frac{\partial^2 L_i}{\partial \beta_j} = -p_{ij}^L, \quad j, k = 0, 1, 2; \quad \frac{\partial^2 L_i}{\partial \lambda} = \frac{\partial^2 L_i}{\partial c} = 0.
\]

\[
\frac{\partial^2 L_i}{\partial \lambda^2} = -p_{ij}^L \{\alpha + (1-\alpha) f_1(u)\}, \quad j, k = 0, 1, 2; \quad \frac{\partial^2 L_i}{\partial \alpha} = p_i (\alpha-1) f_\lambda(u); \quad \frac{\partial^2 L_i}{\partial c} = p_i (\alpha-1) f_c(u);
\]

\[
\frac{\partial^2 L_i}{\partial \alpha^2} = -p_i \{1 - f_1(u)\}.
\]

The second derivatives of the \(L_c\)'s are

\[
\frac{\partial^2 L_i}{\partial \beta_j \partial \beta_k} = p_{ijk}^L f_1(t), \quad j, k = 0, 1, 2; \quad \frac{\partial^2 L_i}{\partial \beta_j \partial \lambda} = p_{ij}^L f_\lambda(t); \quad \frac{\partial^2 L_i}{\partial \beta_j \partial c} = p_{ij}^L f_c(t);
\]

\[
\frac{\partial^2 L_i}{\partial \beta_j} = \frac{\partial^2 L_i}{\partial \lambda} = \frac{\partial^2 L_i}{\partial c} = 0.
\]

For \(t > \alpha\),

\[
\frac{\partial^2 L_i}{\partial \beta_j} = \frac{\partial^2 L_i}{\partial \lambda} = \frac{\partial^2 L_i}{\partial c} = 0.
\]

\[
\frac{\partial^2 L_i}{\partial \alpha} = p_i f_L(t); \quad \frac{\partial^2 L_i}{\partial \lambda^2} = \frac{\partial^2 L_i}{\partial c^2} = \frac{\partial^2 L_i}{\partial \alpha^2} = 0.
\]

\[
\frac{\partial^2 L_i}{\partial \beta_j \partial \beta_k} = -p_{ijk}^L, \quad j, k = 0, 1, 2; \quad \text{All other 2nd derivatives of } L_{\lambda,\alpha} \text{ are zero.}
\]
\[
\frac{\partial^2 L_{IV}}{\partial \beta_j \partial \beta_k} = -p''_{ijk} \{\alpha+(1-\alpha)F_1(u)\}, j,k=0,1,2; \quad \frac{\partial^2 L_{IV}}{\partial \beta_j \partial \lambda} = -(1-\alpha)p'_{ij}F_1(u); \quad \frac{\partial^2 L_{IV}}{\partial \beta_j \partial c} = -(1-\alpha)p'_{ij}F_c(u) - j=0,1,2.
\]

\[
\frac{\partial^2 L_{IV}}{\partial \beta_j \partial \alpha} = -p'_{ij}[1-F_1(u)].
\]

\[
\frac{\partial^2 L_{IV}}{\partial \alpha^2} = p_1(\alpha-1)F_\lambda(u); \quad \frac{\partial^2 L_{IV}}{\partial c^2} = p_1(\alpha-1)F_c(u); \quad \frac{\partial^2 L_{IV}}{\partial \lambda \partial c} = p_1(\alpha-1)F_\lambda(u).
\]

\[
\frac{\partial^2 L_{IV}}{\partial \alpha \partial \lambda} = p_1F_\lambda(u); \quad \frac{\partial^2 L_{IV}}{\partial \alpha \partial c} = p_1F_c(u); \quad \frac{\partial^2 L_{IV}}{\partial \lambda^2} = 0.
\]

Chapter 4, Model B.

We have \( q_i = \left[1+\exp\left(-\sum_{j=0}^{2} X_{ij}^* \beta_j + \beta_3\right)\right]^{-1}. \)

Derivatives of \( L_1, L_2 \) as for Model A (but substitute \( \beta_3 \) for \( \alpha \)).

The first derivatives of \( L_{II}, L_{IV} \) are:

\[
\frac{\partial L_{II}}{\partial \beta_j} = q_{ij}f_1(t), j=0,1,2; \quad \frac{\partial L_{II}}{\partial \beta_3} = q_{ij}f_3(t); \quad \frac{\partial L_{II}}{\partial \lambda} = q_{ij}f_\lambda(t); \quad \frac{\partial L_{II}}{\partial c} = q_{ij}f_c(t).
\]

\[
\frac{\partial L_{IV}}{\partial \beta_j} = -p_{ij}F_1(u) - q_{ij}(1-F_1(u)), j=0,1,2; \quad \frac{\partial L_{IV}}{\partial \beta_3} = -q_{ij}[1-F_1(u)]; \quad \frac{\partial L_{IV}}{\partial \lambda} = (q_i-p_i)F_\lambda(u);
\]

\[
\frac{\partial L_{IV}}{\partial c} = (q_i-p_i)F_c(u).
\]

and the second derivatives:

\[
\frac{\partial^2 L_{II}}{\partial \beta_j \partial \beta_k} = q_{ijk}f_1(t), j,k=0,1,2; \quad \frac{\partial^2 L_{II}}{\partial \beta_j \partial \lambda} = q_{ijk}f_\lambda(t); \quad \frac{\partial^2 L_{II}}{\partial \beta_j \partial c} = q_{ijk}f_c(t); \quad \frac{\partial^2 L_{II}}{\partial \beta_3 \partial \lambda} = q_{ij3}f_\lambda(t); \quad \frac{\partial^2 L_{II}}{\partial \beta_3 \partial c} = q_{ij3}f_c(t)
\]

\[
\frac{\partial^2 L_{II}}{\partial \beta_j \partial \lambda} = q_{ij}f_\lambda(t); \quad \frac{\partial^2 L_{II}}{\partial \beta_j \partial c} = q_{ij}f_c(t); \quad \frac{\partial^2 L_{II}}{\partial \lambda \partial c} = q_{ij}f_\lambda(t);
\]

\[
\frac{\partial^2 L_{II}}{\partial \lambda^2} = q_{ij}f_\lambda(t); \quad \frac{\partial^2 L_{II}}{\partial \lambda^2} = q_{ij}f_\lambda(t); \quad \frac{\partial^2 L_{II}}{\partial \lambda^2} = q_{ij}f_\lambda(t).
\]
\[ \frac{\partial^2 L_{IV}}{\partial \beta_j \partial \beta_k} = -p_{ij}^t F_1(u) - q_{ij}^t [1-F_1(u)], j=0,1,2; \quad \frac{\partial^2 L_{IV}}{\partial \beta_j \partial \lambda} = (q_{ij}^t - p_{ij}^t) F_\lambda(u) \]

\[ \frac{\partial^2 L_{IV}}{\partial \beta_j \partial c} = (q_{ij}^t - p_{ij}^t) F_c(u), \quad j=0,1,2. \]

\[ \frac{\partial^2 L_{IV}}{\partial \beta_j \partial \beta_3} = q_{i3}^t F_\lambda(u); \quad \frac{\partial^2 L_{IV}}{\partial \beta_j \partial \lambda} = q_{i3}^t F_c(u); \quad \frac{\partial^2 L_{IV}}{\partial \lambda^2} = (q_{ij}^t - p_{ij}^t) F_{\lambda\lambda}(u); \quad \frac{\partial^2 L_{IV}}{\partial c^2} = (q_{ij}^t - p_{ij}^t) F_{cc}(u); \]

\[ \frac{\partial^2 L_{IV}}{\partial \lambda \partial c} = (q_{ij}^t - p_{ij}^t) F_{\lambda c}(u). \]

Chapter 5, Uniform Model.

\( q_1 \) as for Model B.

Derivatives of \( L_{III} \) are as for Model A and of \( L_{IV} \) as for Model B (substitute \( \beta_3 \) for \( \alpha \) in Model A results).

The first derivatives of \( L_I, L_{II} \) are:

\[ L_I(s>b): \quad \frac{\partial L_I}{\partial \beta_j} = \frac{p_{ij}^t}{b-a} [F_1(s-a)-F_1(s-b)], j=0,1,2; \quad \frac{\partial L_I}{\partial \beta_3} = 0; \quad \frac{\partial L_I}{\partial \lambda} = \frac{p_i}{b-a} [F_\lambda(s-a)-F_\lambda(s-b)]; \]

\[ \frac{\partial L_I}{\partial c} = \frac{p_i}{b-a} [F_c(s-a)-F_c(s-b)]. \]

\[ L_I(s\leq b): \quad \frac{\partial L_I}{\partial \beta_j} = \frac{p_{ij}^t}{b-a} F_1(s-a), j=0,1,2; \quad \frac{\partial L_I}{\partial \beta_3} = 0; \quad \frac{\partial L_I}{\partial \lambda} = \frac{p_i}{b-a} F_\lambda(s-a); \quad \frac{\partial L_I}{\partial c} = \frac{p_i}{b-a} F_c(s-a). \]

\( L_{II}(s>b, u<s-b): \) as for \( L_I(s>b) \), but substitute \( q_i \) (and derivatives) for \( p_i \).

In addition: \( \frac{\partial L_{II}}{\partial \beta_j} = \frac{q_{ij}^t}{b-a} [F_1(s-a)-F_1(s-b)]. \)

\[ L_{II}(s>b, s-b\leq u<s-a): \quad \frac{\partial L_{II}}{\partial \beta_j} = \frac{p_{ij}^t}{b-a} [F_1(u)-F_1(s-b)] + \frac{q_{ij}^t}{b-a} [F_1(s-a)-F_1(u)], j=0,1,2. \]

\[ \frac{\partial L_{II}}{\partial \beta_3} = \frac{q_{i3}^t}{b-a} [F_1(s-a)-F_1(u)]; \quad \frac{\partial L_{II}}{\partial \lambda} = \frac{p_i}{b-a} [F_\lambda(u)-F_\lambda(s-b)] + \frac{q_i}{b-a} [F_\lambda(s-a)-F_\lambda(u)]; \]

\[ \frac{\partial L_{II}}{\partial c} = \frac{p_i}{b-a} [F_c(u)-F_c(s-b)] + \frac{q_i}{b-a} [F_c(s-a)-F_c(u)]. \]
\( L_{II}(s>b, u>s-a): \) as for \( L_{I}, \ s > b. \)

\[
L_{II}(s \leq b, s-b \leq u \leq s-a): \quad \frac{\partial^2 L_{II}}{\partial \beta_j \partial \beta_k} = \frac{p_{ij}}{b-a} F_1(u) + \frac{q_{ij}}{b-a} [F_1(s-a) - F_1(u)], \quad j, k = 0, 1, 2;
\]

\[
\frac{\partial^2 L_{II}}{\partial \beta_j} = \frac{q_{ij}}{b-a} [F_1(s-a) - F_1(u)]; \quad \frac{\partial^2 L_{II}}{\partial \alpha} = \frac{p_i}{b-a} F_\lambda(u) + \frac{q_i}{b-a} [F_\lambda(s-a) - F_\lambda(u)];
\]

\[
\frac{\partial^2 L_{II}}{\partial \alpha \partial c} = \frac{p_i}{b-a} F_c(u) + \frac{q_i}{b-a} [F_c(s-a) - F_c(u)];
\]

\( L_{II}(s \leq b, u \leq s-a): \) as for \( L_{I}, \ s \leq b. \)

and the second derivatives:

\[
L_{I}(s>b): \quad \frac{\partial^2 L_{I}}{\partial \beta_j \partial \beta_k} = \frac{p_{ijk}}{b-a} [F_1(s-a) - F_1(s-b)], \quad j, k = 0, 1, 2;
\]

\[
\frac{\partial^2 L_{I}}{\partial \beta_j \partial \alpha} = \frac{p_{ij}}{b-a} F_\lambda(s-a), \quad \frac{\partial^2 L_{I}}{\partial \beta_j} = \frac{q_{ij}}{b-a} [F_\lambda(s-a) - F_\lambda(s-b)];
\]

\[
\frac{\partial^2 L_{I}}{\partial \alpha \partial c} = \frac{p_i}{b-a} F_c(s-a); \quad \frac{\partial^2 L_{I}}{\partial \alpha \partial \alpha} = \frac{p_i}{b-a} F_{cc}(s-a) - F_{cc}(s-b).
\]
$L^{(s > b, u < s - a)}$: All non-zero second derivatives as for $L^{(s > b)}$, but replacing $p_i$ by $q_i$. In addition:

$$\frac{\partial^2 L^{(s > b, u < s - a)}}{\partial \beta_j \partial \beta_k} = \frac{q''_{ij}}{b-a} [F_1(s-a)-F_1(s-b)], \quad j=0,1,2; \quad \frac{\partial^2 L^{(s > b, u < s - a)}}{\partial \beta^2} = \frac{q''_{33}}{b-a} [F_1(s-a)-F_1(s-b)];$$

$$\frac{\partial^2 L^{(s > b, u < s - a)}}{\partial \beta_j \partial \lambda} = \frac{q_{ij}}{b-a} [F_\lambda(s-a)-F_\lambda(s-b)]; \quad \frac{\partial^2 L^{(s > b, u < s - a)}}{\partial \beta_j \partial c} = \frac{q_{ij}}{b-a} [F_c(s-a)-F_c(s-b)].$$

$L^{(s > b, s > a < u < s - a)}$: for $L^{(s > b)}$, $s > b$.

$$\frac{\partial^2 L^{(s > b, u < s - a)}}{\partial \beta_j \partial \beta_k} = \frac{p''_{ijk}}{b-a} F_1(u) + \frac{q''_{ijk}}{b-a} [F_1(s-a)-F_1(u)], \quad j,k=0,1,2;$$

$$\frac{\partial^2 L^{(s > b, u < s - a)}}{\partial \beta_j \partial \lambda} = \frac{p_{ij}}{b-a} [F_\lambda(s-a)-F_\lambda(s-b)] + \frac{q_{ij}}{b-a} [F_\lambda(s-a)-F_\lambda(u)]; \quad j=0,1,2; \quad \frac{\partial^2 L^{(s > b, u < s - a)}}{\partial \beta_j \partial c} = \frac{q_{ij}}{b-a} [F_\lambda(s-a)-F_\lambda(u)];$$

$$\frac{\partial^2 L^{(s > b, u < s - a)}}{\partial \beta_j \partial \alpha} = \frac{q_{ij}}{b-a} [F_c(s-a)-F_c(s-b)] + \frac{q_{ij}}{b-a} [F_c(s-a)-F_c(u)].$$

$L^{(s > b, s > a < u < s - a)}$: as for $L^{(s > b)}$, $s > b$. 

$$\frac{\partial^2 L^{(s > b, s > a < u < s - a)}}{\partial \beta_j \partial \beta_k} = \frac{q''_{ijk}}{b-a} F_1(u) + \frac{q''_{ijk}}{b-a} [F_1(s-a)-F_1(u)], \quad j,k=0,1,2;$$

$$\frac{\partial^2 L^{(s > b, s > a < u < s - a)}}{\partial \beta_j \partial \lambda} = \frac{p_{ij}}{b-a} [F_\lambda(s-a)-F_\lambda(s-b)] + \frac{q_{ij}}{b-a} [F_\lambda(s-a)-F_\lambda(u)]; \quad j=0,1,2; \quad \frac{\partial^2 L^{(s > b, s > a < u < s - a)}}{\partial \beta_j \partial c} = \frac{q_{ij}}{b-a} [F_\lambda(s-a)-F_\lambda(u)];$$

$$\frac{\partial^2 L^{(s > b, s > a < u < s - a)}}{\partial \beta_j \partial \alpha} = \frac{q_{ij}}{b-a} [F_c(s-a)-F_c(s-b)] + \frac{q_{ij}}{b-a} [F_c(s-a)-F_c(u)].$$
\[
\frac{\partial^2 L_{II}}{\partial \lambda^2} = \frac{p_i}{b-a} F_\lambda(u) + \frac{q_i}{b-a} [F_\lambda(s-a) - F_\lambda(u)]; \quad \frac{\partial^2 L_{II}}{\partial c^2} = \frac{p_i}{b-a} F_c(u) + \frac{q_i}{b-a} [F_c(s-a) - F_c(u)];
\]

\[
\frac{\partial^2 L_{II}}{\partial \lambda \partial c} = \frac{p_i}{b-a} F_\lambda(u) + \frac{q_i}{b-a} [F_\lambda(s-a) - F_\lambda(u)].
\]

\[L_{II}(s \leq b, u \geq s-a) \text{ as for } L_{I}, s \leq b.\]

Chapter 5, Trapezium Model.

\[q_i \text{ as for Model B.}\]

Derivatives of \( L_{III} \) are as for Model A and of \( L_{IV} \) as for Model B
(substitute \( \beta_3 \) for \( \alpha \) in Model A results).

\( f_1(\cdot) \) and \( F_1(\cdot) \) and derivatives as in definitions, but with constraint
\( c = 1. \)

\[
d_1 = \frac{(a_1 - a_2)(b_1 + b_2 - a_1 - a_2)}{2}, \quad d_2 = \frac{(a_1 - a_2)(b_2 - b_1)(b_1 + b_2 - a_1 - a_2)}{2}.
\]

The first derivatives of \( L_{I} \) are:

\[
\frac{\partial L_{I}}{\partial \beta_3} = 0 \text{ for all values of } s; \quad \frac{\partial L_{I}}{\partial \beta_j} = p_{ij} f_3(s), j = 0, 1, 2, \text{ where } f_3(s)
\]

is given by (5.7);

\[
\frac{\partial L_{I}}{\partial \lambda} = \frac{p_i \partial f_3(s)}{\partial \lambda} = \begin{cases}
-p_i [F_1(s-a_2) + \lambda F_\lambda(s-a_2)]/d_1, & \text{if } a_2 \leq s < a_1, \\
p_i [(F_1(s-a_1) - F_1(s-a_2)) + \lambda (F_\lambda(s-a_1) - F_\lambda(s-a_2))] / d_1, & \text{if } a_1 \leq s \leq b_1 \\
p_i [(b_2 - b_1)(F_1(s-a_1) - F_1(s-a_2)) + (a_1 - a_2) F_1(s-b_1)] / d_2, & \text{if } b_1 \leq s \leq b_2 \\
p_i [(b_2 - b_1)(F_\lambda(s-a_1) - F_\lambda(s-a_2)) + (a_1 - a_2) F_\lambda(s-b_1)] / d_2, & \text{if } s > b_2;
\end{cases}
\]
and the second derivatives of $L_I$:

$$\frac{\partial^2 L_I}{\partial \beta_j \partial \beta_k} = p_{ijk} f_3(s), \ j,k = 0,1,2 \text{ where } f_3(s) \text{ is given by (5.7)};$$

$$\frac{\partial^2 L_I}{\partial \beta_3 \partial \alpha} = \frac{\partial^2 L_I}{\partial \beta_3 \partial \alpha} = \frac{\partial^2 L_I}{\partial \beta_3^2} = 0;$$

$$\frac{\partial^2 L_I}{\partial \beta_j \partial \alpha} = p_{ij} \frac{\partial f_3(s)}{\partial \alpha}, \ j = 0,1,2 \text{ where } \frac{\partial f_3(s)}{\partial \alpha} \text{ is given in the expression for } \frac{\partial L_I}{\partial \alpha} \text{ above.}$$

$$\frac{\partial^2 L_I}{\partial \alpha^2} = p_i \frac{\partial f_3(s)}{\partial \alpha^2} = \begin{cases} -p_i \left[ 2F_\lambda(s-a_2) + \lambda F_\lambda(s-a_2) \right]/d_1, & \text{if } a_2 \leq s < a_1, \\
p_i \left[ 2 \{F_\lambda(s-a_1) - F_\lambda(s-a_2)\} + \lambda \{F_\lambda(s-a_1) - F_\lambda(s-a_2)\} \right]/d_1, & \text{if } a_1 \leq s \leq b_1, \\
p_i \left[ 2 \{(b_1-b_2)(F_\lambda(s-a_1) - F_\lambda(s-a_2)) + (a_1-a_2)F_\lambda(s-b_1)\} + \lambda \{(b_1-b_2)(F_\lambda(s-a_1) - F_\lambda(s-a_2)) + (a_1-a_2)F_\lambda(s-b_1)\} \right]/d_2, & \text{if } b_1 < s \leq b_2, \\
p_i \left[ 2 \{(b_2-b_1)(F_\lambda(s-a_1) - F_\lambda(s-a_2)) + (a_1-a_2)F_\lambda(s-b_1) - F_\lambda(s-b_2)\} + \lambda \{(b_2-b_1)(F_\lambda(s-a_1) - F_\lambda(s-a_2)) + (a_1-a_2)(F_\lambda(s-b_1) - F_\lambda(s-b_2))\} \right]/d_2, & \text{if } s > b_2. \\
\end{cases}$$

$L_{II}(s > b_2, u < s - b_2)$:

Derivatives as for $L_I$ (case $s > b_2$) above, replacing $p_i$ and derivatives by $q_i$ and derivatives, when non-zero. In addition, derivatives w.r.t. $\beta_3$ are:

$$\frac{\partial L_{II}}{\partial \beta_3} = q_{ij} f_3(s); \quad \frac{\partial^2 L_{II}}{\partial \beta_3 \partial \alpha} = q_{ijk} f_3(s), \ j,k = 0,1,2; \quad \frac{\partial^2 L_{II}}{\partial \alpha^2} = q_{ij} \frac{\partial f_3(s)}{\partial \alpha}$$

where $f_3(s)$ takes the form for $s > b_2$ in (5.7)
\[ \frac{\partial L_{II}}{\partial \beta_j} = [\lambda q_{ij}^1(b_2-b_1)\left(F_1(s-a_1)-F_1(s-a_2)\right) + \lambda(a_1-a_2)(q_{ij}^1-F_1(s-b_1)-p_{ij}^1F_1(s-b_2)) + (a_1-a_2)(b_2-s+u)(1-F_1(u))q_{ij}^1p_{ij}^1 - \lambda(a_1-a_2)(q_{ij}^1p_{ij}^1-F_1(u)])/d_2, \ j=0,1,2; \]

\[ \frac{\partial L_{II}}{\partial \beta_3} = q_{i3}^1[\lambda(b_2-b_1)\left(F_1(s-a_1)-F_1(s-a_2)\right) + \lambda(a_1-a_2)(F_1(s-b_1)-F_1(u)) + (a_1-a_2)(b_2-s+u)(1-F_1(u))]/d_2; \]

\[ \frac{\partial L_{II}}{\partial \lambda} = [\lambda q_{ij}^1(b_2-b_1)\left(F_1(s-a_1)-F_1(s-a_2)\right) + \lambda(a_1-a_2)(q_{ij}^1-F_1(s-b_1)-p_{ij}^1F_1(s-b_2)) - (a_1-a_2)(b_2-s+\lambda+u)q_{ij}^1p_{ij}^1-F_1(s-a_2)] + (a_1-a_2)(q_{ij}^1-F_1(s-b_1)-p_{ij}^1F_1(s-b_2)-(a_1-a_2)(q_{ij}^1p_{ij}^1-F_1(u)])/d_2; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_j \partial \beta_k} : \text{as } \frac{\partial L_{II}}{\partial \beta_j} , \text{ replacing } p_{ij}^1 \text{ by } p_{ijk}^1, \ q_{ij}^1 \text{ by } q_{ijk}^1, \ j, k = 0,1,2; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_j \partial \beta_3} : \text{as } \frac{\partial L_{II}}{\partial \beta_j} , \text{ replacing } q_{i3}^1 \text{ by } q_{ij3}^1, \ j = 0,1,2; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_j \partial \lambda} : \text{as } \frac{\partial L_{II}}{\partial \lambda} , \text{ replacing } q_{ij}^1 \text{ by } q_{ij}^1, \ p_{ij}^1 \text{ by } p_{ij}^1; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_3^2} : \text{as } \frac{\partial L_{II}}{\partial \beta_3} , \text{ replacing } q_{i3}^1 \text{ by } q_{i33}^1; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_3 \partial \lambda} = q_{i3}^1\left[(b_2-b_1)\left(F_1(s-a_1)-F_1(s-a_2)\right) + \lambda F_1(s-a_1)-\lambda F_1(s-a_2)] + (a_1-a_2)(F_1(s-b_1)-F_1(u)+\lambda F_1(s-b_1))-(a_1-a_2)(b_2-s+\lambda+u)F_1(u)])/d_2; \]

\[ \frac{\partial^2 L_{II}}{\partial \lambda^2} = [q_{ij}^1(b_2-b_1)\left(2(F_1(s-a_1)-F_1(s-a_2)) + \lambda F_1(s-a_1)-\lambda F_1(s-a_2)] + (a_1-a_2)(q_{ij}^1(2F_1(s-b_1)+\lambda F_1(s-b_1))-p_{ij}^1(2F_1(s-b_2)+\lambda F_1(s-b_2)) - (a_1-a_2)(q_{ij}^1p_{ij}^1\left(2F_1(u)+(b_2-s+\lambda+u)F_1(u)])/d_2; \]

\[ \frac{L_{II}}{(s-b_2,s-b_2<s-b_1)}: \]
\[ L_{II} (s > b_2, s - b_1 \leq \alpha \leq s - a_2) : \]

\[ \frac{\partial L_{II}}{\partial \beta_j} = \left[ \lambda q_{ij} (b_2 - b_1) (F_1(s-a_1) - F_1(s-a_2)) + \lambda p_{ij} (a_1 - a_2) (F_1(s-b_1) - F_1(s-b_2)) \right. \]
\[ + (a_1 - a_2) (b_2 - b_1) (q_{ij} - p_{ij} (1 - F_1(u))) / d_2 \]; \[ j = 0, 1, 2; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_3 \partial \lambda} = q_{ij} \left[ (b_2 - b_1) (F_1(s-a_1) - F_1(s-a_2)) + (a_1 - a_2) (b_2 - b_1) (1 - F_1(u)) \right] / d_2; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_j \partial \lambda} = \left[ \lambda q_{ij} (b_2 - b_1) (F_1(s-a_1) - F_1(s-a_2)) + \lambda p_{ij} (a_1 - a_2) (F_1(s-b_1) - F_1(s-b_2)) \right. \]
\[ + (a_1 - a_2) (b_2 - b_1) (q_{ij} - p_{ij} (1 - F_1(u))) / d_2 \]; \[ j = 0, 1, 2; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_k \partial \beta_3} = q_{ij} \left[ (b_2 - b_1) (F_1(s-a_1) - F_1(s-a_2)) + (a_1 - a_2) (b_2 - b_1) (1 - F_1(u)) \right] / d_2; \]

\[ \frac{\partial^2 L_{II}}{\partial \beta_3 \partial \beta_j} = \left[ \lambda q_{ij} (b_2 - b_1) (F_1(s-a_1) - F_1(s-a_2)) + \lambda p_{ij} (a_1 - a_2) (F_1(s-b_1) - F_1(s-b_2)) \right. \]
\[ + (a_1 - a_2) (b_2 - b_1) (q_{ij} - p_{ij} (1 - F_1(u))) / d_2 \]; \[ j = 0, 1, 2; \]

\[ \frac{\partial L_{II}}{\partial \beta_j} = \left[ \lambda q_{ij} (b_2 - b_1) (F_1(s-a_1) - F_1(s-a_2)) + \lambda p_{ij} (a_1 - a_2) (F_1(s-b_1) - F_1(s-b_2)) \right. \]
\[ + (p_{ij} - q_{ij} (b_2 - b_1) (a_2 - s + u) (1 - F_1(u)) - \lambda (p_{ij} - q_{ij} (b_2 - b_1) F_1(u))) / d_2, \]
\[ j = 0, 1, 2; \]

\[ \frac{\partial L_{II}}{\partial \beta_3} = q_{ij} \left[ (b_2 - b_1) (F_1(u) - F_1(s-a_2)) + (b_2 - b_1) (a_2 - s + u) (1 - F_1(u)) \right] / d_2; \]
\[
\frac{\partial L_{II}}{\partial \lambda} = \left[ \lambda p_i (a_1 - a_2) (F_\lambda (s-b_1) - F_\lambda (s-b_2)) + \lambda (b_2 - b_1) (p_i F_\lambda (s-a_1) - q_i F_\lambda (s-a_2)) \right. \\
- (p_i - q_i) (b_2 - b_1) (a_2 - s + u + \lambda) F_\lambda (u) + p_i (a_1 - a_2) (F_\lambda (s-b_1) - F_\lambda (s-b_2)) \\
+ (b_2 - b_1) (p_i F_\lambda (s-a_1) - q_i F_\lambda (s-a_2)) - (p_i - q_i) (b_2 - b_1) F_\lambda (u)] / d_2; \\
\]

\[
\frac{\partial^2 L_{II}}{\partial \beta_j \partial \lambda} = \frac{\partial^2 L_{II}}{\partial \beta_k \partial \lambda}, \frac{\partial^2 L_{II}}{\partial \beta_j \partial \lambda} = \frac{\partial^2 L_{II}}{\partial \beta_3^2} \text{ obtained from first derivatives using replacements as for case } (s-b_2 \leq s-b_1); \\
\]

\[
\frac{\partial^2 L_{II}}{\partial \beta_3 \partial \lambda} = q_i' (b_2 - b_1) [F_\lambda (u) - F_\lambda (s-a_2) - \lambda F_\lambda (s-a_2) + (a_2 - s + u + \lambda) F_\lambda (u)] / d_2; \\
\]

\[
\frac{\partial^2 L_{II}}{\partial \lambda^2} = \left[ p_i (a_1 - a_2) (2 (F_\lambda (s-b_1) - F_\lambda (s-b_2))) + \lambda (F_\lambda \lambda (s-b_1) - F_\lambda \lambda (s-b_2)) \right. \\
+ 2 (b_2 - b_1) (p_i F_\lambda (s-a_1) - q_i F_\lambda (s-a_2)) + (b_2 - b_1) (p_i F_\lambda \lambda (s-a_1) - q_i F_\lambda \lambda (s-a_2)) \\
- (p_i - q_i) (b_2 - b_1) (2 F_\lambda (u) + (a_2 - s + u + \lambda) F_\lambda \lambda (u))] / d_2. \\
\]

\[L_{II}(s>b_2, u>s-a_2) : \]

Derivatives as for \( L_I \) (case \( s>b_2 \)) above.

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\( q_i \) as for Model B.

Derivatives of \( L_{III} \) are as for Model A and of \( L_{IV} \) as for Model B (substitute \( \beta_3 \) for \( \alpha \) in Model A results).

\( f_1(\cdot) \) and \( F_1(\cdot) \) and derivatives as in definitions, but with constraint \( c = 1. \)

We write \( s_A = \frac{s(\gamma-\lambda)}{\gamma \lambda}, u_A = \frac{u(\gamma-\lambda)}{\gamma \lambda}, s' = s-\delta, \) and assume \( \gamma \neq \lambda. \)

\[
L_I : \frac{\partial L_I}{\partial \beta_j} = \frac{p_i' j (e^{-s'} - e^{-s' \gamma})}{(\gamma - \lambda)}, \quad j = 0, 1, 2; \quad \frac{\partial L_I}{\partial \beta_3} = 0; \\
\]

\[
\frac{\partial L_I}{\partial \lambda} = \frac{p_i}{(\gamma - \lambda)^2} \left[ e^{-s'} - \left( 1 + \frac{s' \gamma}{\lambda^2} - \frac{s' \gamma}{\lambda} \right) e^{-s' \gamma} \right]; \quad \frac{\partial L_I}{\partial \gamma} = \frac{p_i}{(\gamma - \lambda)^2} \left[ e^{-s'} (s' \gamma - s' \lambda - \gamma^2) + \gamma^2 e^{-s' \gamma} \right]. \\
\]
\[ \frac{\partial^2 L_1}{\partial \beta_j \partial \beta_k} = \frac{\partial''_{ij} (e^{-Y-e^\lambda})}{(Y-\lambda)} \ , \ j,k=0,1,2; \]
\[ \frac{\partial^2 L_1}{\partial \lambda \partial \beta_3} = \frac{\partial^2 L_1}{\partial \gamma \partial \beta_3} = \frac{\partial^2 L_1}{\partial \beta_3^2} = 0; \]
\[ \frac{\partial^2 L_1}{\partial \beta_j \partial \lambda} = \frac{p_i}{(Y-\lambda)^2} \left[ \frac{-s'}{Y} - \frac{1}{(1+s'/2e^\lambda)}e^{\lambda} \right] \]
\[ \frac{\partial^2 L_1}{\partial \beta_j \partial \gamma} = \frac{p_i}{(Y-\lambda)^2} \left[ e^{-Y}(s'y-s'y^2+2e^\lambda) \right] \]

\[ \frac{\partial^2 L_1}{\partial \lambda^2} = \frac{p_i}{(Y-\lambda)^2} \left[ \frac{-s'}{2(Y-\lambda)} - \frac{s'}{2(1+s^2/2e^\lambda)(Y-\lambda)} \right] \]
\[ \frac{\partial^2 L_1}{\partial \lambda \partial \gamma} = \frac{p_i}{(Y-\lambda)^3} \left[ e^{-Y}(s'-2s'y^2+2e^\lambda) \right] \]
\[ \frac{\partial^2 L_1}{\partial \gamma^2} = \frac{p_i}{(Y-\lambda)^3} \left[ -2Y_3e^\lambda + (Y-\lambda)e^{\lambda} (s'y-s'y^2+2e^\lambda) - 2s'y^2 - 2(Y-\lambda)(s'y-s'y^2+2e^\lambda) e^{\lambda} \right] \]

\[ \frac{\partial L_{II}}{\partial \beta_j} = \frac{e^{-Y}}{(Y-\lambda)} \left[ p_i (1-e^{-u_A}) + q_i (e^{-u_A-e^{-s_A}}) \right] \]
\[ \frac{\partial L_{II}}{\partial \beta_3} = \frac{e^{-Y}}{(Y-\lambda)} \left[ -u_A - -s_A \right] \]
\[ \frac{\partial L_{II}}{\partial \lambda} = \frac{e^{-Y}}{(Y-\lambda)^2} \left[ \frac{1}{2} (p_i (1-e^{-u_A}) + q_i (e^{-u_A-e^{-s_A}})) + \frac{1}{(Y-\lambda)^2} \left[ u(q_i - p_i) e^{-u_A - sq_i e^{-s_A}} \right] \right] \]
\[ \frac{\partial L_{II}}{\partial \gamma} = \frac{e^{-Y}}{(Y-\lambda)^2} \left[ (s'y-s'y^2+2e^\lambda) (p_i (1-e^{-u_A}) + q_i (e^{-u_A-e^{-s_A}})) + (Y-\lambda) (p_i - q_i) (u e^{-u_A + sq_i e^{-s_A}}) \right] \]
\[
\frac{\partial^2 L_{ij}}{\partial \beta_j \partial \beta_k} = \frac{e^{\gamma}}{(\gamma - \lambda)} \left[ p'_{ij} (1 - e^{-u_A}) + q'_{ij} (e^{-u_A} - s_A) \right], \quad j, k = 0, 1, 2;
\]

\[
\frac{\partial^2 L_{ij}}{\partial \beta_j \partial \gamma} = \frac{e^{\gamma}}{(\gamma - \lambda)} \left[ q''_{ij} (e^{-u_A} - s_A) \right];
\]

\[
\frac{\partial^2 L_{ij}}{\partial \beta_j \partial \beta_k} = \frac{e^{\gamma}}{(\gamma - \lambda)^2} \left[ q''_{ij} (e^{-u_A} - s_A) \right];
\]

\[
\frac{\partial^2 L_{ij}}{\partial \beta_j \partial \gamma} = \frac{e^{\gamma}}{(\gamma - \lambda)^2} \left[ \frac{1}{2} (s' \gamma - s' \lambda - \gamma) (p'_{ij} (1 - e^{-u_A}) + q'_{ij} (e^{-u_A} - s_A)) \right]
+ \frac{1}{(\gamma - \lambda)^2} \left[ u (q'_{ij} - p'_{ij}) e^{-u_A} - s_A \right] \right];
\]

\[
\frac{\partial^2 L_{ij}}{\partial \beta_j \partial \gamma} = \frac{e^{\gamma}}{(\gamma - \lambda)^2} \left[ (s' \gamma - s' \lambda - \gamma) (p'_{ij} (1 - e^{-u_A}) + q'_{ij} (e^{-u_A} - s_A)) \right]
+ \frac{1}{(\gamma - \lambda)^2} \left[ u (q'_{ij} - p'_{ij}) e^{-u_A} - s_A \right] \right];
\]

\[
\frac{\partial^2 L_{ij}}{\partial \beta \partial \beta_k} = \frac{e^{\gamma} q'_{ij}}{(\gamma - \lambda)^2} \left[ (1 - e^{-u_A}) + \frac{1}{2} (e^{-u_A} - s_A) \right];
\]

\[
\frac{\partial^2 L_{ij}}{\partial \beta_j \partial \beta_k} = \frac{e^{\gamma}}{(\gamma - \lambda)^2} \left[ q''_{ij} (e^{-u_A} - s_A) \right];
\]

\[
\frac{\partial^2 L_{ij}}{\partial \gamma \partial \beta_k} = \frac{e^{\gamma}}{2 (\gamma - \lambda)^2} \left[ s' \gamma - s' \lambda - \gamma \right] (e^{-u_A} - s_A) + (\gamma - \lambda) (se^{-u_A} - u_A) \right];
\]

\[
\frac{\partial^2 L_{ij}}{\partial \beta \partial \gamma} = \frac{e^{\gamma} q'_{ij}}{(\gamma - \lambda)^2} \left[ (1 - e^{-u_A}) + \frac{2}{(\gamma - \lambda)^2} \left[ u (q'_{ij} - p'_{ij}) e^{-u_A} - s_A \right] \right]
+ \frac{1}{(\gamma - \lambda)^4} \left[ u^2 (q'_{ij} - p'_{ij}) e^{-u_A} - s_A \right] \right];
\]
\[ \frac{\partial^2 L_{II}}{\partial \gamma^2} = \frac{e^2}{\gamma^2} \left( \gamma s' - s^2 \gamma + s^2 \gamma^2 \right) \{ p_i (1 - e^{-s^2 \gamma}) + q_i (e^{-s^2 \gamma} - e^{-s^2 \gamma^2}) \} \]

\[ + \frac{(\lambda^2 - s^2 \gamma + s^2 \gamma^2)}{(\gamma - \lambda)^2 \lambda^2} \{ u(p_i - q_i) e^{-u \lambda + s^2 \gamma} - e^{-u \lambda + s^2 \gamma^2} \} + \frac{1}{(\gamma - \lambda)^2 \lambda^2} \{ u^2 (p_i - q_i) e^{-u \lambda + s^2 \gamma} - e^{-u \lambda + s^2 \gamma^2} \}; \]

\[ \frac{\partial^2 L_{II}}{\partial \gamma^2} = \frac{e^2}{\gamma^2} \{ p_i (1 - e^{-u \lambda + s^2 \gamma}) + q_i (e^{-u \lambda + s^2 \gamma} - e^{-u \lambda + s^2 \gamma^2}) \} \}

\[ s'(s' - 2 \gamma)(\gamma - \lambda)^2 - 2 \gamma^2 (s' - 2 \gamma)(\gamma - s^2 \gamma^2) \}

\[ + \frac{s'}{(\gamma - \lambda)^2 \gamma} \{ (p_i - q_i) e^{-u \lambda + s^2 \gamma} - e^{-u \lambda + s^2 \gamma^2} \} \{ 2 s'(\gamma - \lambda) + 2 \gamma (\lambda - 2 \gamma) \}

\[ + \frac{s'}{(\gamma - \lambda)^2 \gamma} \{ -(p_i - q_i) u^2 e^{-u \lambda - s^2 \gamma} - e^{-u \lambda + s^2 \gamma} \}. \]
APPENDIX D: ASYMPTOTIC NORMALITY OF THE ESTIMATES

For any particular form of the model, the overall likelihood for the data set is constructed from the individual contributions $L_1, L_{II}, L_{III}$ and $L_{IV}$ pertaining to the four different types of contacts. Thus the observations on which the maximum likelihood estimates (m.l.e.'s) are based are independent, but not identically distributed (i.n.i.d.).

Asymptotic properties of the m.l.e.'s when the observations are independent identically distributed (i.i.d.) are well-established, the estimates being consistent and asymptotically normally distributed under some mild regularity conditions. However, Hoadley (1971) considers an i.n.i.d. case which in many ways is similar to ours, and he gives sets of conditions, implying consistency and asymptotic normality of the estimates, which may be applied to our l.c.'s. These conditions have been checked for the simple and exponential models, both of which have demonstrated reasonable fits to the data in Chapters 4 and 5. We therefore state the conditions below, and indicate where appropriate some details of the proof for the simple model. We use the following notation:

$$
\theta' = (\theta_0, \beta_1, \beta_2, \beta_3, \lambda, \epsilon),
$$

$$
g(s_i|\theta, u_i) = \begin{cases} 
L_{I1}(\theta) = p_i f_3(s_i), & \text{if } s_i < \infty, u_i \geq s_i - \epsilon, \\
L_{I2}(\theta) = q_i f_3(s_i), & \text{if } s_i < \infty, u_i < s_i - \epsilon, \\
L_{I3}(\theta) = 1 - p_i, & \text{if } s_i = \infty, u_i = \infty \\
L_{I4}(\theta) = 1 - p_i F_1(u_i) - q_i (1 - F_1(u_i)), & \text{if } s_i = \infty, u_i < \infty,
\end{cases}
$$

where $\epsilon = \text{constant length of incubation period (}>0, \text{ see } \S 4.1.2)$,
\[ p_i = \left(1 + \exp\left(-\sum_{n=0}^{2} \beta_n \right)\right)^{-1}, \]
\[ q_i = \left(1 + \exp\left(-\sum_{n=0}^{2} \beta_n - \beta_3 \right)\right)^{-1}, \]
\[ f_1(u_i) = \begin{cases} 
1 - e^{-\left(u_i / \lambda\right)^c} & u_i \geq 0, \\
0 & \text{elsewhere},
\end{cases} \]
\[ f_3(s_i) = \begin{cases} 
\frac{ct^c - e^{-\left(\frac{t_i}{\lambda}\right)^c}}{\lambda^c} & \text{if } t_i = s_i - \lambda > 0, \\
0 & \text{if } t_i = s_i - \lambda \leq 0.
\end{cases} \]

\( g(\cdot) \) is also clearly conditional on the covariates. We shall assume that the covariates are bounded, and have an empirical distribution function which converges to some distribution function. Similarly, we assume that the empirical distribution of the \( \{u_i\} \) tends to some distribution on \([0, \infty)\).

Thus \( \{L_{ij}\} \) (\( j = 1, 2, 3, 4 \)) represents the l.c.'s for the four types of contacts for the simple Model B of Chapter 4. \( f_3(s_i) \) represents the (shifted) Weibull density used to represent the time between the appearance of symptoms in the primary and secondary of household \( i \) (conditional on both being infected). We denote the log likelihood contributions by \( \{l_{ij}\} \), i.e. \( l_{ij} = \ln L_{ij}, j = 1, 2, 3, 4. \)

Conditions for Consistency.

C1: The parameter space is a closed subset of \( \mathbb{R}^6 \).

For our model, we may assume that the overall likelihood

\[ L = \prod_{i=1}^{n} g(s_i \mid \theta, u_i) \]

is maximised over a closed subset \( \Theta \) which may be defined by

\[ ||\beta_j|| \leq \Lambda, \quad j = 0, 1, 2, 3; \]
\[ \lambda \in [\varepsilon_1, M_1]; \]
\[ c \in [\varepsilon_2, M_2]; \]
for \( A, M_1, M_2 < \infty, \varepsilon_1, \varepsilon_2 > 0. \)

Also, the covariates may be regarded as being bounded (for the whooping cough data, all were non-negative, integer-valued). Therefore we can find \( K_1, K_2 \) independent of the covariate and parameter values such that
\[ 0 < K_1 \leq e^{-\|x_i\| \|\beta\|} \leq e^{-\frac{x_i'\beta \|x_i\|}{K_2}} \leq K_2 < \infty, \]
(this follows since \( (x'\beta)^2 \leq (\|x\| \|\beta\|)^2 \)).

Thus
\[ 0 < \frac{1}{1+K_2} \leq \frac{p_i}{1+K_1} < \frac{1}{1+K_1}, \tag{D1} \]
i.e. each individual's susceptibility is bounded uniformly away from 0 and 1.

C2: Each of the likelihood contributions is an upper semicontinuous function of \( \theta \).

Since all functions involved in the definition of \( g(\cdot) \) are continuous in \( \theta \), this condition is clearly satisfied.

C3': In order to satisfy Hoadley's condition C3', it is sufficient to show that, if \( \theta_0 \) is the true parameter vector, then the second moment of
\[ \sup \left\{ \frac{\text{ln} \left( \frac{g(s_i|\theta, u_i)}{g(s_i|\theta_0, u_i)} \right)}{\text{sup}} \right\} \]
evaluated at \( \theta_0 \), must be bounded \( \forall \theta \in \Theta \).

This in turn will be satisfied if we can show that
\[ R_{ij}(\Theta, \Theta_0) = \text{ln} \left( \frac{L_{ij}(\theta)}{L_{ij}(\theta_0)} \right) < K^* < \infty, \quad \forall \theta \in \Theta, j = 1, 2, 3, 4, \]
i.e. the ratio is finite and bounded for each of the \( \{L_{ij}\} \), since then the required expected values will also be finite and bounded.

We investigate this condition for each of the \( \ell.c.'s \) in turn. For Type III contacts \( (L_{i3}) \) the condition is satisfied immediately by result D1. For Type IV contacts \( (L_{i4}) \) we have

\[
R_{i4}(\theta, \theta_0) = \ln \left[ \frac{1-p_i F_1(u_i) - q_i (1-F_1(u_i))}{1-p_{i0} F_{01}(u_i) - q_{i0} (1-F_{01}(u_i))} \right],
\]

using an obvious notation for the value of \( L_{i4} \) at \( \theta_0 \). When \( p_i > q_i (\beta_3 < 0) \), then the numerator satisfies

\[
1-p_i F_1(u_i) - q_i (1-F_1(u_i)) \geq 1-p_i F_1(u_i) - p_i (1-F_1(u_i)) = 1-p_i \geq c_1 > 0,
\]

and

\[
1-p_i F_1(u_i) - q_i (1-F_1(u_i)) \leq 1-q_i F_1(u_i) - q_i (1-F_1(u_i)) = 1-q_i \leq c_2 < 1,
\]

since a similar result to D1 may be obtained for \( q_i \).

Similarly, the denominator may be shown to be bounded uniformly away from 0 and 1, and thus \( R_{i4}(\theta, \theta_0) \) is seen to be finite and bounded (a similar result can be proved for \( \beta_3 > 0 \)).

For \( L_{i1} \) and \( L_{i2} \) we are required to show the boundedness of integrals of the form

\[
\int_a^b |\&nt|^p t^q f(t) dt
\]

where \( p \) and \( q \) are bounded,

\[
0 \leq a < b \leq \infty,
\]

\( f(t) \) is the Weibull density function.

For \( a > 0 \) this is no problem, since

\[
|\&nt| < |\&na| < \infty \quad a < t < 1,
\]

and

\[
|\&nt| < t \quad t \geq 1,
\]

and all moments of the Weibull distribution exist. For the case \( a = 0 \) we may assume w.l.o.g. that \( b = 1 \), and we obtain
by substituting for the Weibull density and observing that $e^{-\frac{(\xi)^c}{\lambda}} \leq 1$.

Then using the transformations

$$y = \ln t,$$

$$x = -(q+c)y$$

in turn, we obtain

$$\int_0^1 \ln t \left| p_t q f(t) dt \leq \frac{c\Gamma(p+1)}{\lambda^c (q+c)^{p+1}},$$

which is finite and bounded by the definition of $\theta$ in $C_1$.

$C_4'$ relates to the unique maximisation of $L$ over $\theta$ for large sample size $n$.

$C_4'$ (i) requires that

$$\lim_{n \to \infty} n^{-1} \sum_{i=1}^n E_{\theta,0} \left[ \ln \left( \frac{g(S_i | \theta, u_i)}{g(S_i | \theta_0, u_i)} \right) \right] < 0, \quad \theta \neq \theta_0.$$

If the covariates are not collinear, then the model is identifiable; this follows essentially from the identifiability of the Weibull and logistic forms in the $\{L_{ij}\}$. Using this identifiability and a result of Wald (1949) it follows immediately that

$$E_{\theta,0} \left[ \ln \left( \frac{g(S_i | \theta, u_i)}{g(S_i | \theta_0, u_i)} \right) \right] < 0, \quad \theta \neq \theta_0.$$

$C_4'$ (i) is thus seen to be satisfied.

$C_4''$ (ii) requires that $r$ such that

$$\lim_{n \to \infty} n^{-1} \sum_{i=1}^n E_{\theta,0} \left[ \sup \left\{ \ln \left( \frac{g(S_i | \theta, u_i)}{g(S_i | \theta_0, u_i)} \right) : \|\theta\| > r \right\} \right] < 0.$$

Close examination of Hoadley's proof of consistency reveals that this condition is only required when $\theta$ is essentially unbounded. Since we have been able to propose a bounded parameter space in $C_1$, this condition is not necessary for our model.
C5: The \( \{ \xi_{ij} \} \) are measurable functions of \( \{ S_i \} \).

This is clearly satisfied.

**Conditions for Asymptotic Normality.**

N1: The true parameter value \( \theta_0 \) is an interior point of \( \Theta \).

Clearly, \( A, \varepsilon_1, \varepsilon_2, M_1, M_2 \) can be chosen to satisfy this condition.

N2: The estimates must be consistent.

This has been demonstrated by satisfying conditions C1-C5 above.

N3: \( \frac{\partial (\ln g(S_i | \theta, u_i))}{\partial \theta} \) and \( \frac{\partial^2 (\ln g(S_i | \theta, u_i))}{\partial \theta \partial \theta'} \) exist.

This condition is clearly satisfied, since the \( \frac{\partial \xi_{ij}}{\partial \theta} \) and \( \frac{\partial^2 \xi_{ij}}{\partial \theta \partial \theta'} \) exist, \( \forall j \); the derivatives of the \( \{ L_{ij} \} \) are given in Appendix C, and \( L_{ij} > 0, \forall i,j \).

N4: \( \frac{\partial^2 (\ln g(S_i | \theta, u_i))}{\partial \theta \partial \theta'} \) is a continuous function of \( \theta \).

Inspection of the \( \frac{\partial^2 \xi_{ij}}{\partial \theta \partial \theta'} \) shows that this is satisfied, \( \forall j \).

N5, N6: For these standard regularity conditions, it is sufficient to show that differentiation under the integral sign (twice for N6) is valid for the \( \{ \xi_{ij} \} \).

This condition is easily checked by elementary calculus.

N7: The mean sample information matrix, \( \Gamma_n' (\theta) \) must converge to some positive definite limit \( \Gamma (\theta) \).

To show that the mean converges, we may appeal to the strong law of large numbers. If we define

\[
\sigma_i^2 = \sigma_i^2 (x_i, u_i) = \text{Var} \left[ \frac{\partial^2 \xi_{ng(S_i | \theta, u_i)}}{\partial \theta \partial \theta'} \right]
\]

then by the Kolmogorov Criterion (see Feller, 1968, p.259), the convergence of the series...
is a sufficient condition for the strong law of large numbers to apply to the sequence \( \frac{\partial^2 \log(S_1|\theta, u_i)}{\partial \theta \partial \theta} \). In N9 we show that the \( \left\{ \frac{\partial^2 \log(S_1|\theta, u_i)}{\partial \theta \partial \theta} \right\} \) are bounded uniformly in \( \theta \), thus the variances \( \{\sigma_i^2\} \) must be finite and bounded, and the criterion is satisfied.

Thus for given \( x_i, u_i \), the limit matrix is a covariance matrix, since

\[
\text{Cov} \left( \frac{\partial^2 \log(S_1|\theta, u_i)}{\partial \theta \partial \theta_k}, \frac{\partial^2 \log(S_1|\theta, u_i)}{\partial \theta \partial \theta_l} \right) = \int \frac{3\partial \log(S_1|\theta, u_i)}{3\theta_k} \cdot \frac{3\partial \log(S_1|\theta, u_i)}{3\theta_l} \cdot g \, ds \\
= E \left( \frac{\partial^2 \log(S_1|\theta, u_i)}{\partial \theta_k \partial \theta_l} \right),
\]

by N5,N6 above, which is non-negative definite. Consequently \( \bar{F}(0) \) is also non-negative definite. In order to show that \( \bar{F}(\theta) \) is actually positive definite, and thus invertible, it will be necessary to impose some conditions on the covariates. Amemiya (1973) considers a similar situation, in which he places restrictions on the distributions of a set of covariates, in order to prove the consistency and asymptotic normality of the m.l.e.'s for the Tobin model. One of the conditions imposed in the discussion of C4 was that the covariates should not be collinear. This implies that

\[
\lim_{n \to \infty} \frac{1}{n} \sum_{i=1}^{n} x_1 x_i' = \Sigma
\]

must be positive definite, precisely the same condition as Amemiya's Assumption 3. We conjecture that this is a sufficient condition for the positive definiteness of \( \bar{F}(\theta) \).

N8': \( E \left| \frac{\partial^2 \log(S_1|\theta_0, u_i)}{\partial \theta_k \partial \theta_l} \right|^3 \leq K^*, \text{ for } \theta_k = \theta_0, \ldots, c. \)
Therefore we need to show that the $\frac{\partial^3 \theta_1}{\partial \theta^3}$ have bounded expectation $V_j$. (Hoadley takes the expectations at $\theta_0$, although our bounds will apply everywhere in $\theta$). We need to check that the following are all bounded:

1. $\int_0^1 p_{i1} f_3(y) dy$;  
2. $\int_0^\infty p_{i1} f_3(y) dy$;  
3. $\int_0^1 q_{i1} f_3(y) dy$;  
4. $\int_0^\infty (1-p_i) dy$;  
5. $\frac{3\theta_{i1}}{\partial \theta} \{1-p_{i1}F_1(u_i)-q_{i1}(1-F_1(u_i))\}$.

(a)-(e) are easily seen to be bounded for the derivatives w.r.t. the $\{\beta_k\}$: the expressions obtained involve the covariates, $p_i$, $q_i$ and $F_1(u_i)$, all of which we have seen previously to be bounded.

Considering the derivatives w.r.t. $\lambda$, then for expressions (a), (b) and (c) we require that

$$\int_a^b p_{i1} f_3(y) dy$$

be bounded, where $0 \leq a < b \leq \infty$, and $f_3(y)$ is the Weibull density function. Thus the integral reduces to finite moments of the Weibull distribution, which are bounded. For (d), the derivative w.r.t. $\lambda$ yields zero, whilst (e) gives

$$\frac{(u_i \lambda)^3 \left[c|p_i-q_i|\right]^3}{\left[1-p_{i1}F_1(u_i)-q_{i1}(1-F_1(u_i))\right]^2},$$

which is easily seen to be bounded. (See C3' for bounds away from 0 and 1 on the denominator).

When we consider the derivatives w.r.t. $c$, for expressions (a), (b) and (c) we require that integrals of the form

$$\int_a^b \frac{\partial}{\partial c} p_{i1} f_3(y) dy$$
be bounded, where $0 \leq a < b \leq \infty$, and we have already shown this for condition C3'. For (d), the required derivative is again zero, and for (e) we obtain

$$
\frac{|p_i - q_i|^3 \exp\left(\frac{u_i}{\lambda}\right) \frac{3}{\lambda} \{1 - F_i(u_i)\}^3}{\{1 - p_i F_i(u_i) - q_i (1 - F_i(u_i))\}^2}
$$

which again is easily seen to be bounded.

**N9:** We require a bound (uniform in $\theta$) for each of the second derivatives

$$
\left\{ \frac{\partial^2 \log(S_i(\theta, u_i))}{\partial \theta^2} \right\}
$$

near $\theta_0$, which has a finite and bounded $(1+\delta)$th moment.

We consider first the l.c. $L_{i1}(\theta) = p_i f_3(s_i)$. Many of the required second derivatives of $L_{i1}$ are simply functions of $p_i$ and the covariates, or are zero, and hence boundedness follows immediately. Three exceptions are:

(i) \[ \frac{\partial^2 L_{i1}}{\partial \theta^2} \leq a_1 + a_2 t_i^3, \]

(ii) \[ \frac{\partial^2 L_{i1}}{\partial c^2} \leq b_1 + b_2 t_i^3 |\log t_i| b_4, \]

(iii) \[ \frac{\partial^2 L_{i1}}{\partial \theta \partial c} \leq d_1 + d_2 t_i^3 + d_4 |\log t_i| t_i^5, \]

where $t_i = s_i - \lambda$ as before, and \{a_i\},\{b_i\},\{d_i\} are finite constants.

The expectations of these bounds can clearly be shown to be finite and bounded by the technique employed for integrals of the form

$$
\int_a^b |\log t|^q t^p f(t) dt
$$

considered in C3'.

Boundedness of the \[ \left\{ \frac{\partial^2 L_{i2}}{\partial \theta^2} \right\} \] follows in a very similar fashion.
The \( \frac{\partial^2 \kappa_{i3}}{\partial \theta \partial \theta'} \) are all zero, or functions of \( p_i \) and the covariates, and so are immediately bounded.

The \( \frac{\partial^2 \kappa_{i4}}{\partial \theta \partial \theta'} \) are all functions of the covariates, \( p_i, q_i, \lambda, c \) and \( \{u_i\} \), and all have denominator

\[
(1-p_i F_i(u_i)-q_i(1-F_i(u_i)))^2
\]

which we have shown to be bounded away from 0 and 1 in C3'. Although some of the expressions appear complicated initially, the boundedness follows easily from the definition of \( \Theta \) in C1 and the bounds on the covariates and \( \{u_i\} \).

Thus N9 is satisfied for the simple model.

Conditions for the exponential model.

For the exponential model, we can proceed in a similar manner, defining

\[
\begin{align*}
\theta^* &= (\beta_0, \beta_1, \beta_2, \beta_3, \lambda, \gamma) \\
L_{i1}(\theta^*) &= \begin{cases} 
  p_i f_3(s_i) & \text{if } s_i < \infty, u_i \geq s-\delta, \gamma \neq \lambda \\
  p_i f_3(s_i) & \text{if } s_i < \infty, u_i \geq s-\delta, \gamma = \lambda 
\end{cases} \\
L_{i2}(\theta^*) &= \begin{cases} 
  \frac{-\tau_i}{\gamma} & \text{if } s_i < \infty, u_i < s-\delta, \gamma \neq \lambda, \\
  \frac{-\tau_i}{\lambda} & \text{if } s_i < \infty, u_i < s-\delta, \gamma = \lambda 
\end{cases} \\
L_{i3}(\theta^*) &= t_i = s_i - \delta \quad (\delta > 0; \text{see } \S 5.3), \\
L_{i4}(\theta^*) &= (1-p_i F_i(u_i) - q_i(1-F_i(u_i))) \quad \text{if } s_i = \infty, u_i < \infty,
\end{align*}
\]

where \( p_i \) and \( q_i \) are as defined for the simple model,
\[ f_3(s_i) = \begin{cases} \frac{1}{\gamma \lambda} \left( e^{-\frac{t_i}{\gamma}} - e^{-\frac{t_i}{\lambda}} \right) & \text{if } t_i = s_i - \delta > 0 \\ 0 & \text{if } t_i = s_i - \delta \leq 0, \end{cases} \]

\[ f_3^*(s_i) = \begin{cases} \frac{t_i e^{-\frac{t_i}{\lambda}}}{\lambda^2} & \text{if } t_i = s_i - \delta > 0, \\ 0 & \text{if } t_i = s_i - \delta \leq 0, \end{cases} \]

\[ F_1(u_i) = \begin{cases} 1 - e^{-\frac{u_i}{\lambda}} & \text{if } u_i \geq 0, \\ 0 & \text{elsewhere}. \end{cases} \]

The \{L_{ij}^*\} represent the \(c.l.c.'s\) for the four types of contacts for the exponential model of Chapter 5. The alternative forms of \(L_{i1}^*\) and \(L_{i2}^*\) accommodate the cases \(\gamma \neq \lambda\) and \(\gamma = \lambda\).

The proof of Hoadley's conditions follows very much as for the simple model above, but appealing to the finite moments of the gamma, rather than Weibull, distribution where appropriate. When checking some of the conditions for \(L_{i1}^*, L_{i2}^* (\gamma \neq \lambda)\), we need first to impose the constraint

\[ |\gamma - \lambda| > \epsilon \]

for some \(\epsilon > 0\), the case \(\gamma = \lambda\) being dealt with separately. Obviously

\[ L_{i3}^* = L_{i3}, \quad \text{and} \quad L_{i4}^* = L_{i4}\big|_{c=1}, \]

so these \(c.l.c.'s\) have already been shown to satisfy the conditions.


Gart, J.J. (1968). The mathematical analysis of an epidemic with
two kinds of susceptibles. Biometrics, 24, 557-566.

Gart, J.J. (1972). The statistical analysis of chain-binomial
epidemic models with several kinds of susceptibles. Biometrics,
28, 921-930.

Biometrika, 64, 559-565.


Greenwood, M. (1949). The infectiousness of measles. Biometrika,
36, 1-8.

Griffiths, D.A. (1973a). Maximum likelihood estimation for the beta-
binomial distribution and an application to the household distribution
of the total number of cases of a disease. Biometrics, 29, 637-648.

Griffiths, D.A. (1973b). The effect of measles vaccination on the
incidence of measles in the community. J.R. Statist. Soc. A,
136, 441-449.

on severity and dissemination of whooping cough. Brit. Med. J.,
282, 1925-1928.

common-cold epidemics on Tristan da Cunha. J. Hyg. Camb.,
69, 423-433.


The paper entitled "An Analysis of Resistance Times to Infection under Treatment" by Hilary Kimber and Martin Crowder, published in Statistics in Medicine (1984), Volume 3, No.2 (165-171), is based on the work which appears in Chapter 4 of this thesis.