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Abstract

Detailed individual data are used to estimate the number of infectious contacts in the population due to an outbreak of smallpox. The data is known due to a contact tracing conducted during the epidemic. This gives individual data on date of probable infection and different stages in the disease.
We have fitted different distributions to the observed times spent in different states of the infection process. The states considered are incubation and period with fever until rash.
We have also considered if there is any difference in infectiousness during the prodromal compared with the rash period.
Estimations are made in respect to community, household and hospital based spread of infection.
The major finding is that many estimates are very dependent of population structure, making comparisons with other studies cumbersome.

KEY WORDS: Smallpox, Variola, vaccination, epidemic model.

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Abstract

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We have fitted different distributions to the observed times spent in different states of the infection process. The states considered are incubation and period with fever until rash.
We have also considered if there is any difference in infectiousness during the prodromal compared with the rash period.
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1 Introduction

This paper describes the analysis of data from the last outbreak of smallpox in Sweden, which occurred during the summer and autumn of 1963. Models for epidemic spread are developed which take households and hospitals into account since most of the spread during the outbreak was concentrated here. We have aimed specifically at two questions:

- How big are the number of infectious contacts per time unit at different locations, i.e. within community, households and hospitals?
- How do the different assumptions of the length of the infectious period fit the data?

Even for a "well known" disease as smallpox there exist many open questions. How infectious are individuals before the onset of rash, is there variability in infectiousness during the rash period? For the Stockholm outbreak we possess individual data from the outbreak concerning probable dates of infection, onset of fever, onset of rash etc. Apart from this it is also known how many were not infected in the cases families and hospital wards if they were hospitalized.

These data are applied into an epidemic model taking hospital and household setting into account. The hypothesis of interest is whether there are differences in infectiousness between the prodromal and the rash period. Also to

calculate the number of infectious contacts at different settings of infection.

We have taken the approach of calculating the infection pressure on individuals in the population. The model takes individual dates for infection into account and calculates the total force of infection experienced by the non infected in the population.

Our population structure shows a great difference in R_0 if we assume a homogeneous population or a heterogeneous mixing assumption. This also means that R_0 is a very unclear measure without a definite meaning. This makes comparisons with other studies very difficult.

The second part concerns time spent in different disease states, which is analyzed separate to the first epidemic model. We use available data from cases and compare these under different distributions, showing that assuming an exponential distribution does not fit the data very well, neither does a period of constant length.

2 Materials and methods

2.1 General description of the epidemic

The outbreak was initiated by a Swedish seaman who flew home from Australia via New Zealand, Singapore, India, Pakistan, Iran, Switzerland, Germany and Denmark. At that time there were smallpox outbreaks in India and Pakistan, and it is probable that this individual was infected in one of these two countries. This is the first documented case of transmission of smallpox during an airport transfer.

The seaman had previously been vaccinated against smallpox. Two weeks after arrival in Stockholm, he developed fever followed by reddish rashes. Since he thought it was acne, he did not seek a physician and stayed at home instead. There he was taken care of by his 80 year old grandmother who two weeks later became ill with similar symptoms and was suspected to have chickenpox. A third family member later also became ill. Later on the grandmother was transfered to a hospital where she infected other people.

A community nurse visited the grandmother on a daily basis became infected and later also infected her family.

It took one month before the first diagnosis of smallpox was made at Danderyds sjukhus.

The major part of the outbreak was concentrated in three families and three different hospitals. The spread within hospitals was due to incorrect diagnosis. The probably infected persons were not isolated but were under observation in large dormitories where nurses went around and observed the patients. After smallpox was diagnosed the patients were isolated.

A total of 27 persons were infected, and four of these died. Three of the 27 had not been vaccinated prior to the epidemic, two of these died. With vaccination we mean that the individual has been vaccinated as a child, in military service and / or before travel to a country with smallpox. Only persons vaccinated before the epidemic are considered as vaccinated, not those receiving vaccine after a probable infection of smallpox.

During the epidemic a massive vaccination campaign was launched. Involving both contact tracing of possible infectious contacts as well as a mass vaccination of more than 112 000 persons. It took approximately four months until the last infected person recovered and no new cases were found.

Some unexpected infectious routes were identified. An embalmer (a person involved in the cleaning of corpses) was infected by contact with a corpse. Another individual was infected through transporting laundry from one of the hospitals, when he came in contact with clothes from one of the isolation rooms. He also delivered food to a nearby hospital causing secondary cases at that location.

For a general overview of how cases infected one another please see Figure 4 on page 23 and Figure 5 on page 24.

2.2 Data

The data from this outbreak was obtained from (Ström [1966]), a TV documentary (Wallén [1964]) and medical journals at the Swedish Institute for Infectious Disease Control. Since contact tracing of possible contacts was undertaken, information is available regarding both cases as well as persons who were exposed but not infected (i.e non cases). The following data are available:

For the cases:

- Whom they were probably infected by
- Which phase of disease the infectious person was in at probable contact
- Possible dates of infection
- Date of onset of fever
- Date of onset of rash
- Date of isolation
- Date discharged from the hospital / death
- Vaccination status for smallpox, in some cases also the time of vaccination
- Which family they belonged to and number of family members
- Where they were hospitalized and in which ward

For the non cases:

- Probable infectious contacts
- Possible dates of infection
- If they belonged to a family
- Where they were hospitalized and in which ward

The date for probable infectious contact is not used in the calculations because not all possible contacts are known. Information regarding vaccination status of non cases was unfortunately not available. We only know that they were given boosters after contact tracing. We assume no asymptomatic cases (i.e infected without symptoms) existed, since this is very unlikely for smallpox.

Short summary of data concerning cases is shown in Table 1.

Variable	Number of observations		
Vaccination status	27	24 vaccinated	
Family size	27	$(1-4)$	
Hospital ward size	27	$(27-51)$	
Time period		Mean	Standard deviation
Infection to onset of fever	26	11.73	4.47
Onset of fever to rash	23	3.17	1.61

Table 1: Short summary of data for cases

2.3 Smallpox in general

Smallpox also known as Variola Major or Variola Minor, is a disease which is eradicated worldwide since 1979. It was a much feared infectious disease and the first vaccines were developed in the 19th century.

The virus transmits through air and body fluids and often through close contacts with infectious individuals.

The typical presentation of disease is that first symptoms appear two weeks after infection in the form of high fever. This lasts for about three days after which a rash appears on the body, which is similar to chickenpox or acne in the beginning. These rashes last 2-3 weeks and the person is bedridden during this stage.

Variola Major can be of four different types: ordinary (more than 90% of cases), modified (mild, common for previously vaccinated persons), flat and hemorrhagic.

The case fatality rate (CFR) for Variola Major of ordinary type is approximately 30%. For flat and hemarrhagic it is almost 100%, modified is rarely lethal. For Variola Minor CFR is approximately 1%.

Protection against smallpox can be acquired in two ways, immunity following infection or through vaccination. The vaccine is called Variola and gives protection for a certain period, the protective effect decreasing with time. One advantage is that it decreases the severity of infection, i.e individuals will develop Variola Major modified as opposed to Variola Major ordinary. This gives a much higher probability of survival given infection.

In Sweden vaccination was a part of the childhood vaccination program until 1976, with an indicator of successful vaccination being a circular scar. After the virus was eradicated from the world, vaccination ceased. The last known case was diagnosed in Somalia october 1977. Global eradication was certified by World Health Organisation in 1979. A laboratory associated smallpox death occurred at University of Birminghan, England 1978.

The long term protection of the vaccine is questionable, with some studies having shown protection after 20 years (Eichner [2003]).

2.4 Progress of infection

We will give a crude sketch of both of how the infectious disease and the infection spread develops in theory (Giesecke [2002]).

As an infectious disease it can be viewed in the following stages, see also Figure 1:

1. Healthy: The person has not yet been infected and is not protected against it.
2. Incubation period: A susceptible person gets infected by an infectious individual. Incubation period is the period of time between initial infection and the onset of clinical disease (these manifestations may not always be clinically visible).
3. Clinical disease: Appearance of visible symptoms
4. Resistant: The person has recovered from the disease, or has been successfully immunized through vaccination.

How infection is spread differs from the above because an individual can be infectious before the stage of clinical disease, see also Figure 2:

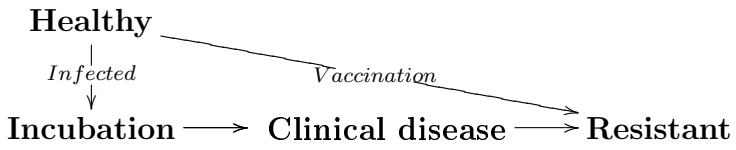

Figure 1: Progress of infectious disease

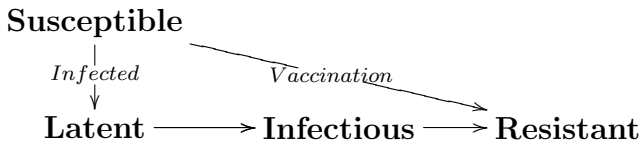

Figure 2: Progress of infection

1. Susceptible: The person has not yet been infected and is not protected against it.
2. Latent period: When a person becomes infected by an infectious individual.
3. Infectious period: The person is now infectious and can transmit the disease to others
4. Resistant: The person has recovered from the disease, or has been successfully immunized through vaccination.

This is modeled by assuming that there is a certain amount of transition between the different states. The transition in our case is in one direction:

For infectious agents like influenza the recovered person can be susceptible again, depending on which type of influenza is circulating the next influenza season. But in our case everyone who is resistant will remain resistant.

Infected persons are assumed to meet other individuals in the population according to a Poisson process. This implies that the number of contacts in any time period is a Poisson distributed random variable. If a proportion of the population is immune the number of contacts that will result in a new infection will reduce in correspondence to this.

2.4.1 Fitting distributions to observed time observations

The data used will be the available data for the periods. These transition periods investigated are the following: infected to onset of fever and fever to onset of rash. The time from onset of rash until discharged has not been analyzed since it does not measure how long time a person is infectious. We want to emphasize that we are not estimating these parameters through our epidemic model. Each phase in infection will be analyzed separately.

2.4.2 Time spent in different states

When trying to model the transitions between different states the time spent in different states, many times it is assumed to be exponentially distributed. This allows the possibility to use Markovian properties to calculate, for example, the size of the epidemic. Many studies have used or are using this distribution. The limitation is that no diseases have shown to follow an exponential distribution in the different states, making this approach mostly of academic interest.

Another approach is to assume that the time spent in the different states is constant or to find a suitable balance between the exponentially and constantly distributed transition times.

We will be using an approach by assuming the occupation times to follow a gamma distribution.

2.4.3 Basic reproductive number R_0

A parameter of interest in this case is the so called "basic reproductive number", denoted R_0. This is a crude measure of how many infected persons are generated by one infectious individual entering a totally susceptible population. If $R_0 < 1$ no large outbreaks will occur, only a small outbreak is possible. If $R_0 > 1$ there will be a positive probability for a large outbreak, meaning that a considerable proportion of the population could get infected.

2.5 The epidemic model used

As in (Eichner and Dietz [2003]) we are using a $SEIR$ model to describe the progress of the disease.

- $\boldsymbol{S}$ =Susceptible
- $\boldsymbol{E}$ =Exposed (latent period)
- $\boldsymbol{I}$ =Infectious period, which is divided into two parts:
  - $\boldsymbol{I}_{Fever}$ = Fever to onset of rash
  - $\boldsymbol{I}_{Rash}$ = Rash until recovered / death
- $\boldsymbol{R}$ = Resistant / death

Given infection the person will first be in the exposed (latent) period for about two weeks. This is followed by the fever phase which last about three days. Then a rash starts to appear and recovering from this stage takes an additional 1-3 weeks. There are two possible outcomes, namely death or recovery. Schematically this model is showed in Figure 3.

When establishing the model we are also interested in any differences in "infectiousness" in the states $\boldsymbol{I}_{Fever}$ and $\boldsymbol{I}_{Rash}$, this ratio being denoted by b.

2.6 Notations

The following notation is used:

- $t^i_{\mathbf{Infected}}$ = Time point for infection, when several days exist we have taken their mean value.
- $t^i_{\boldsymbol{F}}$ = Time point for onset of fever
- $t^i_{\boldsymbol{Rash}}$ = Time point for onset of rash
- $t^i_{\boldsymbol{Isolated}}$ = Time point for isolation / recovery (recovery for cases not isolated)
- N =population size
- n = number of cases

2.7 Calculation of infectiousness

We have adopted the approach to calculate the infection pressure on individuals in the population. This is done by calculating the number of individuals who are in the fever or rash period at a certain point in time. The effect of different infectiousness in the fever and rash period is also taken into account

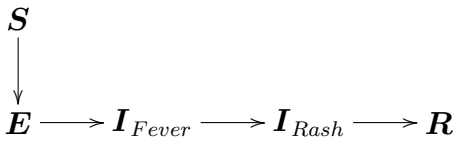

Figure 3: Epidemic model used

through the variable b.

Let $h_j(t)$ measure the infectious status of person j at time j. These are $\boldsymbol{I}_{Fever}$, $\boldsymbol{I}_{Rash}$ and not infectious. Let $\mathbf{J}$ be an indicator function.

$$h_j(t) = b\mathbf{J}_{\{t^j_{\boldsymbol{F}} \leq t < t^j_{\boldsymbol{Rash}}\}} + \mathbf{J}_{\{t^j_{\boldsymbol{Rash}} \leq t \leq t^j_{\boldsymbol{Isolated}}\}}$$

To calculate the total "infection pressure" individual i is exposed to, $\lambda_i(t)$ at a certain time point t. The $h_j(t)$ for all cases j are summarized and multiplied by the number of infectious contacts per day.

$$\lambda_i(t) = \sum_{j=1}^{27} h_j(t) * \text{number of infectious contacts per day}$$

2.7.1 Population structure

A number of different structures for the population is possible. We have assumed two different models for dynamics in our population. One assumes homogeneous mixing, that is no family or hospital effects are taken into account. The second approach takes into account the effect of family and hospital on infectious contacts.

In the homogeneous mixing model a number of contacts per day κ is assumed and this is spread uniformly within the rest of the population. If the population size is N, one infectious individual is in mean transmitting $\frac{\kappa}{N-1}$ infectious contacts to any other individual.

In the heterogeneous mixing we have attempted to set up a population structure with households and hospitals taken into account. If a persons belongs to multi households he will be exposed to two rates, κ and κ_F. Here κ_F is an addition per family members. If he belongs to a single household his exposure is the rate κ. If a person belong to a hospital he is exposed to a rate κ_H. We assume only infectious contacts within hospitals.

- $\widehat{\kappa}$ = Number of infectious contacts per day with any person in a population with hospitals and households

- κ = Number of infectious contacts per day with any person in a population with hospitals and households
- κ_F = Number of infectious contacts per day with a certain family member
- κ_H = Number of infectious contacts per day with any person in a hospital
- N = Population size
- n_H^i = Number of people in the hospital ward where person i is situated

Letting $h_j(t)$ denote in which infectious state person j is at a certain time point we can describe the population structure. Assuming an homogeneously mixing population the force of infection $\lambda_i(t)$ follows as:

$$\lambda_i(t) = \sum_{j=1}^{n} h_j(t)\left(\frac{\kappa}{N-1}\right)$$

If a heterogeneously mixing population is used:

$$\begin{aligned}\lambda_i(t) &= \sum_{j=1}^{27} h_j(t)\mathbf{J}(hosp_i(t)=0)\left(\mathbf{J}(f_j=f_i)\left(\frac{\kappa}{N-1}+\kappa_F\right)+\mathbf{J}(f_j\neq f_i)\frac{\kappa}{N-1}\right)+ \\ &+ \sum_{j=1}^{27} h_j(t)\mathbf{J}(hosp_i(t)=1)\left(\frac{\kappa_H}{n_H^i-1}\right)\end{aligned}$$

Here f_i is the family identity for person i, $hosp_i(t)$ is an indicator if person i is in hospital at time t. The procedure is to first check if person i is in hospital. If yes ($hosp_i(t)=1$), he is exposed to certain number of infectious contacts. If no ($hosp_i(t)=0$), he is exposed to some other infectious contacts on which family he belongs to. **J** is an indicator function.

2.7.2 Calculation of R_0

Assuming that we know the parameters of interest, this allows us to calculate R_0, the expected number of infectious contacts during the infectious time period. We define it as a product of number of infectious contacts per day multiplied with the total length of the two infectious periods. Using the same notations as before, the parameters of interest are the scale factor b, number of infectious contacts per day κ, κ_F, κ_H and the length of the infectious time

periods (prodromal + rash).

Concerning the length of the infectious periods, the prodromal period (fever to rash) has the mean length based on our data. The rash period is probably overestimated in this data, and this is the reason for including other time periods as well. We are assuming that the two time periods are distributed as a gamma distribution.

$$\begin{aligned} \boldsymbol{I}_{Fever} &\sim \Gamma(\alpha_f, \beta_f) \\ \mathrm{E}[\boldsymbol{I}_{Fever}] &= \frac{\alpha_f}{\beta_f} = \mu_{Fever} \\ \boldsymbol{I}_{Rash} &\sim \Gamma(\alpha_r, \beta_r) \\ \mathrm{E}[\boldsymbol{I}_{Rash}] &= \frac{\alpha_r}{\beta_r} = \mu_{Rash} \end{aligned}$$

Now R_0 can be estimated in the situation with homogeneous or heterogeneous mixing assumptions:

Homogeneously mixing population:

$$R_0 = (N-1)\frac{\widehat{\kappa}}{N-1}\Big(b\mu_{Fever} + \mu_{Rash}\Big) = \widehat{\kappa}\Big(b\mu_{Fever} + \mu_{Rash}\Big)$$

Heterogeneous mixing population with a single household:

$$R_0 = (N-1)\frac{\kappa}{N-1}\Big(b\mu_{Fever} + \mu_{Rash}\Big) = \kappa\Big(b\mu_{Fever} + \mu_{Rash}\Big)$$

Heterogeneous mixing population with a multi person household:
Let f_i and f_j be family indicators for person i and j. Calculate the number of infectious contacts caused by person i. $\mathbf{J}$ is an indicator function. Let n_F denote the number of additional family members in a household.

$$\begin{aligned} R_0^F &= \sum_{j \neq i} \Big(\mathbf{J}(f_i = f_j)\frac{\kappa}{N-1} + \mathbf{J}(f_i = f_j)\kappa_F\Big)\Big(b\mu_{Fever} + \mu_{Rash}\Big) = \\ &= \Big(\frac{n_F}{N-1}\kappa + n_F\kappa_F\Big)\Big(b\mu_{Fever} + \mu_{Rash}\Big) \end{aligned}$$

Heterogeneous mixing population with within hospital infection:
Let $hosp(i)$ and $hosp(j)$ be hospital ward indicators for person i and j. Calculate the number of infectious contacts caused by person i. $\mathbf{J}$ is an indicator function.

$$\begin{aligned} R_0^H &= \left(\frac{\kappa_H}{n_H^i}\sum_{j\neq i}\mathbf{J}(hosp(i)=hosp(j))\right)\Big(b\mu_{Fever}+\mu_{Rash}\Big) = \\ &= \left(\frac{\kappa_H}{n_H^i}n_H^i\right)\Big(b\mu_{Fever}+\mu_{Rash}\Big) = \kappa_H\Big(b\mu_{Fever}+\mu_{Rash}\Big) \end{aligned}$$

We note that in the case of heterogeneous mixing the calculation is made as an expected value, not as most often the largest eigenvalue of a mixing matrix.

2.7.3 Likelihood calculations

The infectious contacts are assumed to follow a Poisson process with intensity $\lambda_i(t)$ where $\lambda_i(t)$ is calculated in Section 2.7. The probability to become infected at time s, given no infection before is $\lambda_i(s)e^{-\int_0^s \lambda_i(\tau)d\tau}$. If we know the time of infection $t^i_{\boldsymbol{Infected}}$ and the vaccine efficacy v we can calculate the likelihood for the cases and non cases as follows:

- v = vaccine efficacy.
- δ_i = Vaccination status for case number i, 1 if vaccinated, 0 otherwise
- $t^i_{\mathbf{Infected}}$ = Day of infection for case number i.
- $\lambda_i(t)$ = Force of infection on individual i, day number t.
- $\mathcal{N}_c$ = set consisting of all cases
- $\mathcal{N}_p^v$ = set consisting of vaccinated non cases cases not belonging to a household or hospital during the epidemic
- $\mathcal{N}_p$ = set consisting of non vaccinated non cases cases not belonging to a household or hospital during the epidemic
- $\mathcal{N}_F$ = set consisting of non cases belonging to a household but not belonging to a hospital during the epidemic

- $\mathcal{N}_H^v$ = set consisting of vaccinated non cases not belonging to a household but belonging to a hospital during the epidemic
- $\mathcal{N}_H$ = set consisting of non vaccinated non cases not belonging to a household but belonging to a hospital during the epidemic

The likelihood functions can be calculated as follows (Eichner and Dietz [2003]):

$$\begin{aligned}
P_i(\text{case}) &= (1-v)^{\delta_i}\lambda_i(t^i_{\boldsymbol{Infected}})e^{-\int_0^{t^i_{\boldsymbol{Infected}}}\lambda_i(\tau)d\tau} \\
P_i(\text{non case}) &= (1-v)^{\delta_i}e^{-\int_0^{\infty}\lambda_i(\tau)d\tau} \\
L &= \prod_{i\in\{\text{cases}\}} P_i(\text{case}) \prod_{\text{i}\in\{\text{non case}\}} \text{P}_\text{i}(\text{non case}) = \\
&= \prod_{i\in\mathcal{N}_c} P_i(\text{case}) \prod_{\text{i}\in\mathcal{N}_\text{p}^\text{v}} \text{P}_\text{i}(\text{non case}) \prod_{\text{i}\in\mathcal{N}_\text{p}} \text{P}_\text{i}(\text{non case}) \\
&\quad \prod_{i\in\mathcal{N}_F} P_i(\text{non case}) \prod_{i\in\mathcal{N}_H^v} P_i(\text{non case}) \prod_{i\in\mathcal{N}_H} P_i(\text{non case})
\end{aligned}$$

$$\begin{aligned}
\log L &= \sum_{i=1}^{n}\delta_i \log(1-v) + \sum_{i=1}^{n}\log\lambda_i(t) - \sum_{i=1}^{n}\int_0^{t^i_{\boldsymbol{Infected}}}\lambda_i(\tau)d\tau + \\
&+ \sum_{i\in\mathcal{N}_p^v}\log\left(v+(1-v)e^{-\int_0^{\infty}\lambda_i(\tau)d\tau}\right) + \\
&+ \sum_{i\in\mathcal{N}_F}\log\left(v+(1-v)e^{-\int_0^{\infty}\lambda_i(\tau)d\tau}\right) + \\
&+ \sum_{i\in\mathcal{N}_H^v}\log\left(v+(1-v)e^{-\int_0^{\infty}\lambda_i(\tau)d\tau}\right) - \\
&- \sum_{i\in\mathcal{N}_p}\int_0^{\infty}\lambda_i(\tau)d\tau - \sum_{i\in\mathcal{N}_H}\int_0^{\infty}\lambda_i(\tau)d\tau
\end{aligned}$$

The likelihood for the cases is calculated by taking the family- and hospital place at different times into account. This is included in the calculation of $\lambda(t)$. For non cases there is a division made depending if they are in a multi person household or hospital. In a household due to the high vaccination proportion in the population all are considered to be vaccinated. In a hospital the number of vaccinated and unvaccinated are rounded off to the closest

Time period	α	β	Expected value	Std	n
infected to fever	7.58	0.64	11.73	4.26	26
fever to rash	4.05	1.28	3.17	1.58	23

Table 2: Parameters for duration in different states

integer.

The likelihood for non cases is depending on the proportion vaccinated prior the epidemic. We have assumed this to be the same as the proportion for cases. This is of course questionable, sensitivity analysis could be made or an implication of the the EM-algorithm to estimate the "expected proportion".

To estimate the parameters of interest profile likelihood methods have been used. This is done by fixing one parameter and varying the others. The maximum of these is taken as the likelihood for the fixed parameter. Then the fixed parameter is given a new value and it is maximized again over the other ones. The maximum likelihood estimation for the fixed parameter will be the point at which the maximum value for the likelihood is obtained.

3 Results

3.1 Times spent at different states

Assuming that the amount of time spent in different states follows a $\Gamma(\alpha, \beta)$-distribution with expected value $\frac{\alpha}{\beta}$ and variance $\frac{\alpha}{\beta^2}$. The parameters α (shape) and β (scale) are estimated through maximum likelihood. The yielded estimates are shown in Table 2.

The times for rash to recovered are overestimated since the recorded recovery date is probably over-exaggerated in order to ensure that the patient is no longer infective.

The infected to fever period and the prodromal period (2 weeks and 3 days respectively) are similar to those found in other studies.

When comparing this with an exponential distribution we know that the

variable	value	95% confidence interval
scale	0.51	(0.1 - 1.5)
vaccine efficacy	0.98	(0.95 - 0.99)
κ	0.47	(0.25 - 0.85)
κ_H	0.54	(0.31 - 0.92)
κ_F	0.057	(0.015 - 0.12)

Table 3: Estimates for parameters of interest, heterogeneous mixing

shape parameter α should be around 1 in the Γ-distribution. Following our estimations this value is far from one, indicating that an exponential distribution is not suitable in the case of smallpox. This is enough only if we are interested in how big the outbreak will become.

3.2 Estimation of parameters of interest

Estimating our parameters of interest are shown in Table 3.

The wide interval on the scale parameter b indicates that there is uncertainty concerning a difference in infectiousness at different infectious states.

The vaccine efficacy v seems to be high. We are unsure of the number of vaccinated individuals in the total population and how the protective effect diminishes over time.

The number of infectious contacts are approximately 0.5 per day in community and hospitals. We want to emphasize that by varying the population structure these values can change considerably.

4 Discussion

The major finding is that although very detailed data, it is very hard to find "good" estimates for even the most basic measures of interest. In our case these are the number of infectious contacts per day and the length of the infectious period.

These two parameters are crucial to estimate R_0 and are very sensitive to the structure given to the population. We have also compared with a homogeneously mixing population and the results differ dramatically from the values obtained in our heterogeneous population. Also when changing the infectiousness within families, assuming some infectious contacts with all population and extra infectiousness spread among family members, altered the results. This means that interpreting and comparing R_0 values obtained in different studies is very difficult since usually the population structures are different. When simulating possible smallpox outbreaks the results should vary. This also for the case with same value on R_0 but different population structures.

Testing infectiousness in the prodromal period with the rash period gives no significant difference. The estimate is about 0.5. If we assume a homogeneous mixing population the infectiousness in the prodromal period is about the same as with heterogeneous mixing. Still this is far from the assumption used in (Halloran et al. [2002]) where a 10 times higher infectiousness is assumed in the prodromal period.

Our calculations are also perturbated by the fact that a number of infectious contacts occur in unexpected places. Some scenarios are hard to put into the model. For example in the beginning of the outbreak a home visiting nurse is infected. In the model she belongs to the first affected family in the beginning but must at one time point be transfered to her own family where she infects her relatives. Also the person transporting clothes from the hospital and the embalmer are unusual occupations to include in a realistic way. In our case these infectious contacts are taking place at a hospital.

We have also assumed that no more infectious contacts will take place while a person is isolated in the infectious disease hospital. The embalmer is an example that this is not a completely true assumption.

The largest error is probably the fact that in calculating "R_0" it is assumed that the populations remain the same. But in the event of an epidemic situation people are probably much more attentive to their contacts thus the structure could change dramatically. In our case the extensive vaccination campaign of over 112 000 individuals vaccinate should also matter concerning the proportion resistant in the population at different time points. Also the fact that large populations surrounding the infected households were mass vaccinated must affect the result. These events would decrease the number of infectious contacts per day, suggesting that at the beginning the the number of infectious contacts should be higher than at the end of the epidemic.

Our results show that on using values of R_0 in simulations of possible small-

pox outbreaks, great care should be taken when interpreting the meaning of outputs. Are the assumptions similar to our model, if not how will they change the outcome?

As noted in the beginning of discussion, only a small number of parameters are possible to estimate reasonably. One can only raise the question in many simulations where maybe more than 15 parameters are used. How reliable are these? Probably only two are known and the rest are "estimated" through some medical expertise. The known parameters may be the length of the infectious period and the number of infectious contacts which are already very unsure. Leading to the conclusion that we probably know nothing with certain for these parameters. In such case it is probably wiser to use much simpler models for more realistic situations, than using many values for the unknown parameters as in (Kretzschmar et al. [2004] and E.H.Kaplan et al. [2002]). An extreme example is (Epstein et al. [2004]) where 30 parameters are used.

The inportant feature with the Stockholm outbreak was that a large part of it occurred within households. It is a striking contrast with many other study findings where hospitals have been the coins for infection transmission.

5 Acknowledgments

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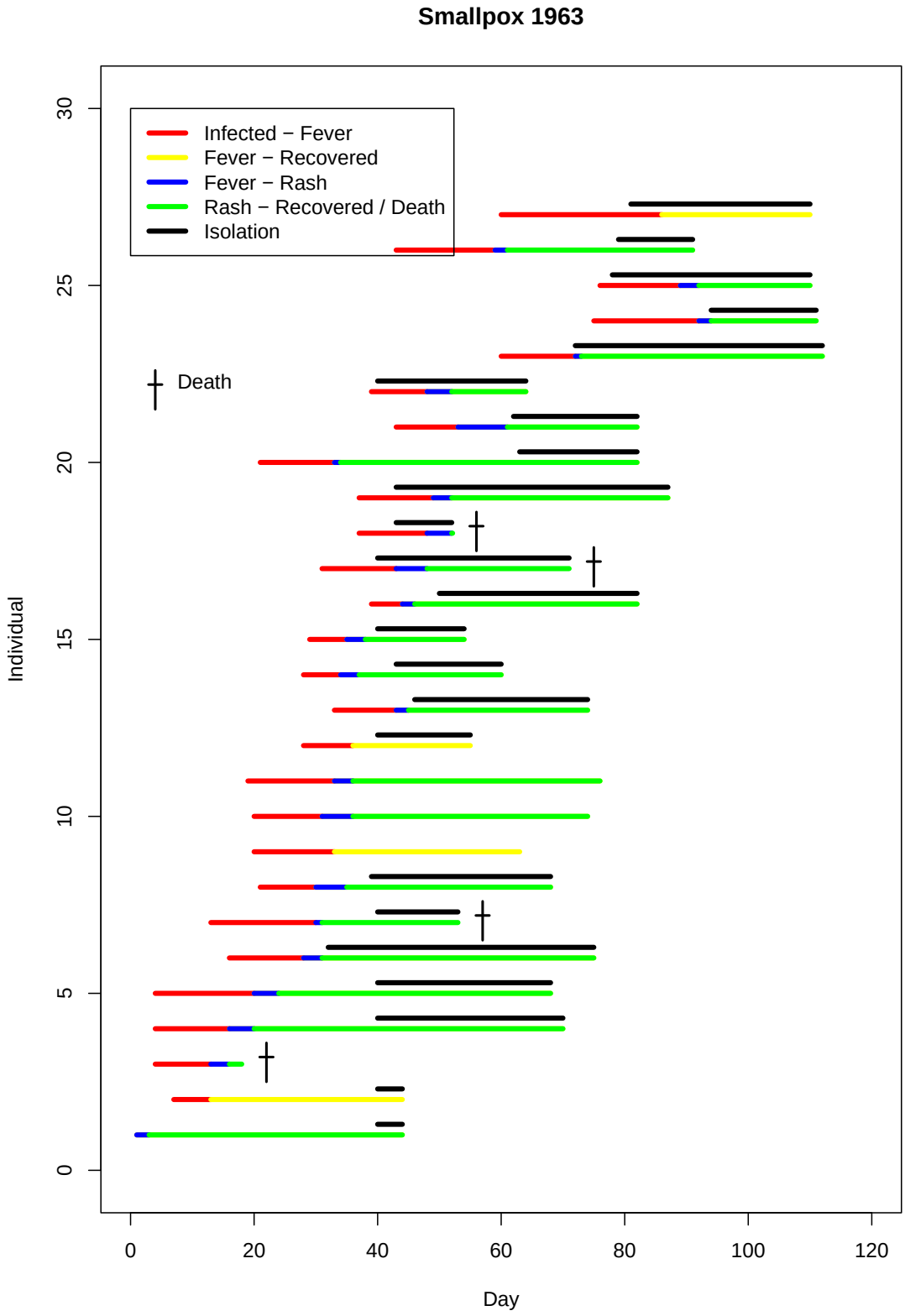

Figure 4: Available data on infected persons after the onset of fever of the first person. Scale on x-axis = Number of days.

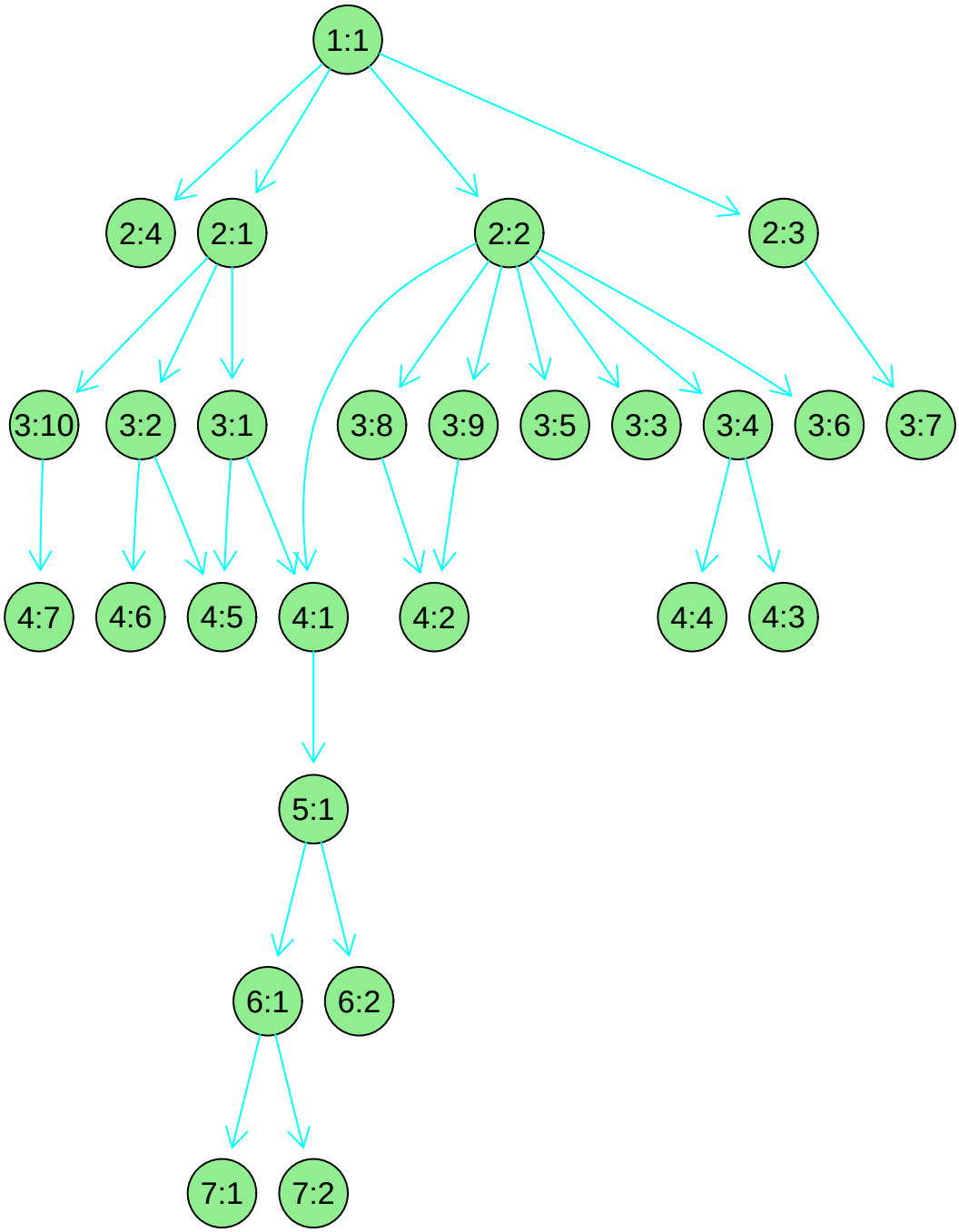

Figure 5: Schematic overview of the epidemic, how cases infected each other.

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