PROBABILITY OF PELVIC INFLAMMATORY DISEASE IN CHLAMYDIA TRACHOMATIS INFECTION

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Contents

1. Problem Specification

To fix notation, assume the 4 mutually exclusive and exhaustive health states 'CT+, symptomatic' ,'CT+, asymptomatic', 'CT-', and 'PID' (Figure 1). In the k-th patient group (case series, cohort; $k \in \{1, \ldots, K\}$), the respective probabilities at time t are $S_{k1}(t)$, $S_{k2}(t)$, $S_{k3}(t)$, and $S_{k4}(t)$. For the follow-up period of the empirical studies in Section 3 the probability of dying is very small and explicitly set to 0, and no health state for death exists. The system is closed, i.e., no new patients enter and no patients are lost over time. Thus, we repre

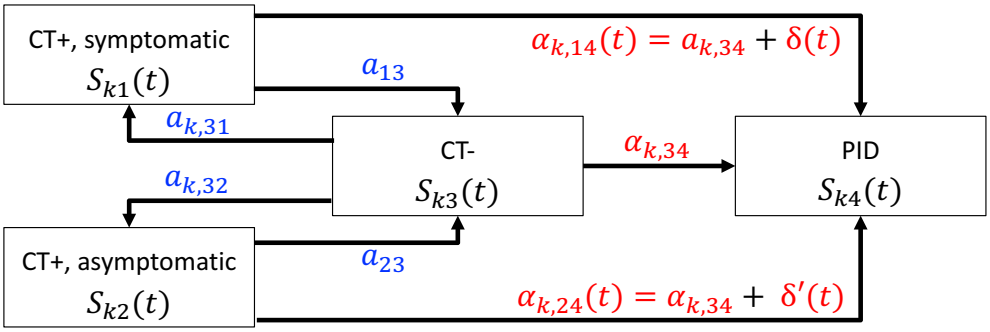

FIGURE 1. **States and between-state transition rates (hazard rates).**

1.1. **Assumptions and notation.**

In Figure 1, rates in blue font are estimated from information external to the K strata, and rates in red font are estimated based on data from the K patient strata. Write $\alpha_{k,ij}$ for the transition rate from state i to state j in the k-th patient group at time t, and $a_{k,ij} = a_{ij}$ for transition rates that are assumed constant across the K groups. Time varying quantities are explicitly called out as functions of time t.

Infection clearance rates α_{13}, α_{23}.

The clearance rate α_{13} for symptomatic and α_{23} for asymptomatic CT+ persons are obtained from the literature. Both clearance rates are assumed to be constant across studies, because the pathophysiology of the disease, once contracted, is expected to be similar across populations.

All symptomatic patients are assumed to seek and receive treatment. The clearance rate under treatment, α_{13}, is assumed to correspond to a uniformly-distributed disease duration between 4 and 8 weeks as in [11] and to be constant across studies. This assumes that people may take between 3 and 7 weeks from the beginning of the infection to initiate a week-long doxacycline treatment. While this assumption appears clinically reasonable, results are not particularly sensitive to this rate.

The clearance rate without treatment, α_{23}, is assumed constant across studies and estimated at 0.74 (95% Credible Interval: 0.61 to 0.89) per year. The estimate is based on baseline CT infection prevalence data following the approach described in [10]. This corresponds approximately to an average of 1 to 1.5 years of asymptomatic CT duration, and

agrees with a SEIRS (susceptible-exposed-infected-recovered-susceptible) model that estimated an asymptomatic duration of 14 months from published data [1]. It also agrees well with our own analyses of the baseline prevalence studies in Section 3 in which we assumed that the empirical proportions were in equilibrium (analyses not shown here.[1])

Reinfection rates $\alpha_{k,31}, \alpha_{k,32}$.

The rate $\alpha_{k,31}$ for symptomatic and the rate $\alpha_{k,32}$ for asymptomatic (re)-infection are allowed to vary across the K strata, because they are taken to depend on the characteristics (behavior) of each population. We identify $\alpha_{k,31}, \alpha_{k,32}$ through their sum

$$\lambda_{kI} = \alpha_{k,31} + \alpha_{k,32}. \tag{1.1}$$

and the proportion of new infections that are symptomatic

$$\phi = \frac{\alpha_{k,31}}{\alpha_{k,31} + \alpha_{k,32}}. \tag{1.2}$$

Then

$$\alpha_{k,31} = \lambda_{kI}\ \phi, \text{and} \tag{1.3}$$

$$\alpha_{k,32} = \lambda_{kI}\ (1 - \phi). \tag{1.4}$$

For *screening cohorts*, we assume that CT- people are at risk of infection $\lambda_{kI} = \lambda_{screening}$ at an incidence of 5% per year following [11]. This estimate agrees well with our own analyses of baseline prevalence data from CT screening studies, where we assumed that the empirical proportions were in equilibrium (not shown). For *case series or for cohorts from STI clinics*, we assume that CT- people are at risk for reinfection, which is approximately 3 times higher than the risk of infection, or 15% per year.[5, 11] The probability ϕ that an incident CT infection is symptomatic was estimated to be 0.24 (95%CI 0.17, 0.32) from [2, 11]. It is assumed to be constant across studies, because it pertains mainly to the pathophysiology of the disease. Results are not particularly sensitive to the estimate for ϕ.

[1] I will add these analyses in an appendix to the paper version of this document.

Rates of pelvic inflammatory disease $\alpha_{k,14}(t), \alpha_{k,24}(t)$.
The rate of pelvic inflammatory disease (PID) for symptomatic $\alpha_{k,14}(t)$ and asymptomatic $\alpha_{k,24}(t)$ infections is decomposed in to a background PID rate $\alpha_{k,34}$ attributed to causes other than CT infection and potentially time varying rates of PID $\delta(t)$ and $\delta'(t)$ attributable to symptomatic and asymptomatic CT infection, respectively:

$$\alpha_{k,14}(t) = \alpha_{k,34} + \delta(t), \tag{1.5}$$

$$\alpha_{k,24}(t) = \alpha_{k,34} + \delta'(t). \tag{1.6}$$

Rate $\alpha_{k,34}$ can be interpreted as a background PID infection rate and is assumed to vary across strata following a rational analogous to that for λ_{kI} and related rates. It is also assumed to be constant over time and unrelated to the timing of a CT infection or re-infection.

The rates of PID that is attributable to symptomatic and asymptomatic CT, $\delta(t)$ and $\delta'(t)$ respectively, are a function of time. It may be argued that the rate of PID is higher early in the infection period, because the infection load may be higher early on.[11] However, in our analyses we assume that $\delta(t) = \delta, \delta'(t) = \delta'$ for all t for identifiablity.[2]

Along the same lines, it may be argued that $\delta(t) \geqslant \delta'(t)$, because symptomatic CT may be associated with a higher infection load and, thus, with more complications. However, in this analysis we assume $\delta(t) = \delta'(t)$. Taken together these assumptions imply that (1.6) and (1.6) become

$$\alpha_{k,14}(t) = \alpha_{k,24}(t) = \alpha_{k,*4} = \alpha_{k,34} + \delta. \tag{1.7}$$

1.2. **Dynamics.**

System of differential equations.
Because the system in Figure 1 is closed, i.e., no patients enter or exit the system, the law

[2]We performed numerical identifiability analyses. They suggest that in our model, as well as in the model used in [11], one cannot uniquely identify time-varying functions for $\delta(t), \delta'(t)$. I suspect that this can also be shown analytically. I therefore do not place much credence on the model selection scheme described in [11].

of total probability implies that

$$S_{k1}(t) + S_{k2}(t) + S_{k3}(t) + S_{k4}(t) = 1. \tag{1.8}$$

Figure 1 represents a dynamic system whose evolution is determined by a known initial condition at $t = 0$

$$\big(S_{k1}(0), S_{k2}(0), S_{k3}(0), S_{k4}(0)\big) = [\text{known}] \tag{1.9}$$

and 4 differential equations

$$\begin{aligned}
\frac{dS_{k1}(t)}{dt} &= -S_{k1}(t)\alpha_{13} - S_{k1}(t)\alpha_{k,14}(t) + S_{k3}(t)\alpha_{k,31},\\
\frac{dS_{k2}(t)}{dt} &= -S_{k2}(t)\alpha_{23} - S_{k2}(t)\alpha_{k,24}(t) + S_{k3}(t)\alpha_{k,32},\\
\frac{dS_{k3}(t)}{dt} &= S_{k1}(t)\alpha_{13} + S_{k2}(t)\alpha_{23} - S_{k3}(t)\alpha_{k,31} - S_{k3}(t)\alpha_{k,32} - S_{k3}(t)\alpha_{k,34}, \text{ and}\\
\frac{dS_{k4}(t)}{dt} &= S_{k1}(t)\alpha_{k,14}(t) + S_{k2}(t)\alpha_{k,24}(t) + S_{k3}(t)\alpha_{k,34}.
\end{aligned} \tag{1.10}$$

The initial condition in (1.9) depends on the characteristics of the k-th patient group. However, the assumptions described in Section 1.1 imply the *homogenous* system

$$\begin{aligned}
\frac{dS_{k1}(t)}{dt} &= -S_{k1}(t)\alpha_{13} - S_{k1}(t)\alpha_{k,*4} + S_{k3}(t)\alpha_{k,31},\\
\frac{dS_{k2}(t)}{dt} &= -S_{k2}(t)\alpha_{23} - S_{k2}(t)\alpha_{k,*4} + S_{k3}(t)\alpha_{k,32},\\
\frac{dS_{k3}(t)}{dt} &= S_{k1}(t)\alpha_{13} + S_{k2}(t)\alpha_{23} - S_{k3}(t)\alpha_{k,31} - S_{k3}(t)\alpha_{k,32} - S_{k3}(t)\alpha_{k,34}, \text{ and}\\
\frac{dS_{k4}(t)}{dt} &= S_{k1}(t)\alpha_{k,*4} + S_{k2}(t)\alpha_{k,*4} + S_{k3}(t)\alpha_{k,34},
\end{aligned} \tag{1.11}$$

which is a simplification of (1.10). In matrix form the system in (1.11) is

$$\begin{pmatrix} \frac{d}{dt}S_{k1}(t) \\ \frac{d}{dt}S_{k2}(t) \\ \frac{d}{dt}S_{k3}(t) \\ \frac{d}{dt}S_{k4}(t) \end{pmatrix} = \begin{pmatrix} -\alpha_{13} - \alpha^{(m)}_{k,*4} & 0 & \alpha_{k,31} & 0 \\ 0 & -\alpha_{23} - \alpha^{(m)}_{k,*4} & \alpha_{k,32} & 0 \\ \alpha_{13} & \alpha_{23} & -\alpha_{k,31} - \alpha_{k,32} - \alpha_{k,34} & 0 \\ \alpha^{(m)}_{k,*4} & \alpha^{(m)}_{k,*4} & \alpha_{k34} & 0 \end{pmatrix} \begin{pmatrix} S_{k1}(t) \\ S_{k2}(t) \\ S_{k3}(t) \\ S_{k4}(t) \end{pmatrix},$$

or

$$\frac{d}{dt}\mathbf{S}(t) = \mathbf{A}\mathbf{S}(t) \tag{1.12}$$

with the obvious definitions for the matrices $\frac{d}{dt}\mathbf{S}(t)$, $\mathbf{S}(t)$ and $\mathbf{A}$.

Solution.

Solving the system in (1.8), (1.9), and (1.12) involves finding closed-form solutions for $\mathbf{S}(t)$. The system is one of ordinary differential equations and can be solved with standard methods, e.g., the eigenvalue method [13, 15]. The current system can be solved in closed-form, but the formulas are unwieldy.[3]

Numerical solution.

The general solution is of the form

$$\mathbf{S}(t) = \mathbf{S}(0)\ \mathrm{MExp}(\mathbf{A}\cdot t), \tag{1.13}$$

where $\mathrm{MExp}(\cdot)$ is the matrix exponential function, a generalization of the exponential function to square matrix arguments. For various definitions of $\mathrm{MExp}(\cdot)$, all equivalent in this application, see [3]. Efficient algorithm implementations for this function are readily available [4]. The computation employed in this work used the function implementation in the *msm* package of *JAGS* [9].

PID attributed to CT infection.

In the homogenous model of Section 1.1, the probability that a given CT infection will cause a PID is the ratio of the rates for transitioning between CT-infected states to PID over all transition rates leaving the CT-infected states

$$\kappa = \phi\frac{\delta}{\alpha_{k,*4} + \alpha_{13}} + (1-\phi)\frac{\delta}{\alpha_{k,*4} + \alpha_{23}}. \tag{1.14}$$

[3]The closed-form solution with the eigenvalue method involves solving the characteristic polynomial of matrix $\mathbf{A}$, which is a 4 degree polynomial. While it is possible to solve 4-th degree polynomials analytically, the formulas are unwieldy. For practical purposes we resort to numerical solutions – which are practically closed form if we consider the matrix exponential function to be readily available to us [3].

One can also estimate the probability of incident PID cases that arise from CT+ states in the interval $(0, 2T]$. Essentially, this is obtained by

$$\xi(2T) = \int_0^{2T} (S_{k1}(t) + S_{k2}(t))\, \delta\, dt. \tag{1.15}$$

We estimate the integral (1.15) numerically, for $2T = 1$ year.[4] For the purposes of a subsequent analysis, we also calculated the quantity

$$\zeta(2T) = \frac{\xi(2T)}{S_{k1}(T) + S_{k2}(T)}, \tag{1.16}$$

which normalizes the probability of an incident CT-infection-attributed PID over the interval from 0 to $2T$ with the mid-interval prevalence of CT.

2. Model of Data

Let $\mathbf{r}_k(0) = (r_{k1}(0), r_{k2}(0), r_{k3}(0), r_{k4}(0))'$ be the number of people in the four health states in stratum k at $t = 0$ and $\mathbf{r}_k(0) = (r_{k1}(0), r_{k2}(0), r_{k3}(0), r_{k4}(0))'$ the corresponding vector at time t. The sample size in stratum k is N_k.

The overall modeling strategy is as follows. We model empirical counts of people in each health state in stratum k and time t to infer the corresponding parameters, i.e., the probability vector $\mathbf{S}_k(t)$. In turn, this informs on the elements of the intensity matrix $\mathbf{A}$ which are functions of the transition rates in Figure 1.

Specifically, we model the counts at baseline as

$$\mathbf{r}_k(0) \sim \text{Multinomial}(\mathbf{S}_k(0), N_k). \tag{2.1}$$

Generally, we would also model the counts in any other time with an analogous multinomial distribution

$$\mathbf{r}_k(t) \sim \text{Multinomial}(\mathbf{S}_k(t), N_k), \tag{2.2}$$

[4]For the actual calculation we leveraged the equivalence between the model described here and an alternative model that splits the 'PID' state into 'PID unrelated to CT infection' and 'PID from CT infection' states. The equivalence can be shown mathematically. Intuitively, 'PID' is an absorbing state, and can be split into several absorbing states that, when merged, reconstruct the original absorbing state.

but, typically, only the counts for $r_{k4}(t)$ are reported in empirical data. The other elements of the $\mathbf{r}_k(t)$ are known up to the sum $r_{k1}(t) + r_{k2}(t) + r_{k3}(t) = N_k - r_{k4}(t)$. Thus, instead, we marginalize over health states 1 to 3 and model only the counts of patients with PID at time t.

$$\mathbf{r}_{k4}(t) \sim \text{Binomial}(\mathbf{S}_{k4}(t), N_k), \tag{2.3}$$

and from (1.13)

$$\mathbf{r}_{k4}(t) \sim \text{Binomial}(\mathbf{S}_{k4}(0)\text{MExp}(\mathbf{A} \cdot t), N_k). \tag{2.4}$$

In turn, the elements of $\mathbf{A}$ are the rates in Section 1.1, and are parameterized as per the equations in Section 1.1. They are assigned priors as described in Section 5.

3. Data

Table 1. Characteristics of eligible studies and number of patients with PID at the end of follow-up. The ? in the counts at the end of follow up means that the corresponding counts are not reported, and are known up to a sum.

Author (year) [Ref]	Design	CT test	Population	Stratum description	λ_{kI}	N_k	$(r_{k1}(0), r_{k2}(0), r_{k3}(0), r_{k4}(0))'$	$(r_{k1}(t), r_{k2}(t), r_{k3}(t), r_{k4}(t))'$	t
Rees (1980) [12]	controlled	Culture	Clinic	CT+, without optimal treatment	0.15	67	(0, 67, 0, 0)	(?, ?, ?, 8)	0.25
Rees (1980) [12]	controlled	Culture	Clinic	CT-, without optimal treatment	0.15	62	(0, 0, 62, 0)	(?, ?, ?, 3)	0.25
Rees (1980) [12]	controlled	Culture	Clinic	CT+, with optimal treatment	0.15	72	(72, 0, 0, 0)	(?, ?, ?, 1)	0.25
Oakeshott (2010) [7]	RCT	NAAT	Screened population	screen, CT+, treated	0.05	63	(63, 0, 0, 0)	(?, ?, ?, 1)	1
Oakeshott (2010) [7]	RCT	NAAT	Screened population	delayed screen, CT+, untreated	0.05	74	(0, 74, 0, 0)	(?, ?, ?, 7)	1
Oakeshott (2010) [7]	RCT	NAAT	Screened population	screen, CT-, untreated	0.05	1128	(0, 0, 1128, 0)	(?, ?, ?, 14)	1
Oakeshott (2010) [7]	RCT	NAAT	Screened population	delayed screen, CT-, untreated	0.05	1112	(0, 0, 1112, 0)	(?, ?, ?, 16)	1
Scholes (1996) [14]	RCT	ELISA+culture	Screened population	unscreened	0.05	1598	(24, 85, 1489, 0)	(?, ?, ?, 33)	1
Scholes (1996) [14]	RCT	ELISA+culture	Screened population	screened, CT+ and treated	0.05	44	(44, 0, 0, 0)	(?, ?, ?, 7)	1
Scholes (1996) [14]	RCT	ELISA+culture	Screened population	screened, CT- not treated	0.05	601	(0, 0, 601, 0)	(?, ?, ?, 2)	1
Ostergaard (2000) [8]	RCT	NAAT	Screened population	home testing	0.05	443	(22, 0, 421, 0)	(?, ?, ?, 9)	1
Ostergaard (2000) [8]	RCT	NAAT	Screened population	office testing	0.05	487	(5, 19, 463, 0)	(?, ?, ?, 20)	1
Morré (2002) [6]	Case-cohort	NAAT	Low risk population	cases	0.05	30	(0, 30, 0, 0)	(?, ?, ?, 0)	1
Morré (2002) [6]	Case-cohort	NAAT	Low risk population	controls (186 of total 714)	0.05	186	(0, 0, 186, 0)	(?, ?, ?, 3)	1

Table 1 shows the characteristics of 5 eligible studies [12, 7, 8, 14, 6]. We included the same studies as [11].

4. Results

This section will be further embelished.

The posterior estimates of δ in Figure 2 are in units year^{-1}.

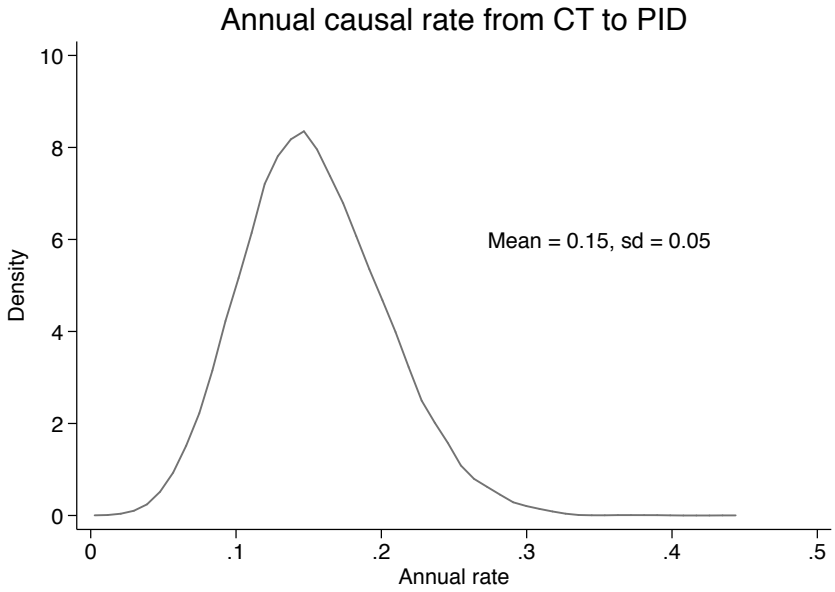

FIGURE 2. **Annual rate of PID attributable to CT.** This is parameter δ. Units are year^{-1}.

Figure 3 shows the estimated probability that a CT infection will result in PID from (1.14).

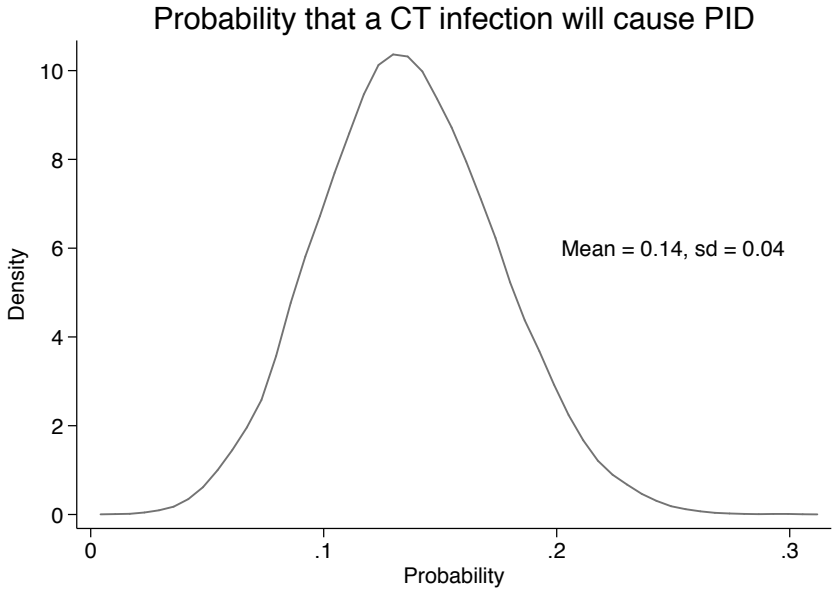

FIGURE 3. **Probability that a CT will result in PID.** This is parameter κ in (1.14).

Figure 4 shows the probability that a CT infection will result in PID over a year normalized by the mid-year prevalence of CT (1.16).

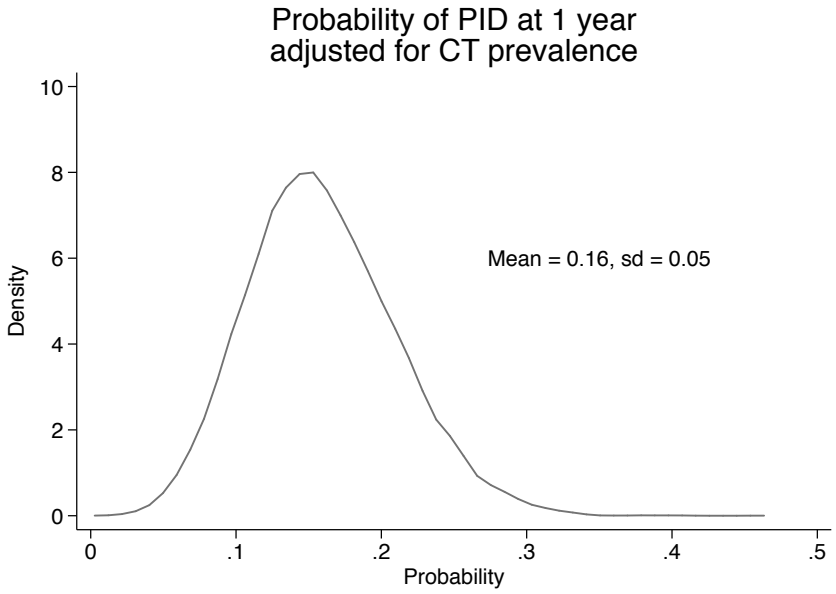

FIGURE 4. **Probability that a CT infection will result in PID over a year normalized by the mid-year prevalence of CT**. This is $\zeta(1)$ in (1.16).

5. JAGS code

```
# Define Q for a 4 state Process with
# States = {S1, S2, S3, S4}
# and dynamics
#  dS1/dt = -S1*a13-S1*(a34+d)       + S3*a31
#  dS2/dt = -S2*a23-S2*(a34+d)       + S3*a32
#  dS3/dt = S1*a13 + S2*a23 -S3*a31-S3*a32 - S3*a34
#  dS4/dt = S1*(a34+d) + S2*(a34+d) +S3*a34
#
# Write
#      | -a13-(a34+d)  |  0             |  Li * phi     | 0 |
# Q  = |       0       |  -a23-(a34+d)  |  Li * (1-phi) | 0 |.
#      | a13           |  a23           |  -Li-a34      | 0 |
#      | a34+d         |  a34+d         |  a34          | 0 |
#
# If Sm(t) = [S1(t), S2(t), S3(t), S4(t)]'
# then, in matrix form, the dynamic system is
# dSm/dt = Qm * Sm
# and there should be a known initial condition Sm(0)



data {

    Li.low <-0.053  # Set assuming that POPI controls are in equilibrium \
                    # and given the prioirs for phi, a13, a23
    Li.high <- 3* Li.low

    #### POPI
    Q.popi[1,2] <- 0
    Q.popi[2,1] <- 0
    Q.popi[1:4,4] <- c(0,0,0,0)

    #### Ostergaard
    Q.ostergaard[1,2] <- 0
    Q.ostergaard[2,1] <- 0
    Q.ostergaard[1:4,4] <- c(0,0,0,0)

    #### Scholes
    Q.scholes[1,2] <- 0
    Q.scholes[2,1] <- 0
    Q.scholes[1:4,4] <- c(0,0,0,0)

    #### Rees
    Q.rees[1,2] <- 0
```

```
    Q.rees[2,1] <- 0
    Q.rees[1:4,4] <- c(0,0,0,0)

    #### Morre
    Q.morre[1,2] <- 0
    Q.morre[2,1] <- 0
    Q.morre[1:4,4] <- c(0,0,0,0)



    #### predicted4 (all PID together)
    Q.pred4[1,2] <- 0
    Q.pred4[2,1] <- 0
    Q.pred4[1:4,4] <- c(0,0,0,0)

    #### predicted 5 states (CT PID not together with other PID)
    Q.pred5[1,2] <- 0
    Q.pred5[2,1] <- 0
    Q.pred5[5,3] <- 0
    Q.pred5[1:5,4] <- c(0,0,0,0,0)
    Q.pred5[1:5,5] <- c(0,0,0,0,0)


}

model {

################################################
#### Likelihood contribution for POPI
################################################

    ## Generator matrix Q.popi
    Q.popi[1,1] <- -a13-(a34.popi + delta)
    #Q.popi[1,2] <- 0
    Q.popi[3,1] <- a13
    Q.popi[4,1] <- a34.popi + delta

    #Q.popi[2,1] <- 0
    Q.popi[2,2] <- -a23-(a34.popi + delta)
    Q.popi[3,2] <- a23
    Q.popi[4,2] <- a34.popi + delta

    Q.popi[1,3] <- Li.low * phi
    Q.popi[2,3] <- Li.low * (1-phi)
    Q.popi[3,3] <- -Li.low - a34.popi
    Q.popi[4,3] <- a34.popi
```

```
    #Q.popi[1:4,4] <- c(0,0,0,0)


    ## POPI, in row j:
    # j=1: screen, ct+, treated
    # j=2: delayed_screen, ct+, untreated
    # j=3: screen, ct-, untreated
    # j=4: delayed_screen, ct-, untreated
    for (j in 1:4) {
        P.t.popi[j, 1:4] <- mexp(Q.popi * t.popi) %*% P0.popi[j,]
        r4.t.popi[j] ~ dbin(P.t.popi[j, 4], N.popi[j])
    }
    # assuming that the proportion of CT+ (S1+S3) in controls at time+ is the
    # same as the proportion at baseline given non-PID status
    P.t.equil.popi <- (sum(P.t.popi[2,1:2])*N.popi[2] +
    sum(P.t.popi[4,1:2])*N.popi[4])/(N.popi[2]+N.popi[4])
    r.t.equil.popi ~ dbin(P.t.equil.popi, N.t.equil.popi)


    ## priors for POPI
    a34.popi ~ dexp(0.00001)

################################################
#### Likelihood contribution for Ostergaard
################################################

    ## Generator matrix Q.ostergaard
    Q.ostergaard[1,1] <- -a13-(a34.ostergaard + delta)
    #Q.ostergaard[1,2] <- 0
    Q.ostergaard[3,1] <- a13
    Q.ostergaard[4,1] <- a34.ostergaard + delta

    #Q.ostergaard[2,1] <- 0
    Q.ostergaard[2,2] <- -a23-(a34.ostergaard + delta)
    Q.ostergaard[3,2] <- a23
    Q.ostergaard[4,2] <- a34.ostergaard + delta

    Q.ostergaard[1,3] <- Li.low * phi
    Q.ostergaard[2,3] <- Li.low * (1-phi)
    Q.ostergaard[3,3] <- -Li.low - a34.ostergaard
    Q.ostergaard[4,3] <- a34.ostergaard

    #Q.ostergaard[1:4,4] <- c(0,0,0,0)
```

```
    ## Ostergaard, in row j:
    ## j=1: home testing
    ## j=2: office testing
    for (j in 1:2) {
        P.t.ostergaard[j, 1:4] <- mexp(Q.ostergaard *
        t.ostergaard) %*% P0.ostergaard[j,]
        r4.t.ostergaard[j] ~ dbin(P.t.ostergaard[j, 4],
        N.ostergaard[j])
    }

    ## priors for Ostergaard
    a34.ostergaard ~ dexp(0.00001)


################################################
#### Likelihood contribution for Scholes
################################################

    ## Generator matrix Q.scholes
    Q.scholes[1,1] <- -a13-(a34.scholes + delta)
    #Q.scholes[1,2] <- 0
    Q.scholes[3,1] <- a13
    Q.scholes[4,1] <- a34.scholes + delta

    #Q.scholes[2,1] <- 0
    Q.scholes[2,2] <- -a23-(a34.scholes + delta)
    Q.scholes[3,2] <- a23
    Q.scholes[4,2] <- a34.scholes + delta

    Q.scholes[1,3] <- Li.low * phi
    Q.scholes[2,3] <- Li.low * (1-phi)
    Q.scholes[3,3] <- -Li.low - a34.scholes
    Q.scholes[4,3] <- a34.scholes

    #Q.scholes[1:4,4] <- c(0,0,0,0)


    ## Scholes, in row j:
    ## j=1: unscreened
    ## j=2: screened, CT+ and treated
    ## j=3: screened, CT- not treated
    for (j in 1:3) {
        P.t.scholes[j, 1:4] <- mexp(Q.scholes * t.scholes) %*%
        P0.scholes[j,]
        r4.t.scholes[j] ~ dbin(P.t.scholes[j, 4], N.scholes[j])
    }
```

```
    ## priors for Scholes
    a34.scholes ~ dexp(0.00001)



###############################################
#### Likelihood contribution for Rees
###############################################

    ## Generator matrix Q.rees
    Q.rees[1,1] <- -a13-(a34.rees + delta)
    #Q.rees[1,2] <- 0
    Q.rees[3,1] <- a13
    Q.rees[4,1] <- a34.rees + delta

    #Q.rees[2,1] <- 0
    Q.rees[2,2] <- -a23-(a34.rees + delta)
    Q.rees[3,2] <- a23
    Q.rees[4,2] <- a34.rees + delta

    Q.rees[1,3] <- Li.high * phi
    Q.rees[2,3] <- Li.high * (1-phi)
    Q.rees[3,3] <- -Li.high - a34.rees
    Q.rees[4,3] <- a34.rees

    #Q.rees[1:4,4] <- c(0,0,0,0)


    ## Rees, in row j:
    ## j=1: unscreened
    ## j=2: screened, CT+ and treated
    ## j=3: screened, CT- not treated
    for (j in 1:3) {
        P.t.rees[j, 1:4] <- mexp(Q.rees * t.rees) %*%
        P0.rees[j,]
        r4.t.rees[j] ~ dbin(P.t.rees[j, 4], N.rees[j])
    }

    ## priors for Rees
    a34.rees ~ dexp(0.00001)



###############################################
```

```
#### Likelihood contribution for Morre
################################################

    ## Generator matrix Q.morre
    Q.morre[1,1] <- -a13-(a34.morre + delta)
    #Q.morre[1,2] <- 0
    Q.morre[3,1] <- a13
    Q.morre[4,1] <- a34.morre + delta

    #Q.morre[2,1] <- 0
    Q.morre[2,2] <- -a23-(a34.morre + delta)
    Q.morre[3,2] <- a23
    Q.morre[4,2] <- a34.morre + delta

    Q.morre[1,3] <- Li.low * phi
    Q.morre[2,3] <- Li.low * (1-phi)
    Q.morre[3,3] <- -Li.low - a34.morre
    Q.morre[4,3] <- a34.morre

    #Q.morre[1:4,4] <- c(0,0,0,0)


    ## Morre, in row j:
    ## j=1: cases (30)
    ## j=2: controls (sample, 186/714)
    for (j in 1:2) {
        P.t.morre[j, 1:4] <- mexp(Q.morre * t.morre) %*%
        P0.morre[j,]
    }
    ## cases data: (r1+r2, r3, r4)
    Pt.cases.morre[1] <- sum(P.t.morre[1,1:2])
    Pt.cases.morre[2:3] <- P.t.morre[1,3:4]
    rt.cases.morre ~ dmulti(Pt.cases.morre[1:3], N.morre[1])
    ##  control data (r1, r2, r3, r4)
    rt.controls.morre ~ dmulti(P.t.morre[2, 1:4], N.morre[2])

    ## priors for Morre
    a34.morre ~ dexp(0.00001)

################################################
#### Prediction for 4 states (all PID together)
################################################

    ## Generator matrix Q.pred4
    Q.pred4[1,1] <- -a13-(a34.pred4 + delta)
    #Q.pred4[1,2] <- 0
```

```
    Q.pred4[3,1] <- a13
    Q.pred4[4,1] <- a34.pred4 + delta

    #Q.pred4[2,1] <- 0
    Q.pred4[2,2] <- -a23-(a34.pred4 + delta)
    Q.pred4[3,2] <- a23
    Q.pred4[4,2] <- a34.pred4 + delta

    Q.pred4[1,3] <- Li.low * phi
    Q.pred4[2,3] <- Li.low * (1-phi)
    Q.pred4[3,3] <- -Li.low - a34.pred4
    Q.pred4[4,3] <- a34.pred4

    #Q.pred4[1:4,4] <- c(0,0,0,0)

    # predition at 0.5 y
    P.t.pred4[1, 1:4] <- mexp(Q.pred4 * 0.5) %*% P0.pred4[1:4]
    P.t.pred4[2, 1:4] <- mexp(Q.pred4 * 1) %*% P0.pred4[1:4]

    ## priors for pred4
    a34.pred4 <- a34.popi



##################################################
#### Prediction for 5 states (CT+ PID separate from other PID)
#### Valid to split because the PID states are absorbing
#### So splitting does the integration easily
##################################################

# Define Q5 for a 5 state Process with
# States = {S1, S2, S3, S4a, S4b}
# and dynamics
#  dS1/dt = -S1*a13-S1*(a34+d)       + S3*a31
#  dS2/dt = -S2*a23-S2*(a34+d)       + S3*a32
#  dS3/dt = S1*a13 + S2*a23 -S3*a31-S3*a32 - S3*a34
#  dS4a/dt = S1*(a34) + S2*(a34) +S3*a34
#  dS4b/dt = S1*(d) + S2*(d)
#
# Write
#      | -a13-(a34+d)  |  0             |  Li * phi     | 0 | 0 |
#      |       0       |  -a23-(a34+d)  |  Li * (1-phi) | 0 | 0 |
# Q5=  | a13           |  a23           |  -Li-a34      | 0 | 0 |.
#      | a34           |  a34           |  a34          | 0 | 0 |
#      | d             |  d             |  0            | 0 | 0 |
#
```

```
# If Sm(t) = [S1(t), S2(t), S3(t), S4a(t), S4b(t)]'
# then, in matrix form, the dynamic system is
# dSm/dt = Q5 * Sm


    ## Generator matrix Q.pred5
    Q.pred5[1,1] <- -a13-(a34.pred5 + delta)
    #Q.pred5[1,2] <- 0
    Q.pred5[3,1] <- a13
    Q.pred5[4,1] <- a34.pred4
    Q.pred5[5,1] <-  delta

    #Q.pred5[2,1] <- 0
    Q.pred5[2,2] <- -a23-(a34.pred5 + delta)
    Q.pred5[3,2] <- a23
    Q.pred5[4,2] <- a34.pred5
    Q.pred5[5,2] <- delta

    Q.pred5[1,3] <- Li.low * phi
    Q.pred5[2,3] <- Li.low * (1-phi)
    Q.pred5[3,3] <- -Li.low - a34.pred4
    Q.pred5[4,3] <- a34.pred4
    #Q.pred5[5,3] <- 0

    #Q.pred5[1:5,4] <- c(0,0,0,0,0)
    #Q.pred5[1:5,5] <- c(0,0,0,0,0)

    # predition at 0.5 y
    P.t.pred5[1, 1:5] <- mexp(Q.pred5 * 0.5) %*% P0.pred5[1:5]
    P.t.pred5[2, 1:5] <- mexp(Q.pred5 * 1) %*% P0.pred5[1:5]

    ## priors for pred5
    a34.pred5 <- a34.popi

    ### Probability of CT+ -caused PID divided by mid-period CT+ prevalence
    prob.star <- P.t.pred5[2,5]/sum(P.t.pred5[1,1:2])


#######################################
#### other priors
#######################################

    # The clearance rate under treatent: uniform rates
    # corresponding to duration between 4-8 weeks
    a13 ~ dunif(52/8, 52/4)
```

```
    # same as Price, but corresponds to the equilibrium in POPI controls (0.77)
    a23 ~ dnorm(0.743, 193)

    delta ~ dexp(0.00001)

    phi ~ dnorm(0.24, 683)  ## proportion with symptoms 0.24 (0.17, 0.32)

    kappa <- (1-phi)*delta/(delta+a23) + phi*delta/(delta+a13)
}
```

References

[1] Christian L Althaus, Janneke CM Heijne, Adrian Roellin, and Nicola Low. Transmission dynamics of chlamydia trachomatis affect the impact of screening programmes. *Epidemics*, 2(3):123–131, 2010.

[2] William M Geisler, Chengbin Wang, Sandra G Morrison, Carolyn M Black, Claudiu I Bandea, and Edward W Hook III. The natural history of untreated chlamydia trachomatis infection in the interval between screening and returning for treatment. *Sexually transmitted diseases*, 35(2):119–123, 2008.

[3] Nicholas J Higham. *Functions of matrices: theory and computation*. Siam, 2008.

[4] Christopher H Jackson et al. Multi-state models for panel data: the msm package for r. *Journal of statistical software*, 38(8):1–29, 2011.

[5] D Scott LaMontagne, Kathleen Baster, Lynsey Emmett, Tom Nichols, Sarah Randall, Louise McLean, Paula Meredith, Veerakathy Harindra, Jean M Tobin, Gillian S Underhill, et al. Incidence and reinfection rates of genital chlamydial infection among women aged 16–24 years attending general practice, family planning and genitourinary medicine clinics in england: a prospective cohort study by the chlamydia recall study advisory group. *Sexually transmitted infections*, 83(4):292–303, 2007.

[6] Servaas A Morré, Adriaan JC Van Den Brule, Lawrence Rozendaal, A Joan P Boeke, Feja J Voorhorst, Sjoerd De Blok, and Chris JLM Meijer. The natural course of asymptomatic chlamydia trachomatis infections: 45% clearance and no development of clinical pid after one-year follow-up. *International journal of STD & AIDS*, 13(1_suppl):12–18, 2002.

[7] Pippa Oakeshott, Sally Kerry, Adamma Aghaizu, Helen Atherton, Sima Hay, David Taylor-Robinson, Ian Simms, and Phillip Hay. Randomised controlled trial of screening for chlamydia trachomatis to prevent pelvic inflammatory disease: the popi (prevention of pelvic infection) trial. *Bmj*, 340:c1642, 2010.

[8] Lars Østergaard, Berit Andersen, Jens K Møller, and Frede Olesen. Home sampling versus conventional swab sampling for screening of chlamydia trachomatis in women: a cluster-randomized 1-year follow-up study. *Clinical Infectious Diseases*, 31(4):951–957, 2000.

[9] Martyn Plummer et al. Jags: A program for analysis of bayesian graphical models using gibbs sampling. In *Proceedings of the 3rd international workshop on distributed statistical computing*, volume 124. Vienna, Austria, 2003.

[10] Malcolm J Price, AE Ades, Daniela De Angelis, Nicky J Welton, John Macleod, Kate Soldan, Katy Turner, Ian Simms, and Paddy J Horner. Mixture-of-exponentials models to explain heterogeneity in studies of the duration of chlamydia trachomatis infection. *Statistics in medicine*, 32(9):1547–1560, 2013.

[11] Malcolm J Price, AE Ades, Daniela De Angelis, Nicky J Welton, John Macleod, Kate Soldan, Ian Simms, Katy Turner, and Paddy J Horner. Risk of pelvic inflammatory disease following chlamydia trachomatis infection: analysis of prospective studies with a multistate model. *American journal of epidemiology*, 178(3):484–492, 2013.

[12] Elisabeth Rees. The treatment of pelvic inflammatory disease. *American Journal of Obstetrics & Gynecology*, 138(7):1042–1047, 1980.

[13] Shepley L Ross. *Introduction to ordinary differential equations*. John Wiley & Sons, 1980.

[14] Delia Scholes, Andy Stergachis, Fred E Heidrich, Holly Andrilla, King K Holmes, and Walter E Stamm. Prevention of pelvic inflammatory disease by screening for cervical chlamydial infection. *New England Journal of Medicine*, 334(21):1362–1366, 1996.

[15] Gilbert Strang. *Introduction to linear algebra*. Wellesley-Cambridge Press Wellesley, MA, 1993.