L07 COVID-19 Outbreak Investigations[1]

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STA427 FS2021
Statistical Methods in Infectious Disease Epidemiology
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[1]LaMo: 2021-04-15 @ 08:48:02

Outline

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Outbreak Investigation

- In this course we have looked a lot at the use of statistical methods for modelling population level time series, i.e. surveillance data
- However, many infectious disease outbreaks are (or start as) as small localized clusters, which can be investigated by *field investigations*.
- Aims of such an outbreak investigation[2]:
  - Control or prevention (knowledge of agent, course of the outbreak, mode of transmission, source)
  - Research opportunity (mode of transmission, incubation period, clinical spectrum, ...)
  - Public, political, or legal concerns
  - Training

[2] Taken from `https://www.cdc.gov/csels/dsepd/ss1978/lesson6/section1.html`

Secondary attack rate

- The *secondary attack rate* is an alternative morbidity measure to, e.g. incidence, and is defined as[3]

$$\text{SAR} = \frac{\text{Number of new cases among contacts}}{\text{Total number of contacts}}$$

- Classical methods for calculating point estimate and CIs for a proportion can be used.
- By calculating the SAR in two groups one can even compute relative risks by classical 2x2 methods.

[3] https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section2.html

Outline

COVID-19 Carnival cluster (1)

- Early COVID-19 outbreak investigation by Bender et al. (2021) in order to determine SAR as well as incubation period, serial interval and generation time.
- Important insight: There seems to be little transmission from completely asymptomatic cases
- SAR for household contacts of lab confirmed cases:

Clinical symptoms source	No. contacts infected[4]	Total no. contacts	SAR
Asymptomatic	0	4	0%
Symptomatic[5]	4	28	14.3%
Total	4	32	12.5%

[4] either tested positive or experienced respiratory symptoms

[5] phase not specified or both

COVID-19 Carnival cluster (2)

- Getting an OR estimate with CI for the SAR of asymptomatic vs. symptomatic is difficult, due to the zero in the 2x2 table

```
##   infected  n    cs_source
## 1        0  4 asymptomatic
## 2        4 28  symptomatic

m_glm <- glm( cbind(infected, n-infected) ~ 1 + cs_source, data=carnival, family=binomial )
confint(m_glm)
## Waiting for profiling to be done...
##                             2.5 %   97.5 %
## (Intercept)                    NA 4097.869
## cs_sourcesymptomatic -3292.433       NA
```

- Problem with zero can be addressed by *exact logistic regression* as implemented in the `elrm` package (Zamar et al. 2007):

```
#devtools::install_github(repo="https://github.com/cran/elrm.git")
m <- elrm::elrm( infected/n ~ cs_source, interest=~cs_source, dataset=carnival, r=2, iter=1.5e4, burnIn=5e3)

c(hat=as.numeric(exp(m$coeffs)), exp(m$coeffs.ci)) %>% unlist
##        hat      lower      upper
## 0.78298817 0.07570849        Inf
```

- OR estimate and CI is close to the RR estimate stated in Bender et al. (2021)

COVID-19 Carnival cluster (3)

- Score interval (Nam 1995):

```
PropCIs::riskscoreci(4, 28, 0, 4, conf.level=0.95)
##
##
##
## data:
##
## 95 percent confidence interval:
##  0.2244315       Inf
```

- Bayes interval with

$$\pi_i | x_i, n_i \sim \mathrm{Be}(0.5 + x_i, 0.5 + (n_i - x_i))$$

posterior for each proportion $i = 1, 2$ and $\theta = \pi_2/\pi_1$ by sampling followed by an equitailed credibility region for θ:

```
PropCIs::rrci.bayes(4, 28, 0, 4, a=1/2, b=1/2, c=1/2, d=1/2, conf.level=0.95)
## [1]    0.24668 1283.83737
```

COVID-19 Carnival cluster (4)

- Same for other contacts of lab confirmed cases

Clinical symptoms source	No. contacts infected[6]	Total no. contacts	SAR
Asymptomatic cases	0	22	0%
Symptomatic[7]	3	25	12.0%
Symptomatic, presymptomatic phase only	15	72	20.8%
Symptomatic, symptomatic phase only	2	29	6.9%
Total	20	148	13.5%

- ORs vs. asymptomatic from exact logistic regression:

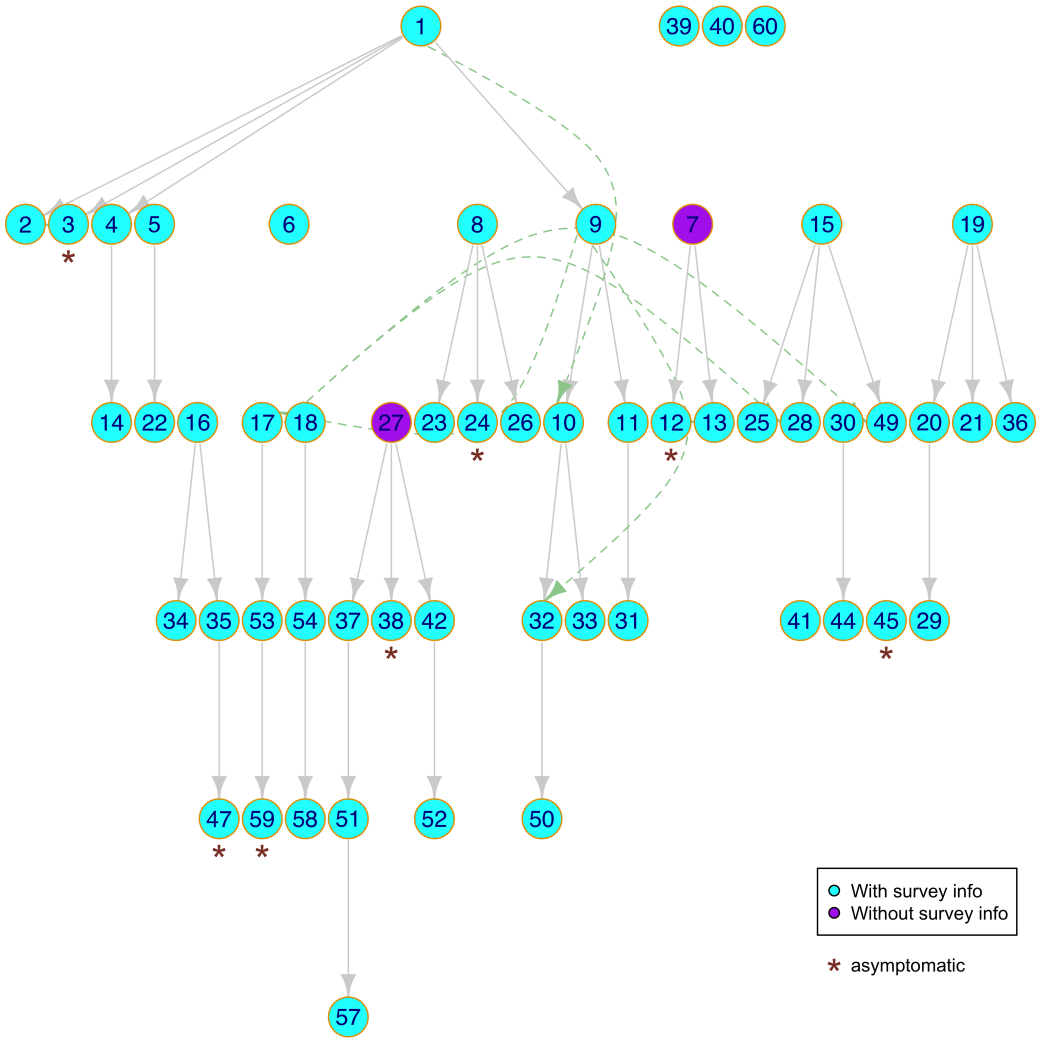
Clinical symptoms source	hat	lower	upper
hat	3.64	0.38	∞
lower	7.65	1.18	∞
upper	1.73	0.12	∞

[6] either tested positive or experienced respiratory symptoms

[7] phase not specified or both

Outline

Transmission Graph(s)



Graph Notation (1)

- We describe the outbreak for the n individuals by the transmission tree $T = (V, E)$. By $v \in V$ with $|V| = n$ denote the nodes of the directed graph and E denotes the set of directed edges.
- For a node v let $\mathrm{pa}(v)$ and $\mathrm{ch}(v)$ denote the set of parents and children, respectively. Since T is a tree $|\mathrm{pa}(v)| = 1$ for any v except for root nodes, which are nodes with $\mathrm{pa}(v) = \emptyset$.
- Assuming the outbreak is observed until its end, the average number of secondary cases a primary cases generates is

$$\frac{1}{|V|} \sum_{v \in V} |\mathrm{ch}(v)|.$$

Graph Notation (2)

- Let $\mathrm{dso}(v)$ denote the day of symptom onset of $v \in V$ and let p_v denote v's parent in T. The empirical distribution of the serial interval time is formed by the values $\mathrm{dso}(v) - \mathrm{dso}(p_v)$, for all v nodes in the set of nodes with known source, i.e.

$$V_p = \{v \in V : |\,\mathrm{pa}(v)| = 1\}.$$

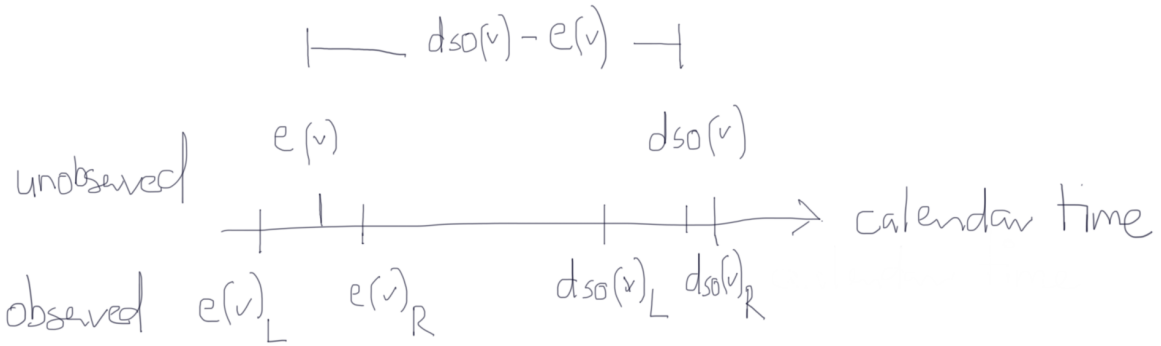
- Let $e(v)$ be the time of exposure of $v \in V$. The empirical *generation time distribution* is formed by the values $t(v) - e(p_v)$, for all nodes $v \in V_p$.
- The empirical *incubation period distribution* is given by the values $\mathrm{dso}(v) - e(v)$ for all $v \in V$.

Interval Censoring (1)

- As noted by Reich et al. (2009) the exact timing of exposition or symptom onset are not always given $\rightarrow$ doubly interval censored data
- If instead the time of exposure and the onset of symptoms are only known to fall within a finite interval, then a typical observation for an infector-infectee pair consist of

$$X(v) = (e(v)_L, e(v)_R, \mathrm{dso}(v)_L, \mathrm{dso}(v)_R).$$

- Illustration:



Interval Censoring (2)

- We follow the approach by Reich et al. (2009).
- Let the incubation period T be a non-negative continuous random variable with PDF $f_\theta(t)$ and let $h_\lambda(e)$ be the PDF of the infecting exposure time E, (in calendar time) and let $g(s)$ to be the PDF of the DSO (in calendar time).
- Assume E to be independent of the incubation period T.
- We have that

$$g(s|e) = f_\theta(s-e|e) = f_\theta(s-e).$$

- The joint PDF of E and the dso is given by

$$p(e,s) = p(e)p(s|e) = h_\lambda(e)g(s|e) = h_\lambda(e)f_\theta(s-e).$$

Interval Censoring (3)

- The likelihood for a single doubly interval-censored observation is therefore

$$L(\theta, \lambda; X) = \int_{E_L}^{E_R} \int_{\mathrm{dso}_L}^{\mathrm{dso}_R} h_\lambda(e) f_\theta(s-e) ds\, de.$$

- Typically, a parametric accelerated failure time model is used to model the incubation period, e.g., a Log-Normal distribution.
- An implementation of this approach exists in the R package `coarseDataTools` (Reich et al. 2019)
- Can extend the modelling of interval censored data with covariates such as age or sex (Werber et al. 2013)

Interval Censoring (4)

```
# Simple dataset with 3 individuals
# type: 0 = doubly interval censored, 1=single interval censored, 2=exact
dat <- data.frame(EL = c(1,2,3), ER=c(2,3,3), SL=c(10,4,9), SR=c(12,7,9), type=c(0,0,2))

# Fit log-normal distribution to the data
coarseDataTools::dic.fit(dat=dat, dist="L")
## Computing Asymptotic Confidence Intervals
## Coarse Data Model Parameter and Quantile Estimates:
##            est   CIlow CIhigh StdErr
## meanlog  1.761   0.648  2.874  0.259
## sdlog    0.417  -0.542  1.376  0.223
## p5       2.929  -3.258  9.116  1.438
## p50      5.818  -0.657 12.293  1.505
## p95     11.557  -8.425 31.538  4.644
## p99     15.358 -19.570 50.285  8.118
##
## -2*Log Likelihood = 10.8
##
## Note: dispersion parameter is exp(sdlog). In this case it is 1.517 (95% CI 0.063-2.971).
```

Multiple trees (1)

- As seen from the transmission tree, it is not always 100% clear who infected who. Instead, up to 3 potential sources could be specified for each case.
- Let $|\,\mathrm{pa}(v)| \geq 1$, $v \in V_p$, denote the set of possible sources in the graph representing transmissions.
- A transmission tree $\mathcal{T}$ can again be obtained by selecting one distinct parent node v_p for each node v with $|\,\mathrm{pa}(v)| > 1$.
- Let $\mathcal{T}$ denote the set of possible transmission trees, i.e.

$$|\mathcal{T}| = \prod_{v \in V_p} |\,\mathrm{pa}(v)|.$$

Multiple trees (2)

- Simple way to average estimation of incubation period, serial interval and generation time over all possible trees:
  - Non-parametric case: for each $T \in \mathcal{T}$ compute the empirical distribution based on the n cases and compute quantiles, mean, etc. based on the set of $n \times |\mathcal{T}|$ values
  - Parametric case: for each $T \in \mathcal{T}$ draw k samples from the respective estimated parametric distribution and compute quantiles, mean, etc. based on the set of $k \times |\mathcal{T}|$ values
- Note: The above averaging approach weighs each $T \in \mathcal{T}$ equally. In principle some trees are more plausible than others $\rightarrow$ Likelihood or Bayesian framework for data augmentation

Results

- Results from Bender et al. (2021) for serial interval (non-parametric), generation time (parametric) and incubation period (parametric)
- A pre-processing step was applied to symptomatic cases filtering out possible sources if they did not meet within 2 days before DSO or 10 days after DSO.
- Results averaged over the 144 possible transmission trees:

	Quantiles							
Time	1%	5%	25%	50%	75%	95%	99%	Mean
Serial interval (d)	−2.0	−1.0	1.0	3.0	6.0	15.0	22.0	4.5
Generation time (d)	0.1	0.3	1.7	3.6	6.6	13.1	21.6	4.9
Incubation period (d)	0.3	0.8	2.5	4.3	6.5	10.6	14.3	4.8

- Note: The serial interval is rather short an can actually be negative. Shows why COVID-19 is hard to control.

Outline

Discussion

- Outbreak investigations are an important tool in the epidemiological toolbox, requires shoe-and-leather epidemiology
- Proper statistical methods as well as software toolboxes, e.g. in the form of R-packages, are needed more than ever! (Höhle 2017)
- For an overview of COVID-19 outbreak investigations in Germany see, e.g., Alpers et al. (2021) (in German)
- Other important COVID-19 investigations are, e.g., Rothe et al. (2020), Russell et al. (2020), Yamagishi et al. (2020) and Murphy et al. (2020).

Literature I


Alpers, Katharina, et al. 2021. "Untersuchung von SARS-CoV-2-Ausbrüchen in Deutschland durch Feldteams des Robert Koch-Instituts, Februar–Oktober 2020". Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz.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Literature II


Nam, Jun-Mo. 1995. "Confidence Limits for the Ratio of Two Binomial Proportions Based on Likelihood Scores: Non-Iterative Method". Biometrical Journal 37 (3): 375–379. doi:10.1002/bimj.4710370311.


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Russell, Timothy W, et al. 2020. "Estimating the infection and case fatality ratio for coronavirus disease (COVID-19) using age-adjusted data from the outbreak on the Diamond Princess cruise ship, February 2020". Eurosurveillance 25 (12).

Werber, D., et al. 2013. "Associations of Age and Sex on Clinical Outcome and Incubation Period of Shiga toxin-producing Escherichia coli O104:H4 Infections, 2011". American Journal of Epidemiology 178 (6): 984–992.

Yamagishi, Takuya, Hajime Kamiya, Kensaku Kakimoto, Motoi Suzuki, and Takaji Wakita. 2020. "Descriptive study of COVID-19 outbreak among passengers and crew on Diamond Princess cruise ship, Yokohama Port, Japan, 20 January to 9 February 2020". Eurosurveillance 25 (23).

Literature IV

Zamar, David, Brad McNeney, and Jinko Graham. 2007. "elrm: Software Implementing Exact-like Inference for Logistic Regression Models". Journal of Statistical Software 21 (3). http://www.jstatsoft.org/.