**Estimating the Force of Infection**

*1. Multi-typic exposures with life-long immunity*

For lifelong immunizing childhood infections for which all individuals are expected to experience infection at some point in their lifetime, the hazard of exposure will compile cumulatively with increasing time since birth (e.g. with age), making time and age interchangeable units. As a result, data describing the age-distribution of exposures can be used to estimate the force of infection (as it varies with time or age or both) in a given system.

Ferguson et al. 19991 presents a system of equations (PDEs) describing the dynamics of a multi-typic dengue infection. These PDEs can be solved to produce a series of expressions describing the time-and-age-dependent population of susceptibles (), the time-and-age-dependent population of individuals exposed to only a primary infection with serotype (), and the time-and-age-dependent population of individuals experiencing any multitypic (2+ exposures) infection :

(1)

(2)

(3)

In equation (1) – (3), the term reflects the inherent confounding between time and age . Following Cummings et al. 20092, we first estimate a time-varying, annual FOI for our Cambodian dengue system, then later add in variation by age class shared across all years and provinces in the dataset.

Cummings et al. 20092 discretized the above, creating a piece-wise solution whereby they estimate an annual mean FOI () representative for all serotypes (because the available data are not serotype-specific, serotype-specific FOIs, , cannot be distinguished). Following Cummings et al. 20092, the integrand in equation 1 can be reformulated as:

(4)

where corresponds to the number of circulating dengue serotypes in the system and corresponds to the duration of time acted on by each , here, for simplicity, always held constant at one year.

Following on above, the second integrand in equation 2 can also be reformulated as:

(5)

where, again, corresponds to the duration of time acted on by each , here held at one year.

We first followed Cummings et al. 20092 to fit the above model to our dataset, estimating 40 , one for each year from 1981-2020, beginning in the birth year (1981) of the oldest individual (22 years) in the first year (2002) of the dataset and extending through the last year of data. Again, following Cummings et al. 20092, we subsequently estimated 40 paired with 10 age-specific variations on the annual which were shared across all provinces and years.

*2. Multi-typic exposures with waning immunity*

Because we observed a sharp increase in the number of dengue cases reported in older (30+ years) individuals in the later years of our dataset, we next extended the model presented in Ferguson et al. 19991 to include a slow rate of waning immunity, which allowed for re-infection with the same serotype in later age classes.

We expressed the first two terms in our system of differential equations as:

(6)

(7)

Where represents the proportion of individuals that demonstrate history of homotypic infection with single strain .

From (6), we can then solve directly for .

(12)

We can then solve for under the assumption that the entire population is born susceptible, From this, we determine that , revealing that the susceptible population is represented by the same expression previously shown for the system without waning immunity in equation 1 above:

(13)

Following Cummings et al. 20092 and using Cambodia data which lack serotype-specific specifications, we can estimate the mean FOI per serotype, assuming circulating serotypes in our system:

(14)

Next, we can solve for the population of individuals exposed to a single serotype () but remaining susceptible to all other serotypes in the system. From equation (7), we show our work to achieve this solution (*blue text indicates notes to guide the analysis*):

*First, replace with .*

(15)

*Following Cummings et al. 2009*2*, we can represent ; as ; and as in the case of serotype-agnostic data:*

(16)

(17)

*Then, rearrange to set up expression in form for application of the integrating factor technique:*

(18)

*Replace term for x with solution from equation (14):*

(19)

*Multiply all terms in expression by integrating factor, :*

(20)

*Simplify using the product rule of differentiation.*

(21)

*Integrate both sides.*

(22)

(23)

As before, we can estimate the proportion of multitypic infections as .

For the purposes of fitting , we can again follow Cummings et al. 20092 to represent the embedded integrand in equation 23 as:

(24)

Then, for the bigger integrand, we do the same… + integration constant???? Not quite sure how to solve this…

When we are using definite integrals (integrating from 0 to a) we do not need to include an integrating constant, you will get the exact same result (if done right).

As for the integrals of integrals, yeah, I think you would do the same thing twice. I don’t think anything unique has to be considered.

OK. So my big question is.. How to best explain the switch from PDEs to ODEs. Do we actually describe a new model with this change in parameter (from t,a to tau), or do we sweep that all under the rug like everyone before us?