**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 with rates in terms of time, , and age, . Ferguson et al. 1999 then derives equivalent 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 . The two variables change at the same rate (i.e. ) and therefore once an individual is born, the difference between their age and the current “time” remains fixed and can be tracked with a single time dependent variable.

Equation (2) describes the population of individuals exposed to only a primary infection with serotype () and can be read as the product of two probabilities:

(the probability of avoiding infection with all serotypes except for up to time t).

(the probability of not avoiding infection with serotype )

Using equation (1), this expression can also be rewritten as:

(4)

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 Ferguson system shown 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:

(5)

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:

(6)

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 can conceptualize our new system in the following box model:



The above diagram assumes two circulating serotypes (represented with subscripts and , keeping with Ferguson’s notation). Additional states could be added if additional serotypes were at play. Then we would use Ferguson’s exact notation where refers to the focal strain and is an index representing all of the other strains. Here, and represent waning from a multi-typic exposure state back to a homotypic exposure state, allowing for re-exposure to and presentation as a reported case. For simplicity, we assume these rates to be constant across age and time. With the exception of the terms, this model is identical to that presented in Ferguson et al. 19991.

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

(7)

(8)

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

From (7), we can then solve directly for .

(9)

Where . We can then solve for (the integration constant) 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:

(10)

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:

(11)

Following Ferguson, we can now derive an expression for . This expression should sum the probabilities of the two disparate routes by which an individual can enter this class, as highlighted in the diagram below—either progressing directly from to (black) or achieving and then waning back into (blue):



We write this new expression as the summed probabilities of the two pathways, with the second pathway described as the product of the sequential probabilities of each of the three steps taken:

(12)

The summation term included with allows for the possibility of including greater than two serotypes by which an individual could wane out of the multitypic exposure state.

After Cummings et al. 20092, we can again discretize the system and estimate the average rate of waning immunity across all serotypes, To this end, we can rewrite the last two integrands in equation (12) as:

(13)

(14)

where, again, corresponds to the duration of time acted on by .