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1 The correlation between infectivity and incubation period of
2 measles, estimated from households with two cases

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10

11 ABSTRACT

12 The generation time of an infectious disease is the time between infection of a primary case
13 and infection of a secondary case by the primary case. Its distribution plays a key role in
14 understanding the dynamics of infectious diseases in populations, e.g. in estimating the basic
15 reproduction number. Moreover, the generation time and incubation period distributions
16 together characterize the effectiveness of control by isolation and quarantine. In modelling
17 studies, a relation between the two is often not made specific, but a correlation is biologically
18 plausible. However, it is difficult to establish such correlation, because of the unobservable
19 nature of infection events. We have quantified a joint distribution of generation time and
20 incubation period by a novel estimation method for household data with two susceptible
21 individuals, consisting of time intervals between disease onsets of two measles cases. We
22 used two such datasets, and a separate incubation period dataset. Results indicate that the
23 mean incubation period and the generation time of measles are positively correlated, and that
24 both lie in the range of 11-12 days, suggesting that infectiousness of measles cases increases
25 significantly around the time of symptom onset. The correlation between times from infection
26 to secondary transmission and to symptom onset could critically affect the predicted
27 effectiveness of isolation and quarantine.

28

29 HIGHLIGHTS

- 30 • Household measles data, consisting of time intervals between symptom onset of two
31 cases, are analysed
- 32 • Correlation between the times from infection to symptom onset (incubation time) and
33 to secondary transmission (generation time) are explicitly modelled
- 34 • Measles incubation time and generation time appear positively correlated, which
35 could affect the effectiveness of case isolation and quarantine

36 **Keywords: serial interval; incubation period; transmission; epidemiology; measles**

37

Accepted manuscript

38 **1. Introduction**

39 To capture the transmission dynamics of infectious diseases appropriately, a good
40 understanding of specific time events and intervals concerning infection processes and onset
41 phenomena is crucial [1-4]. Of the various time intervals describing the intrinsic transmission
42 process, the generation time is defined as the time between infection of a primary case and
43 infection of secondary cases caused by the primary case [5]. Mathematical theory describing
44 the increase in infected individuals shares its origin with that of mathematical demography
45 [6], where the distribution of the generation time (which describes the time from birth to the
46 age at reproduction) has been known to play a key role in describing population dynamics by
47 successive generations of birth events. Similarly, for infectious diseases, it is essential to
48 know the generation time distribution to offer a robust estimate of the reproduction number (a
49 measure for the transmission potential of a disease) from real-time epidemic growth data [3, 7,
50 8].

51 A second important interval is the incubation period, defined as the time between
52 infection and onset of symptoms. Knowing the incubation period distribution is crucial for
53 control of an infectious disease, e.g. to inform how long people should be quarantined, or
54 how long contacts should be traced back to find other cases. The generation time and
55 incubation period distributions together determine the effectiveness of control measures such
56 as ‘transmission-reducing’ treatment, isolation and quarantine [9, 10], through the level of
57 infectivity before onset of symptoms. Current calculations, however, do not make specific
58 assumptions on dependence between generation time and incubation period. Dependency
59 may be expected from a biological perspective and could affect the effectiveness of isolation.
60 More quantitative knowledge on the relationship between infectivity and disease is therefore
61 essential.

62 Whereas for the incubation period, data are often available from persons with a single

63 and known contact to an infected, it is not an easy task to estimate the generation time
64 distribution in practice, because infection events are seldom directly observable. There have
65 been attempts, for example, to estimate the generation time distribution from viral shedding
66 data [11], but it is difficult to link virological findings to the epidemiological phenomenon of
67 secondary transmission without further information (e.g. frequency, mode and degree of
68 contacts).

69 Previously, the distribution of the generation time was implicitly assumed to correspond
70 exactly to that of the serial interval [12], defined as the time from symptom onset in a given
71 case to symptom onset in secondary cases [13-15]. The relation between the two intervals is
72 shown in Figure 1. It shows that the serial interval between two cases δ is in fact an
73 aggregation of three intervals, namely the generation time u and two incubation periods t_1 and
74 t_2 . Here we will assume that t_1 and t_2 are equally distributed, although even this is not obvious
75 if infectiousness and symptoms are correlated. Under this assumption, it is clear that the mean
76 of the generation time and serial interval distributions should be the same, but implicitly
77 assuming that the generation time distribution corresponds exactly to the serial interval
78 distribution is incorrect and may lead to flawed estimation of the reproduction number. A
79 correction of the variance by use of incubation period data could be considered, but is not
80 straightforward, because of the likely dependence between the generation time and incubation
81 period of the primary case.

82 Estimation of the generation time distribution by use of observed intervals between
83 disease onset of two cases, is complicated for more reasons. For instance, it may be that
84 asymptomatic cases are missed so that two cases are not uniquely or only indirectly linked
85 [16]. Also, the secondary case may develop symptoms before the primary case, resulting in a
86 negative serial interval but not observable as such. Finally, cases may have been infected both
87 by an external source (co-primary cases), either at the same time or at different and

88 independent times. We will in the rest of the paper use d to denote any interval between
89 disease onset of two cases, and reserve δ for the theoretical (real) serial interval. When
90 analyzing such data, all possible mechanisms should be accounted for.

91 To tackle this issue, the present study revisits the time interval between onsets of two
92 measles cases in households (i.e. distribution of the time interval between onset of the first
93 case and onset of the second case in families with two susceptible individuals). This type of
94 data, with the characteristic bimodal distribution, has been studied and reviewed extensively
95 [14, 17-19]. In the present study, we propose a new method to estimate the generation time
96 distribution from these data, and we aim at explicitly quantifying the correlation between the
97 generation time and incubation period. Since household contacts are made in intense
98 conditions of close proximity [15], we realize that our estimates cannot directly be
99 extrapolated beyond the household setting. Rather, we aim – for the first time – at specifically
100 addressing the dependence between generation time and incubation period, and at developing
101 a methodological basis to estimate the generation time distribution using observable
102 epidemiological data. In addition, we address identifiability of the model parameters, in
103 particular the correlation coefficient, by analysis of datasets simulated with parameter
104 estimates.

105

106 **2. Materials and methods**

107 *2.1. Data*

108 We analyzed time intervals between onset of first and second cases of measles in
109 households with two susceptible individuals. Here we use the terms “first” and “second”
110 cases (i.e. not primary and secondary cases), because it is unknown whether the second case
111 was infected by the first, the first by the second, or whether they were both infected in the
112 community. While many analyses of the serial interval of measles were performed with Hope

113 Simpson's [20] or Kenyan datasets [21], the present study used two datasets with larger
114 sample sizes which were collected in Rhode Island from 1917-23 [22] and 1929-34 [23] and
115 were previously revisited to estimate latent and infectious periods [24]. Figure 2 shows the
116 observed distributions extracted from the two abovementioned publications, the original data
117 of which are available in Appendix A of the Supplementary Materials.

118 In total, 5,762 and 4,516 intervals between two cases in the households were recorded in
119 1917-23 and 1929-34, respectively. In the former dataset, there were no documented pairs of
120 cases with $d = 0$ (where d is the observed interval in days between onset of the two cases),
121 but there are many pairs with $d = 1$. Following Wilson *and others* [23], we assume that all
122 pairs with $d = 0$ were included in this dataset as $d = 1$. In addition, although both datasets
123 included pairs with $d > 30$ days, all observations of $d > 30$ were grouped together.

124 In addition to the time intervals between two onsets of measles in a household, we
125 extracted a separate incubation period dataset from a different historical publication of
126 measles in 1931 [25, 26] for use in our analyses. In that study, incubation periods were
127 recorded for 116 cases based on detailed observations of contact which arose from cases that
128 experienced only a single day of exposure. Figure 3 illustrates the incubation period
129 distribution, the original data of which are available in Appendix B of the Supplementary
130 Materials. Sample mean (median) and variance of the incubation period were 12.3 (12.0)
131 days and 12.1 days² respectively.

132

133 2.2. Theoretical basis

134 Here we explain the epidemiological mechanisms underlying the bimodal distribution of
135 the time intervals in Figure 2. As noted previously [27, 28], two cases in a household with
136 two susceptible individuals are the result of either (i) community infection in both cases (i.e.
137 "co-primary" cases) or (ii) community infection of the first case and household infection of

138 the second. Possibility (i) is then reflected in the first peak and possibility (ii) corresponds the
 139 second peak. Although previous reviews have discussed this issue implicitly by defining a
 140 cut-off point of d to distinguish (i) from (ii) [14, 18], we do not take this approach and, rather,
 141 employ a mixture distribution. In addition, we allow for a third possible infection history,
 142 namely that both cases were independently infected in the community. Figure 1(a) illustrates
 143 the three mechanisms leading to $f(d)$, the probability distribution of d :

144 *Mechanism 1.* Both cases independently experienced infection in the community, which
 145 accounts for a proportion π_1 of the observations (where $0 \leq \pi_1 \leq 1$).

146 *Mechanism 2.* Both cases were infected at an identical point in time in the community,
 147 which accounts for a proportion π_2 (where $0 \leq \pi_2 \leq 1 - \pi_1$).

148 *Mechanism 3.* One case was infected in the community and the other was infected by the
 149 primary case in the household, which accounts for a proportion $1 - \pi_1 - \pi_2$.

150 If we denote the probability of difference d by mechanisms 1, 2 and 3 by $q_1(d)$, $q_2(d)$ and
 151 $q_3(d)$, respectively, we can express the mixture density $f(d)$ as

$$152 \quad f(d) = \pi_1 (q_1(d) + q_1(-d)) + \pi_2 (q_2(d) + q_2(-d)) + \quad (2.1)$$

$$\quad (1 - \pi_1 - \pi_2) (q_3(d) + q_3(-d))$$

153 That is, we assume that the bimodal distribution in Figure 1 is decomposed into three
 154 underlying epidemiological mechanisms, expressed as a three-component mixture
 155 distribution. The densities q_1 and q_2 are assumed to reflect the difference in onset between the
 156 two cases in random order, which is why all densities q_1 , q_2 , and q_3 , d can be negative and
 157 positive. In $f(d)$, the difference $d \geq 0$.

158

159 2.3. The model

160 Here we describe how the three mechanisms result in three probability distributions,
 161 specifying our parameters of interest. The first term of the mixture distribution, $q_1(d)$, in

162 equation (2.1) is

$$163 \quad q_1(d) = p_{(0, \sigma_1^2)}(d), \quad (2.2)$$

164 which is the density of a normal distribution with mean 0 and variance σ_1^2 . This distribution
 165 arises if measles occur in (seasonal) epidemics, and the dataset does not contain pairs of cases
 166 occurring in different epidemics. Then, the time interval d is the time difference between
 167 onset of two independently sampled cases from an epidemic. Assuming that each epidemic
 168 curve is approximately bell-shaped (Farr's model [29]), d is normally distributed with twice
 169 the variance of the epidemic curve.

170 The probability of observing a difference d owing to mechanism 2 depends on the
 171 density function $g(t)$ of the incubation period of length t . Because the two cases are infected
 172 at the same time, d is the difference (i.e. cross-correlation) of independently and identically
 173 distributed incubation periods. Thus, the probability density function $q_2(d)$ is equal to

$$174 \quad q_2(d) = \int_0^{\infty} g(\tau)g(d + \tau) d\tau \quad (2.3)$$

175 Because either case can be the first to show symptoms, a negative d should be regarded as
 176 one case being the first (e.g. the oldest), and a positive d as the other being the first.

177 Mechanism 3 reflects the serial interval within households. From Figure 1 we see that the
 178 serial interval δ is given by

$$179 \quad \delta = u + t_2 - t_1, \quad (2.4)$$

180 which is interpreted as the sum of the generation time u and incubation period of the
 181 secondary case t_2 minus the incubation period of the primary case t_1 . Thus, if u , t_1 and t_2 were
 182 independent random variables, the serial interval distribution would be the convolution of the
 183 generation time and incubation period distributions followed by the cross-correlation of this
 184 convolution and the incubation period distribution. However, it is biologically natural to
 185 assume that t_1 and u are dependent (e.g. cases with short incubation period may cause

186 secondary transmission earlier on average than cases with long incubation periods). Therefore,
 187 we assume that u and t_1 follow a joint distribution $h(t_1, u)$, so that the probability of observing
 188 difference d due to mechanism 3 depends on the incubation period distribution $g(t_2)$ and on
 189 this joint distribution $h(t_1, u)$. Under this assumption, $g(t)$ is a marginal distribution of $h(t, u)$.
 190 Now, the probability density $q_3(d)$ is equal to

$$191 \quad q_3(d) = \int_0^\infty \int_0^\infty h(\tau, u) g(d - u + \tau) du d\tau \quad (2.5)$$

192

193 2.4. Statistical analysis

194 We fitted a lognormal, gamma, and Weibull distribution to the incubation period data, by
 195 means of maximum likelihood estimation. Akaike's Information Criterion (AIC) was used to
 196 decide which of these distributions to choose for further analysis. The Weibull distribution
 197 was rejected for further use.

198 For construction of joint (cumulative) distribution functions $H(t, u)$, we combined two
 199 lognormal or gamma marginal distributions by use of a Gaussian copula function. Copula
 200 functions provide a correlation structure to sets of marginal distributions [30]. In our case, we
 201 first denote the marginal distribution functions of T and U by $P_T(t)$ and $P_U(u)$, respectively.
 202 Because $0 < P_T(t), P_U(u) < 1$, we can write the joint distribution as

203

$$204 \quad H(t, u) = \Phi_\rho(\Phi^{-1}(P_T(t)), \Phi^{-1}(P_U(u))) \quad (2.6)$$

205

206 Here, Φ is a normal distribution with standard normal marginals [30]. For the marginal
 207 distributions $P_T(t)$ and $P_U(u)$, we chose two lognormal distributions or two gamma
 208 distributions (not Weibull, as argued above), as these are the most commonly used for
 209 generation times and incubation times [2, 12, 31]. We will refer to these distributions as the

210 bilognormal and bigamma distributions.

211 Both distributional assumptions result in distributions with 5 parameters; i.e. two
 212 parameters for the marginal incubation period and generation time distributions in addition to
 213 a correlation parameter ρ . Since we additionally estimate σ_1 , π_1 and π_2 , there are in total 8
 214 parameters to be estimated.

215 Because the density of d with the third mechanism (within household transmission)
 216 includes a convolution of $g(t)$ and the bivariate density $h(t,u)$, a likelihood approach was
 217 computationally too challenging, even in a classic Bayesian procedure where the likelihood
 218 need not be maximized but evaluated at many sampled points in parameter space. Therefore,
 219 we employed Sequential Monte Carlo sampling (SMC), in particular the ABC-PRC algorithm
 220 (Approximate Bayesian Computation – Partial Rejection Control), described by Sisson *and*
 221 *others* [32]. The ABC-PCR algorithm was programmed in R statistical software. A
 222 step-by-step explanation of the algorithm as we used it is given in Appendix C of the
 223 Supplementary Materials. The idea is as follows: the algorithm starts by sampling 2000
 224 parameter sets from prior distributions. Subsequently, a second population of parameter sets
 225 is obtained by sampling from the first, perturbing, simulating a dataset and comparing the
 226 simulated data to the real data. If both datasets are close enough, ie if the χ^2 statistic is below
 227 some selection threshold ε_2 , the parameter set is accepted for the second population. Then a
 228 third population is obtained from the second with a more restrictive selection threshold ε_3 ,
 229 then a fourth, etc, until the final selection threshold ε_{\min} is met. From the final population of
 230 parameter sets, the medians and 95% credible intervals are derived.

231 The fits of the two distributional assumptions, bilognormal and bigamma, were
 232 compared by use of the deviance $-2\sum \{f_i \log(f_i/n_i) - f_i \log(\hat{f}_i/n_i)\}$, in which f_i are the
 233 observed frequencies, \hat{f}_i the expected frequencies, and n_i the total numbers of observations

234 which f_i is part from (5762 or 4516 onset differences, or 116 incubation periods). For the
235 expected frequencies of onset differences a simulated distribution was constructed with
236 100,000 samples with the median parameter estimates. The expected frequencies of the
237 incubation periods were calculated exactly.

238

239 *2.5. Parameter identifiability*

240 To address parameter identifiability of the proposed estimation method while saving
241 substantial time for the iteration procedure, we have made four different assumptions
242 regarding the data generating process of the ‘real model’. That is, we simulated datasets that
243 were similar to the original data under the four assumptions. The simulated datasets were
244 subsequently analyzed using the two models (bivariate lognormal and bivariate gamma), and
245 the resulting estimates were compared to the parameter values used for the simulations. The
246 four assumptions on the real model were:

- 247 (1) a bivariate lognormal distribution of incubation and generation times with
248 positive correlation (20 simulated datasets)
- 249 (2) a bivariate gamma distribution of incubation and generation times with positive
250 correlation (20 simulated datasets)
- 251 (3) a bivariate lognormal distribution of incubation and generation times without
252 correlation (10 simulated datasets)
- 253 (4) a bivariate gamma distribution of incubation and generation times without
254 correlation (10 simulated datasets)

255 Simulations with (1) and (2) were carried out with consensus parameter values based on the
256 four sets of original estimates derived from the two empirical datasets. For simulations with
257 (3) and (4), consensus parameters were obtained after re-analysis of the original datasets,
258 forcing the correlation coefficient at 0 (no correlation), with both lognormal and gamma

259 models.

260 Identifiability was first assessed for each parameter separately. The mean of the posterior
261 medians was calculated, and we determined how frequent the median was lower and higher
262 than the true value. In addition, we determined how frequent the 95% credible interval
263 contained the true parameter value, and we tested whether this was significantly different
264 from 95% (Fisher's exact test). Identifiability for the whole model was quantified by the
265 number of parameters failing the latter test (number of parameters correctly identified).

266

267

268 **3. Results**

269 *3.1. Incubation period data*

270 The fitted lognormal, gamma, and Weibull distributions are shown in Figure 3. The AICs for
271 the three models were 605.7, 608.2, and 626.1, respectively. Thus, we decided not to continue
272 with the Weibull distribution.

273

274 *3.2. Bilognormal distribution*

275 Assuming a bilognormal distribution for $h(t,u)$, the SMC algorithm took 22 and 21 iterations
276 before reaching ϵ_{\min} for the two datasets, respectively. The resulting parameters and 95%
277 percentile intervals are presented in Table 1, where the actual estimates of the distributional
278 parameters have been translated into means and standard deviations of the intervals of Figure
279 1. The mean incubation periods of 11.6 and 11.3 days were very similar to the mean
280 generation times of 12.2 and 11.2 days in the years 1917-1923 and 1929-1934, respectively.
281 This is also reflected in the mean time from onset to secondary transmission, which is close
282 to 0. As expected, the mean serial intervals were equal to the mean generation times, but the
283 standard deviations of the serial intervals are smaller. Both datasets indicate a strong and

284 significant correlation between the generation time and the incubation period, with estimated
285 correlation coefficients of 0.903 and 0.969. Figure 4 shows the densities of the bivariate
286 distributions of incubation and generation times according to the point estimates. Figure 2
287 shows the theoretical distributions of the difference between the days of onset, indicating the
288 contributions of the three mechanisms. It appears that the more irregular 1917-1923 dataset
289 (deviance = 259) results in a slightly worse fit than the 1929-1934 data (deviance = 157).

290

291 *3.3. Bigamma distribution*

292 With the bigamma distribution for $h(t,u)$, the SMC algorithm took 12 and 13 iterations before
293 reaching ε_{\min} for the two datasets, respectively. The results are given in Table 2. Compared to
294 the bilognormal model, the standard deviations of the incubation period and generation time
295 were smaller. Unlike the bilognormal model, the serial intervals now have larger standard
296 deviations than the generation times. The correlation coefficient ρ was smaller as well, and
297 with the first dataset, ρ was not even significantly larger than 0, but with the second dataset it
298 was. With the bigamma distribution, the 1929-1934 data (deviance = 188) fitted better than
299 the 1917-1923 data (deviance = 247), as was the case with the bilognormal distribution.

300 Comparing the two distributional assumptions, the bigamma distribution fitted better with the
301 1917-1923 data, but the bilognormal distribution with the 1929-1934 data. Figure 4 shows
302 estimated bilognormal and bigamma distributions. The contributions of the three mechanisms
303 was also different between the two distributions, but Figure 2 indicates that in all cases the
304 first peak, second peak, and fat tail of the onset difference distribution are clearly explained
305 by the three mechanisms separately.

306

307 *3.4. Parameter identifiability*

308 Table 3 shows a summary of the identifiability analysis, the details of which, including

309 parameter values used for simulation, are given in Appendix D of the Supplementary Material.
310 It turns out that both lognormal and gamma models correctly identify the three components of
311 the mixture distribution, with the bigamma method giving reliable estimates of the
312 proportions of the components in most cases. Regarding the overall performance of the two
313 models, the bivariate gamma model produces more reliable results: with three groups of
314 simulated datasets, all 95% CIs for the eight parameters contained the true values (Table 3).
315 The bivariate lognormal model correctly identified maximally 6/8, in only one case.

316 The correlation coefficient is significantly overestimated by the lognormal model, but
317 correctly identified by the gamma model, although slightly underestimated. The standard
318 deviation of the generation time is also significantly overestimated by the lognormal model,
319 and slightly underestimated by the gamma model. All other parameters are correctly
320 identified or only slightly biased. In summary: only the gamma model produces reliable
321 estimates, especially on the correlation between the incubation and generation times.

322

323 **4. Discussion**

324 The present study revisited the distribution of the time interval between the onsets of
325 two cases of measles in households with two susceptible individuals. We decomposed the
326 observed bimodal distribution into a mixture of three distributions, each explicitly linked to a
327 relevant underlying epidemiological mechanism. We focused in particular on the third
328 mechanism which reflects the time interval required for household transmission between first
329 and second cases. Clearly illustrating the relationship between the incubation period,
330 generation time and serial interval (Figure 1), we developed a method to estimate the
331 generation time distribution, addressing dependence between the generation time and
332 incubation period. To the best of our knowledge, the present study is the first to clearly
333 decompose the observed data into underlying epidemiological mechanisms with realistic

334 definitions of the intrinsic parameters (without arbitrary cut-off values), reasonably deriving
335 parameter estimates for the generation time distribution.

336 We have used two datasets for two periods of observation, and a third dataset with
337 incubation period observations. This third dataset is required to obtain estimates for the
338 marginal incubation period distribution, especially for the mean because the onset difference
339 datasets only contain differences between two incubation periods, and those have a mean of 0
340 by definition. Because the first peak, reflecting the mechanism of dependent community
341 transmission, should contain information on the variance of the incubation period, we tried to
342 carry out the analysis without the incubation period data. That was unsuccessful, because the
343 three mechanisms did explain the onset difference distribution incorrectly: the first peak was
344 explained by mechanism 1 (independent infection outside household) with small σ_1 , whereas
345 the incubation period distribution was estimated to have a short mean and very large variance,
346 thus explaining the fat tail. Fixing the mean incubation period at 12.3 days (the sample mean)
347 so that only the variance needed to be estimated from the onset difference data, did not solve
348 this problem.

349 Ideally, the separate incubation period dataset would have been sampled from the same
350 population as the household data (or even better: from the same households), because
351 incubation periods could differ between situations. By taking a dataset from the same period
352 and a similar population (UK) we have tried to minimize this issue. The results show that,
353 because of the small number of cases in the dataset (116 cases), the parameter estimates for
354 the incubation period distributions are still sensitive to the household data: in fact, the
355 incubation period data could be considered as prior information for the household analysis.

356 The contributions of the three mechanisms to the mixture distribution will not be the
357 same in separate datasets. For instance, a large epidemic with more community transmission
358 will result in more households with mechanism 1 (independent infection in the community),

359 whereas a higher infectiousness and contact rate within the household is related to more
 360 observations of mechanism 3 (within-household transmission). The fact that so many factors
 361 play a role, makes it difficult to use other type of data in the same epidemic to infer on these
 362 mixture probabilities. Fortunately, the three components of the mixture distribution could be
 363 well identified by our method, and the proportions of the three mixture components
 364 reasonably well estimated, at least by the bigamma method.

365 In fact, the identifiability analysis clearly showed that the bigamma model in general
 366 provided much more reliable results than the bilognormal model. With the original data as
 367 well as the simulated data, the bigamma distribution resulted in a smaller correlation
 368 coefficient combined with smaller standard deviations of the incubation and generation times.
 369 This can be understood when realizing what characteristic of the data is indicative of
 370 correlation: the variance of the onset differences resulting from household transmission
 371 (mechanism 3), ie the width of the second peak. These onset differences are the sum of one
 372 independent incubation time T_2 and the difference of a dependent generation time U and
 373 incubation time T_1 . Denoting the single variances by s^2_T and s^2_U , the variance of d_3 is
 374 therefore $\text{var}(d_3) = 2s^2_T + s^2_U - 2\rho s_T s_U$. This means that a particular $\text{var}(d_3)$ in the data can be
 375 a result of either a high correlation coefficient ρ in combination with high s^2_T (as suggested
 376 by the bilognormal model), or of a lower ρ and smaller s^2_T and s^2_U (suggested by the
 377 bigamma model). The identifiability analysis has shown that the bilognormal model
 378 incorrectly favours the first hypothesis, and that the gamma model can correctly distinguish
 379 between the two.

380 Summarizing the results that were obtained for the joint distribution function of the
 381 generation time and incubation period, three findings are notable: (1) the mean incubation
 382 period and mean generation time were very close, ranging from 11-12 days; (2) there was a
 383 positive correlation between the generation time and incubation period, although this was not

384 significant with the bigamma distribution for the 1917-23 data; and (3) compared with
 385 estimates derived from datasets from 1917-23, estimates given by the dataset from 1929-34
 386 suggest shorter generation times and a stronger correlation between the generation time and
 387 incubation period. Findings (1) and (2) reflect transmission under intense contact conditions
 388 of close and prolonged physical proximity in the households [15]. Given this close contact
 389 and our estimates indicating that most secondary transmission of measles must have occurred
 390 before or just after the onset of illness, the infectiousness seems to increase fast just before
 391 symptom onset. With similar reasoning, finding (3) could indicate higher transmissibility of
 392 measles for the observations from 1929-34 compared to those from 1917-23, either due to
 393 more intense contacts or to higher or differently timed virus shedding levels, e.g. because of a
 394 different genotype [33].

395 In recent studies the serial interval δ was decomposed as the sum of time from the onset
 396 of a primary case to secondary transmission, w , and incubation period of secondary cases, t_2
 397 [34-36]. That is, from Figure 1,

$$398 \quad \delta = w + t_2 \quad (4.1)$$

399 has been assumed and further explored. Considering the distributions for each, the
 400 relationship is also expressed as

$$401 \quad f(\delta) = \int_{-x}^{\delta} w(\delta - \tau)g(\tau)d\tau \quad (4.2)$$

402 where x is the potentially contagious period before onset of illness in the primary case. The
 403 function of public health interest has been focused on $w(\delta - \tau)$, as the distribution can suggest
 404 the latest time at which symptomatic cases need to be placed in isolation [37]. Our approach
 405 does provide a distribution for w , with $\mu_w = \mu_U - \mu_T$ and σ_w as estimated, but it is more
 406 informative as it also provides a distribution of the generation time, related to the important
 407 growth rate of an epidemic, and it shows the correlation between disease onset and

408 infectivity.

409 Our datasets are limited to cases with two susceptibles in one household and both cases
410 infected. This is not at all a random sample of person-to-person transmission events during a
411 measles outbreak, and does not indicate either how likely transmission is under similar
412 circumstances. However, this does not affect the validity of our two main conclusions that we
413 can draw for measles, first that a positive correlation between incubation period and start of
414 infectiousness is very likely, and second that the infectiousness rises considerably around
415 symptom onset. For control of measles, the correlation between disease and infectivity imply
416 that isolation of cases and quarantine of traced contacts will be even more successful than
417 already predicted [9, 10].

418 As for future implications, we hope our method will be useful for estimating the
419 generation time of various diseases from well-recorded epidemiological data. Although the
420 generation time estimated from household transmission data is likely to be shorter than that
421 estimated from community transmission data [8, 15], further estimates in the community (or
422 in a specific group of contacts) could be derived from serial intervals based on contact tracing.
423 We believe further clarification of different generation times (e.g. between transmissions in
424 the community and households) would enhance our understanding of the transmissibility of a
425 disease in a heterogeneously mixing population which may be very useful in discussing and
426 appropriately quantifying the transmission dynamics of directly transmitted diseases (e.g.
427 influenza). Another line of future research is concerned with variations of generation time
428 with time, which could also be addressed, analyzing time-varying serial intervals [38]. Given
429 the various future possibilities, we believe our estimation procedure satisfies a need to
430 translate observed datasets into one of the most important key intrinsic parameters of
431 transmission dynamics.

432

433 **Appendix A. Supplementary data**

434 Supplementary data associated with this article can be found in the online version at doi: .

435

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439

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440 **Table 1.**

441 Parameter estimates with the bilognormal distribution

Parameter	1917-1923		1929-1934	
Mean incubation period	11.6	(10.7 ; 12.4)	11.3	(10.6 ; 12.0)
SD incubation period	2.75	(2.44 ; 3.13)	2.37	(2.14 ; 2.61)
Mean generation time	12.2	(11.9 ; 12.5)	11.2	(11.1 ; 11.4)
SD generation time	3.62	(2.98 ; 4.41)	3.13	(2.55 ; 3.68)
Mean time onset-secondary transmission	0.6	(-0.2 ; 1.5)	0.0	(-0.7 ; 0.6)
SD time onset-secondary transmission	1.69	(1.09 ; 2.29)	1.08	(0.57 ; 1.61)
Mean serial interval	12.2	(11.9 ; 12.5)	11.2	(11.1 ; 11.4)
SD serial interval	3.26	(3.05 ; 3.48)	2.62	(2.44 ; 2.79)
Correlation coefficient [ρ]	0.903	(0.732 ; 0.981)	0.969	(0.871 ; 0.997)
Pr(mechanism 1) [π_1]	0.138	(0.0945 ; 0.205)	0.145	(0.0974 ; 0.213)
Pr(mechanism 2) [π_2]	0.238	(0.200 ; 0.273)	0.189	(0.159 ; 0.220)
SD mechanism 1 [σ_1]	20.3	(17.1 ; 24.4)	16.6	(14.4 ; 19.4)
Deviance	259		157	

442 NOTE: Given are the posterior medians and 95% credible intervals. SD is the standard

443 deviation. Mechanism 1 refers to two independent infections outside the household;

444 mechanism 2 refers to two synchronous infections outside the household.

445

446 **Table 2.**

447 Parameter estimates with the bigamma distribution

Parameter	1917-1923		1929-1934	
Mean incubation period	11.5	(10.5 ; 12.5)	11.4	(10.6 ; 12.2)
SD incubation period	2.24	(1.87 ; 2.66)	2.08	(1.69 ; 2.42)
Mean generation time	11.9	(11.5 ; 12.1)	11.1	(10.9 ; 11.3)
SD generation time	1.22	(0.69 ; 2.64)	1.79	(0.79 ; 3.08)
Mean time onset-secondary transmission	0.4	(-0.7 ; 1.5)	-0.3	(-1.1 ; 0.4)
SD time onset-secondary transmission	2.13	(1.41 ; 2.66)	1.29	(0.62 ; 1.91)
Mean serial interval	11.9	(11.5 ; 12.1)	11.1	(10.9 ; 11.3)
SD serial interval	3.08	(2.83 ; 3.36)	2.47	(2.28 ; 2.66)
Correlation coefficient [ρ]	0.413	(-0.511 ; 0.928)	0.837	(0.219 ; 0.982)
Pr(mechanism 1) [π_1]	0.195	(0.132 ; 0.279)	0.188	(0.126 ; 0.253)
Pr(mechanism 2) [π_2]	0.194	(0.153 ; 0.232)	0.162	(0.130 ; 0.195)
SD mechanism 1 [σ_1]	18.0	(15.4 ; 22.1)	15.5	(13.7 ; 18.0)
Deviance	247		188	

448 NOTE: Given are the posterior medians and 95% credible intervals. SD is the standard

449 deviation. Mechanism 1 refers to two independent infections outside the household;

450 mechanism 2 refers to two synchronous infections outside the household.

451

452 **Table 3.**

453 Summary of identifiability analysis.

Estimation model		Simulation model			
		Simulated $\rho = 0.863$		Simulated $\rho = 0$	
		Log-normal	Gamma	Log-normal	Gamma
Lognormal	proportion of correctly identified parameters ^a	6/8	4/8	2/8	3/8
	mean estimated ρ	0.966	0.951	0.801	0.785
	proportion of 95% CI containing real ρ	0/20	1/20	0/10	0/10
Gamma	proportion of correctly identified parameters ^a	6/8	8/8	8/8	8/8
	mean estimated ρ	0.842	0.813	-0.182	-0.253
	proportion of 95% CI containing real ρ	20/20	20/20	10/10	10/10

454 ^a proportion of model parameters of which the true value falls within the 95% CI (sufficiently
 455 frequent, Fisher's exact test). Full results in Supplementary Materials.

456

457

458 **Figure captions**

459 **Fig. 1.** Theoretical basis of the observed time intervals between onset of first and second
460 measles case in households with two susceptible individuals. (a) Three underlying
461 mechanisms: 1. both cases are infected independently in the community; 2. both cases are
462 infected at the same time in the community; 3. secondary transmission in the household, ie
463 the serial interval distribution. (b) The relationship between generation time u , incubation
464 times t_1 and t_2 , serial interval δ , and time from onset to transmission w .

465

466 **Fig. 2.** Datasets with onset intervals from 1917-1923 [22] and 1929-1934 [23], together with
467 fitted distributions, separating the contributions of the three mechanisms. Arrows indicate the
468 extreme values where the predicted numbers of cases with mechanism 3 are still above 0. (a)
469 Data from 1917-1923, bilognormal model; (b) Data from 1917-1923, bigamma model; (c)
470 Data from 1929-1934, bilognormal model; (d) Data from 1929-1934, bigamma model.

471

472 **Fig. 3.** Incubation period dataset, extracted from [25], and three fitted distributions.

473

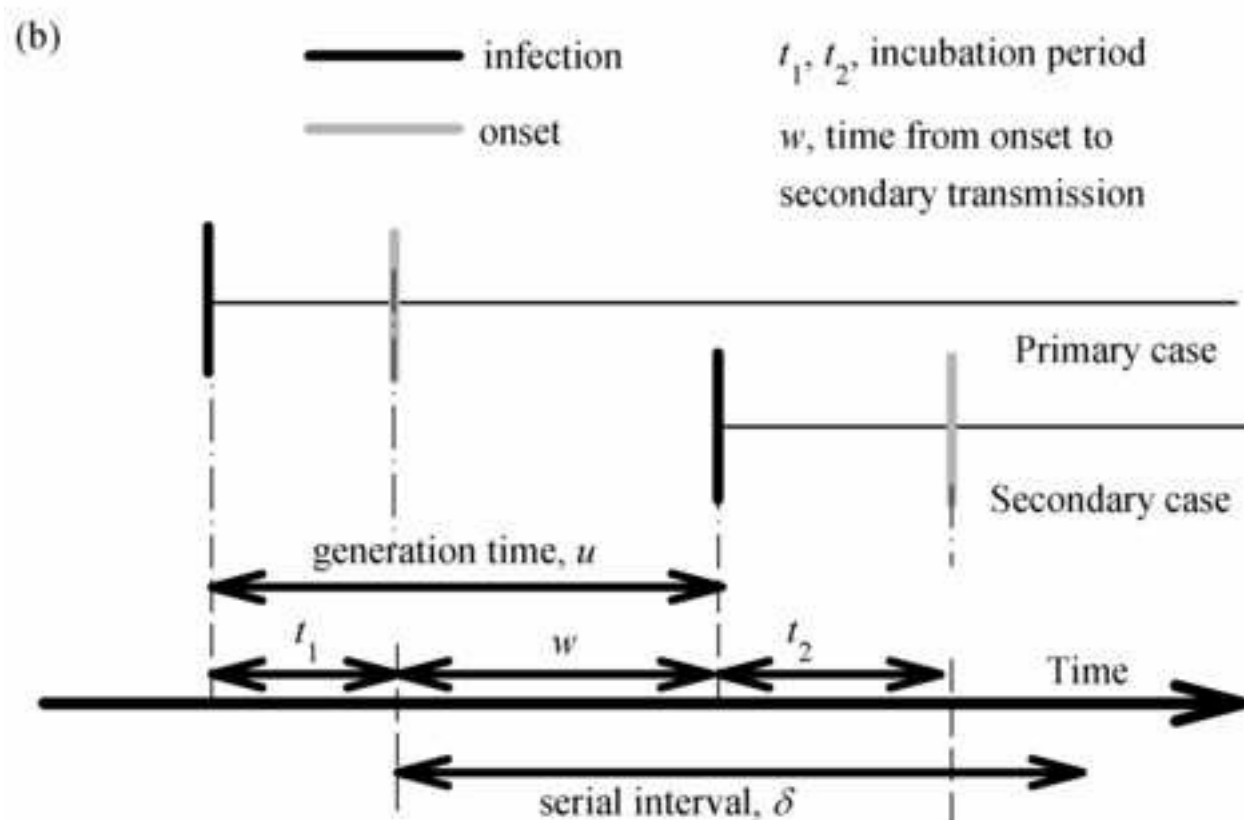
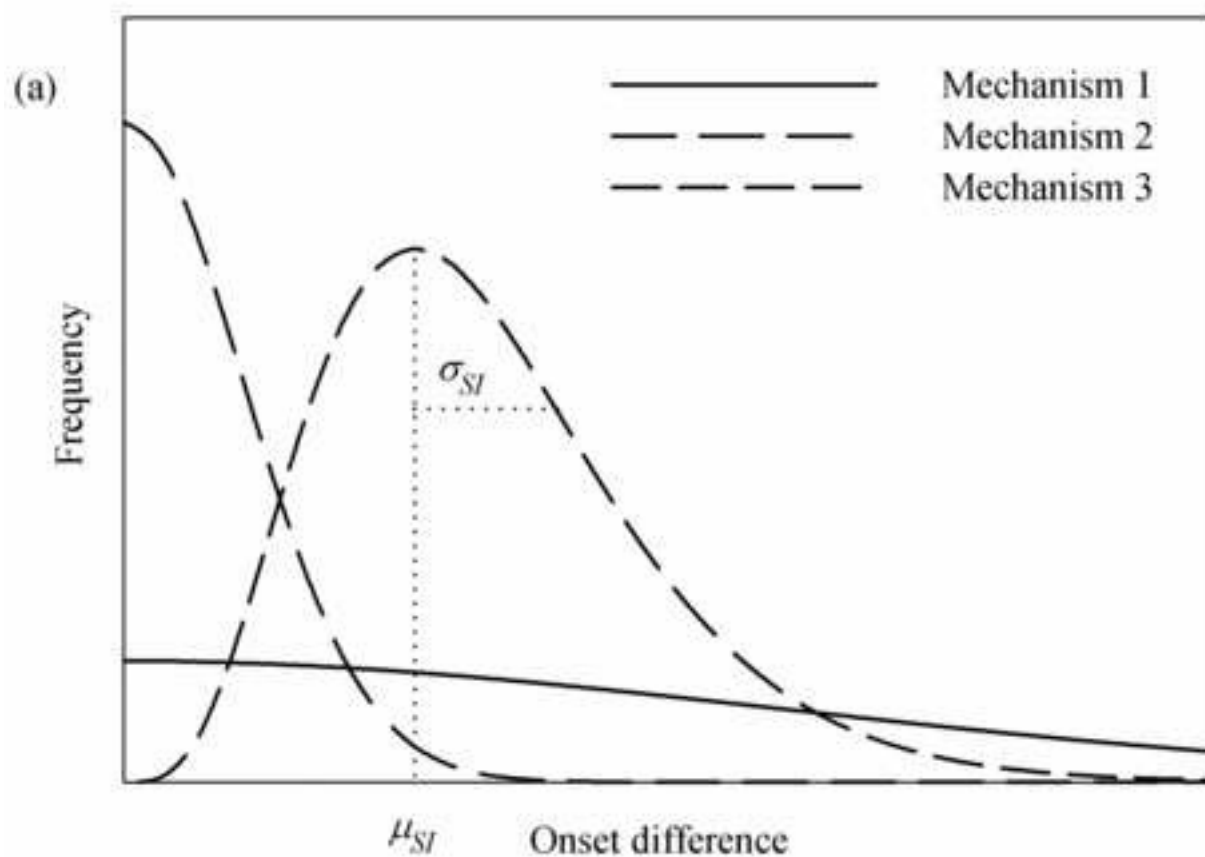
474 **Fig. 4.** Joint distribution densities according to median posteriors, for the two datasets and two
475 model. (a)-(d) as in Fig. 2.

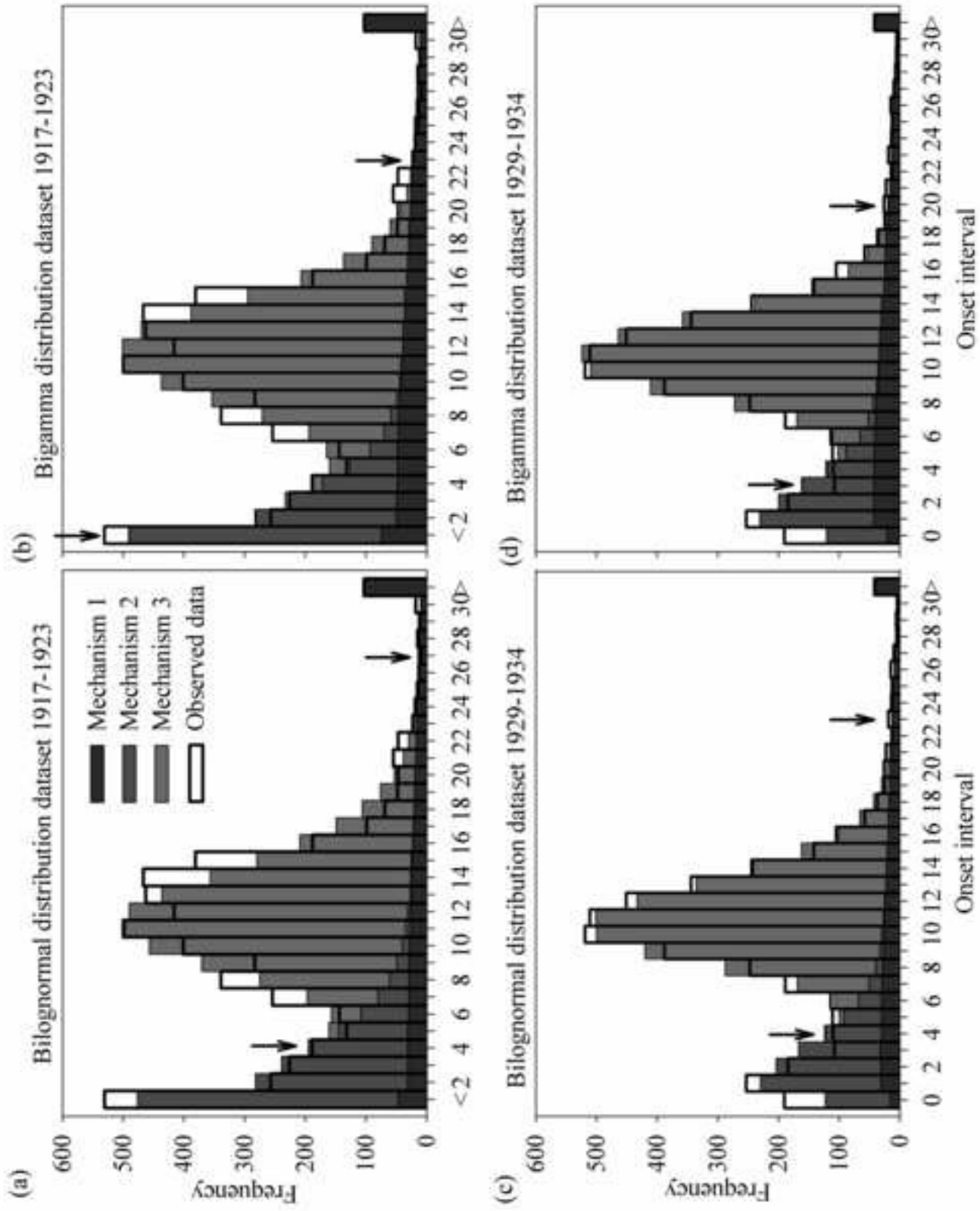
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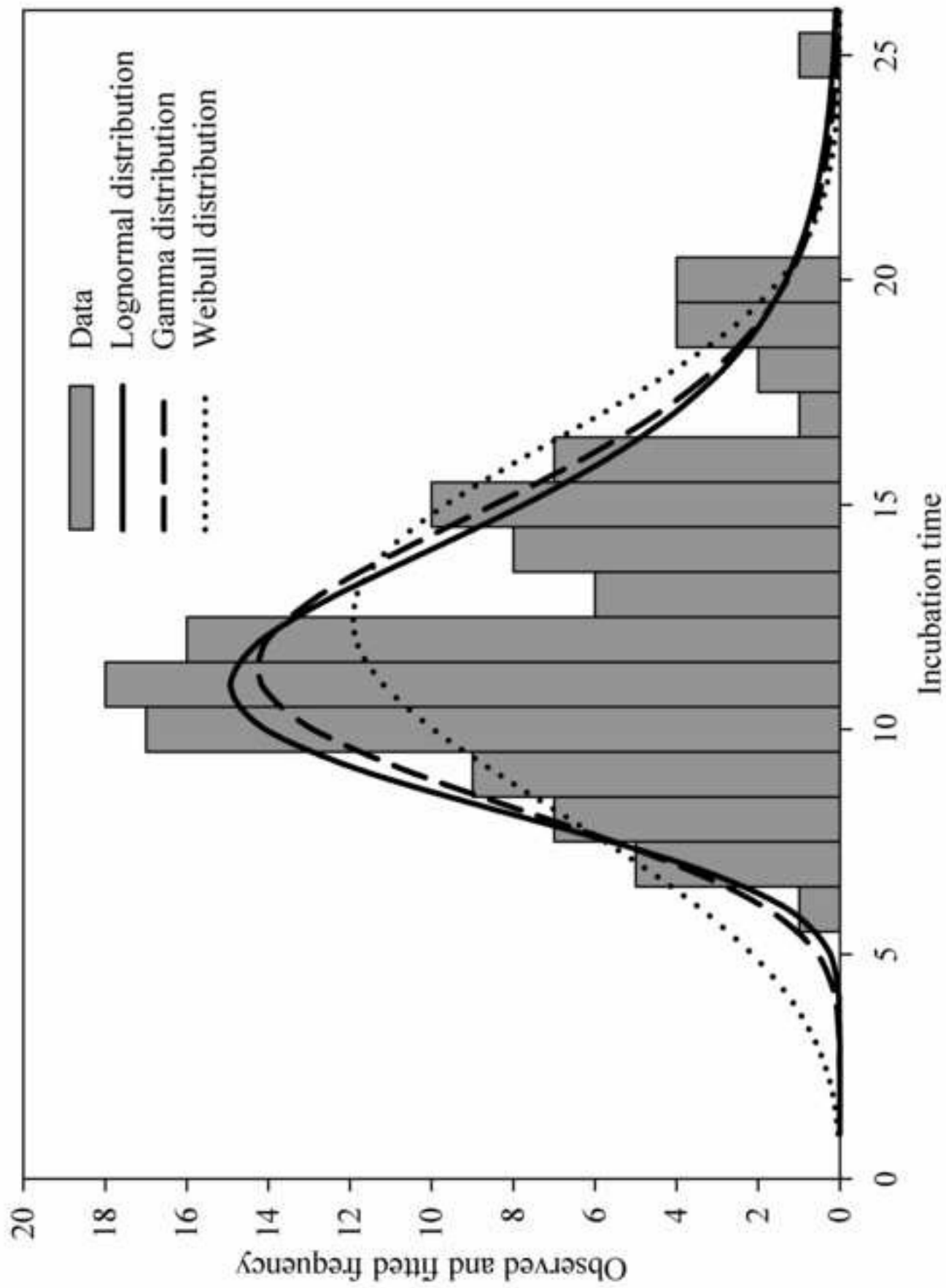
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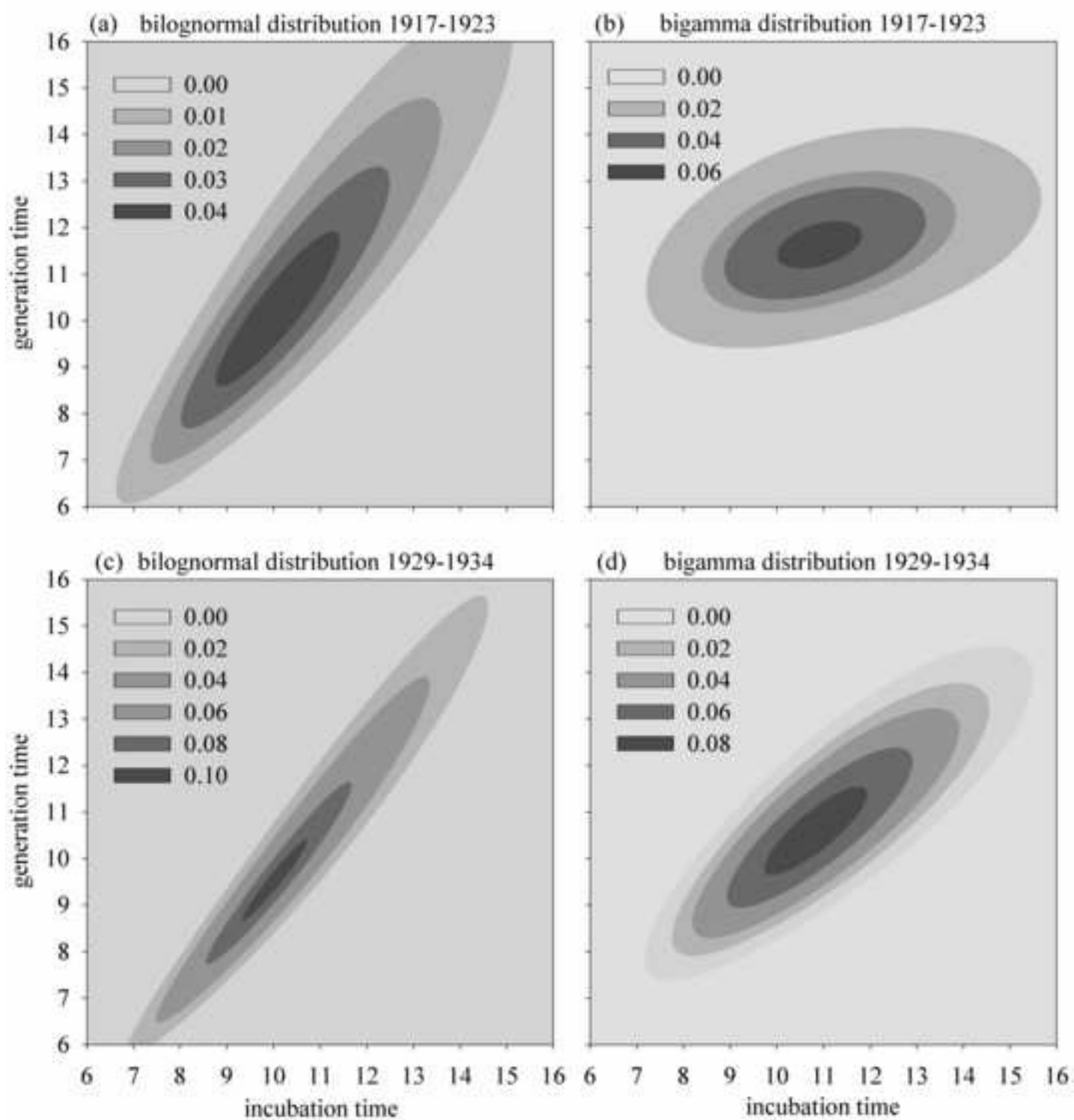
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- 566







4. Figure 3



HIGHLIGHTS

- Household measles data of time intervals between symptom onset of two cases were analysed
- Correlation between incubation time and generation time were explicitly modelled
- Measles incubation time and generation time appear positively correlated
- The positive correlation could affect the effectiveness of case isolation and quarantine

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