Eradication thresholds in deterministic models with an application to Human Papillomavirus (HPV) Types 6 and 11

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- CP, JT, and VD are employees of Merck Sharp & Dohme LLC,a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and may own stock in Merck & Co., Inc., Rahway, NJ, USA.
- EM is an employee of MSD France, Puteaux, France and may hold stock or stock options in Merck & Co., Inc., Rahway, NJ, USA

Eradication Modeling with Deterministic Compartmental Models

It had generally been accepted that modeling for eradication is best done using stochastic models, rather than deterministic ones:

> *"[Deterministic] models cannot capture chance or stochastic phenomena that are particularly important when transmission rates are low." (Smith et al 2017)*

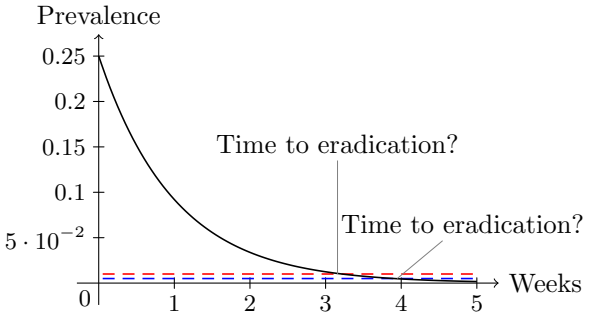
> *"Furthermore, the stochastic framework means we can directly measure EOT (elimination of transmission) in the model outcomes, which cannot be done without defining a threshold of elimination if using a deterministic framework." (Davis et al, 2021)*

However, deterministic compartmental models have enjoyed significant usage in qualitative analyses related to eradication.

Deterministic Compartmental Models and Time-To-Eradication (TTE)

The typical eradication use case for a deterministic compartmental disease model is the computation of the *basic reproduction number* R_0 and determining which sets of parameters lead to $R_0 < 1$.

However, in this type of analysis we cannot know *how long* it will take to achieve eradication. In this case the model must be run and a threshold chosen. But which one?



Examples of Thresholds Used in the Literature

In the literature, many times an "elimination" or "cessation of transmission" threshold will be used in lieu of an eradication threshold. Some examples of this that have come up in the literature:

- Incidence of less than 1 new case per 1 million person-years (Rock et al 2018, Castaño et al 2020).
- Prevalent infection of less than one case (Jiang et al 2017).
- Disease specific "breakpoints" that suggest interruption of transmission (Stolk et al 2015).
- Prevalence of infection below 10 per 100,000 people (Jit et al 2021).
- 99% reductions in infection prevalence from baseline within 70 years (Brisson et al 2021).

Markov's Inequality

Let $\mathcal{I}(t)$ be a discrete random variable representing the number of infected individuals at time t. For $a > 0$ we note that

$$E[\mathcal{I}(t)] \geq \sum_{i=a}^{\infty} iP(\mathcal{I}(t) = i) \geq a \sum_{i=a}^{\infty} P(\mathcal{I}(t)) = aP(\mathcal{I}(t) \geq a)$$

Now Let $a = 1$ and note that $P(\mathcal{I}(t) = 0) = 1 - P(\mathcal{I}(t) \geq 1)$ to get

$$\boxed{P(\mathcal{I}(t) = 0) \geq 1 - E[\mathcal{I}(t)]}$$

So as long as the deterministic compartmental model estimates the expected value of the underlying Markov process, we can relate the model output to the probability of eradication at time t.

Time to Eradication : An Analytical Excursus

The model for clearing infections $I'(t) = -\gamma I(t)$ precisely gives the expected number of infections at time t: $I(t) = E(\mathcal{I}(t))$. Suppose that we begin with I_0 infections, and let $0 < p < 1$. Then, when $I(t) = p$ we have that

$$P(\mathcal{I}(t) = 0) \geq 1 - p$$

Thus $I(t) = p$ is a threshold for a probability of eradication of at least $1 - p$. We can compute the time needed to reach this threshold explicitly:

$$I(\hat{T}) = p \Rightarrow I_0 \exp(-\gamma \hat{T}) = p \Rightarrow \hat{T} = \frac{-\ln\left(\frac{p}{I_0}\right)}{\gamma}$$

Compare this to the actual time to a probability $1 - p$ of eradication:

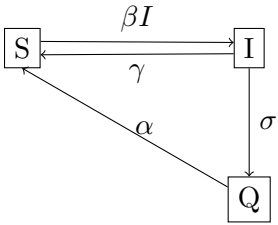
$$T = \frac{-\ln\left(1 - (1-p)^{\frac{1}{I_0}}\right)}{\gamma}$$

Measuring Time to Eradication for Quarantining

$$S' = \alpha Q + \gamma I - \beta SI$$

$$I' = \beta SI - (\gamma + \sigma) I$$

$$Q' = \sigma I - \alpha Q$$



$$R_0 = \frac{\beta}{\gamma},\ R_c = \frac{\beta}{\gamma + \sigma}$$

- We assume that $N = 1200$, $\beta = .75$ and $\gamma = 0.5$ so that $R_0 = 1.5$.
- We assume that the model starts at the endemic equilibrium with no quarantining ($\sigma = 0$). 10 weeks are allowed to pass before quarantining starts, in order to reach the equilibrium distribution.
- For $t > 10$, $\sigma = 1$ so that $R_c = 0.5$.

Repeating the above derivation for clearance of infections, we can show that

$$\frac{d}{dt}E[\mathcal{I}(t)] = \frac{\beta E[\mathcal{I}(t)\mathcal{S}(t)]}{N} - (\gamma + \sigma)E[\mathcal{I}(t)]$$

We do not have, necessarily, that $E[\mathcal{I}(t)\mathcal{S}(t)] = E[\mathcal{I}(t)]E[\mathcal{S}(t)]$, so that a covariance terms is included:

$$\frac{d}{dt}E[\mathcal{I}(t)] = \frac{\beta E[\mathcal{I}(t)]E[\mathcal{S}(t)]}{N} + \frac{\beta \operatorname{Cov}(\mathcal{I}(t)\mathcal{S}(t))}{N} - (\gamma + \sigma)E[\mathcal{I}(t)]$$

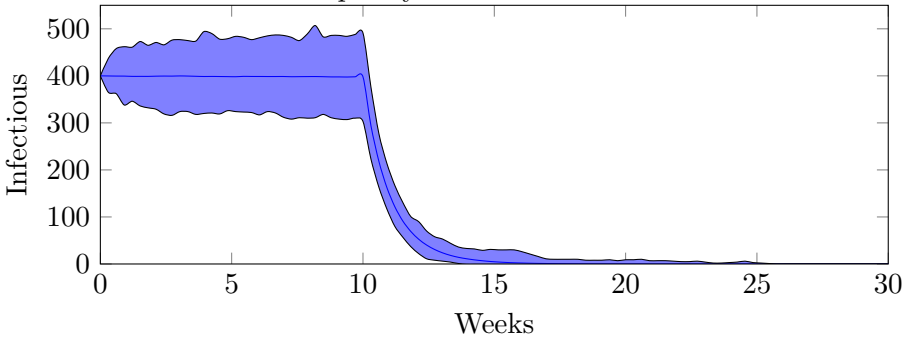
In general, with large and constant population models, it will be the case that the covariance terms that arise due to the non-linearities will be of small magnitude and negative.
As such, the solution to the compartmental model will be an upper bound for the expected value and so:

$$E[\mathcal{I}(t)] \leq I(t) \Rightarrow P(\mathcal{I}(t) = 0) \geq 1 - E[\mathcal{I}(t)] \geq 1 - I(t)$$

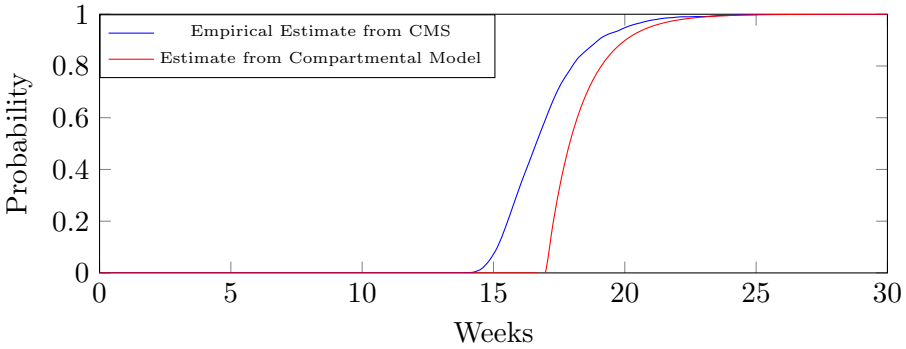
Thus p is still a conservative threshold that corresponds to a probability of eradication that is at least $1 - p$.

Measuring Time to Eradication for Quarantining

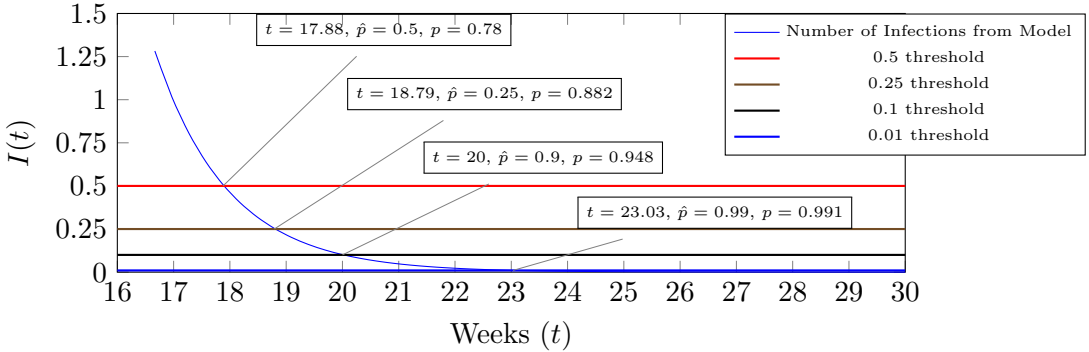
To validate the approach numerically, we implemented the quarantine model in IDM's Compartmental Modeling System (CMS) and empirically estimated the probability of eradication at various times and compared it to the estimates derived from Markov's inequality.



Measuring Time to Eradication for Quarantining



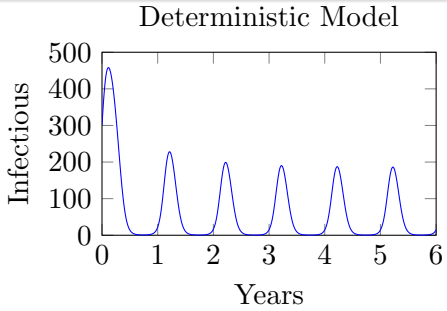
Measuring Time to Eradication for Quarantining



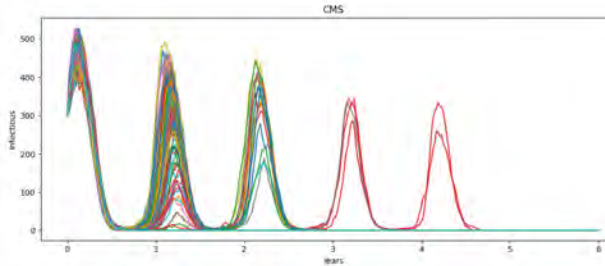
p is the actual probability of eradication when the model hits the threshold, compared to $\hat{p}$ which is the lower bound from Markov's inequality.

An Example with Seasonality

Suppose an SIS model has a seasonal force of infection such that nearly all new infections stop for a large part of the year. The deterministic model has a periodic solution, but the reality is that we expect there to be a probability of extinction on an annual basis. This can be conservatively estimated.

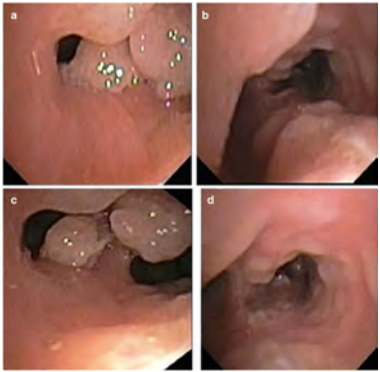


Season	Det. Model	CMS
1	0.1248	0.888
2	0.4352	0.984
3	0.6675	0.996
4	0.8105	0.998
5	0.8932	1.000
6	0.9400	1.000



Juvenile Onset Recurrent Respiratory Papillomatosis (JORRP)

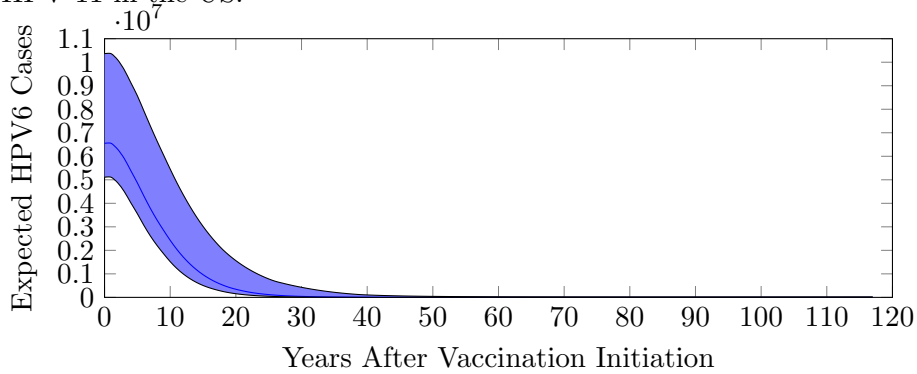
- Oral HPV infections in children following delivery from infected mothers can progress to JORRP, a series of reccuring wart-like growths in the larynx and respiratory tract. Complications include voice loss, respiratory obstruction, and death.
- There is no cure for JORRP, treatments can include multiple annual surgeries, and various therapeutics are in clinical trials.
- 95% of JORRP is caused by HPV types 6 and 11, for which vaccines exist, which also cover other high-risk types.



JORRP in a 11-year-old who had onset at age 3 and had undergone a total of 20 surgeries (Aggarwal, 2021).

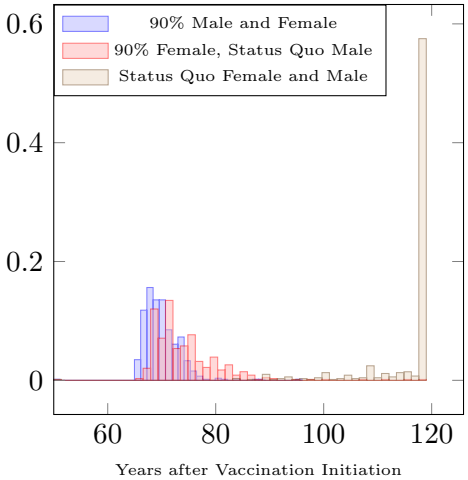
Modeling Eradication of HPV6 and 11 in US

A model of HPV transmission and RRP was calibrated and validated for the US (See Supplemental Slides) and was used to measure the potential impact of HPV vaccination on JORRP, at the current rates. We can also use this model to estimate (subject to some limitations) timing to the eradication of HPV 6 and HPV 11 in the US.

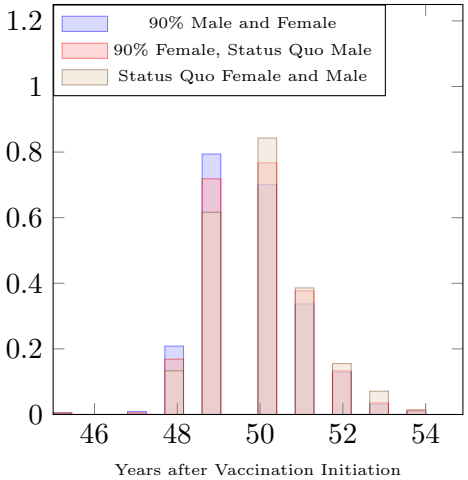


Eradication Under Various Vaccination Scenarios

Year for Probability of HPV6 Eradication of at least 50%

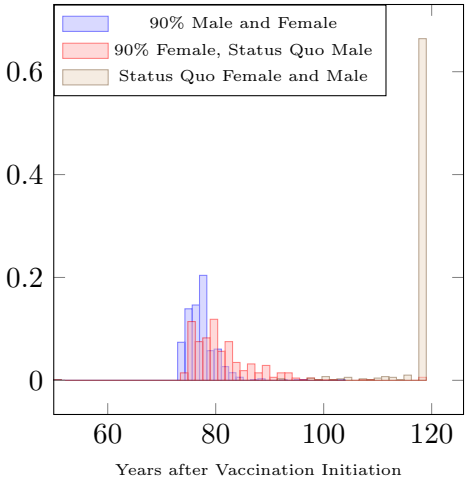


Year for Probability of HPV11 Eradication of at least 50%

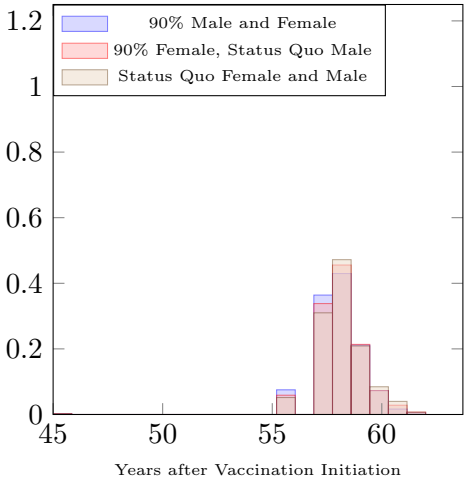


Eradication Under Various Vaccination Scenarios

Year for Probability of HPV6 Eradication of at least 90%



Year for Probability of HPV11 Eradication of at least 90%



Limitations for HPV Eradication

- All eradication modeling comes with substantial limitations, as eradication can be highly sensitive to changes in external factors.
- Changes in sexual behavior are difficult to predict.
- Migration and importation of cases are not accounted for, and could impact the results.
- Difficulties in the implementation of an eradication program are not considered.
- Further analysis at different population scales is required.

Conclusion

- When deterministic, compartmental models are used to estimate the time to eradication (or elimination, or cessation of transmission) a threshold is chosen as a proxy. To our knowledge, no standard threshold exists.
- We have shown that when the model produces an upper bound or close estimate of the expected value, a threshold of p $(0 < p < 1)$ for the expected number of infections in the population corresponds to a probability of eradication of at least $1 - p$.
- This result has been employed to show that HPV6/11 vaccination of females **and** males at high coverage will be essential to eradication of HPV6 and HPV11 in the US, and thus a permanent elimination of 95% of JORRP.

Future Work

- This work has focused on threshold selection, recent work has moved towards analysis and estimation of the distribution of the time of eradication
  - Aliee et al used deterministic models to parameterize a birth–death process and estimate the cumulants of the distribution of eradication times.
  - Hathcock et al have shown that eradication-time distributions in birth–death processes are either Normal, Gumbel, or a skewed class of distributions.
- Our current work is focusing on combining determinstic models with Finite State Projection estimates of the solutions to the master equations in order to relate the probability of eradication to observable quantities.
- If you would like to know more about JORRP, visit the RRP Foundation's website: rrpf.com.

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Supplemental Slides

Relating the Expected Value to the Model

Consider the case of clearance of I_0 infections at rate γ with no new infections, then we can to find the $E[\mathcal{I}(t+\Delta t)]$ we can condition on the value of $E[\mathcal{I}(t)]$:

$$E[\mathcal{I}(t+\Delta t)] = E[E[\mathcal{I}(t+\Delta t)|\mathcal{I}(t)]]$$

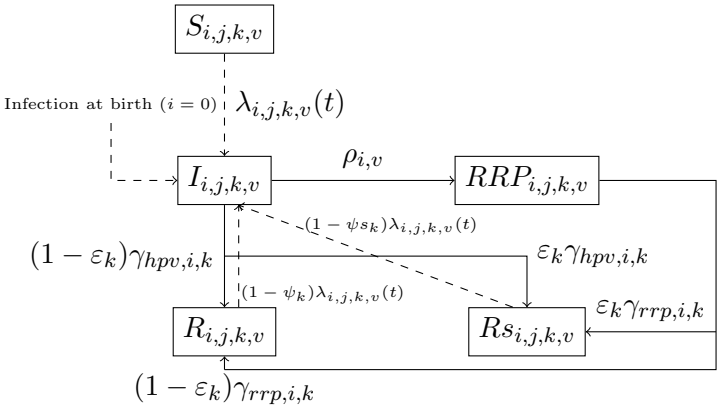
$$= \sum_{i=0}^{I_0} P_i(t) \left(i \exp(-\gamma i \Delta t) + (i-1) i (1 - \exp(-\gamma \Delta t)) + O(\Delta t^2) \right) \Rightarrow$$

$$\frac{E[\mathcal{I}(t+\Delta t)] - E[\mathcal{I}(t)]}{\Delta t} =$$

$$\sum_{i=0}^{I_0} P_i(t) \left(i \frac{\exp(-\gamma i \Delta t) - 1}{\Delta t} + (i-1) i \frac{(1 - \exp(-\gamma \Delta t))}{\Delta t} + O(\Delta t) \right) \Rightarrow$$

$$\frac{d}{dt} E[\mathcal{I}(t)] = \sum_{i=0}^{I_0} P_i(t)(-\gamma i^2 + \gamma i^2 - \gamma i) = -\gamma E[\mathcal{I}(t)]$$

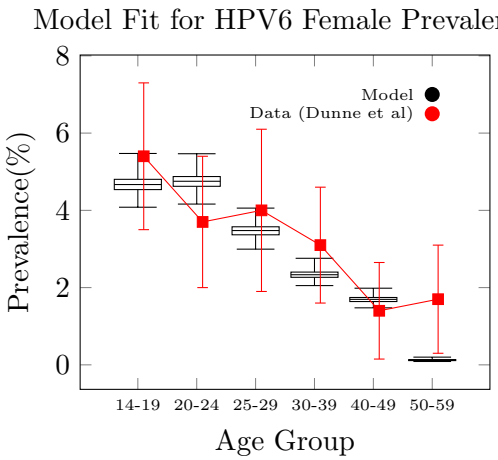
A Model for HPV Infection and JORRP

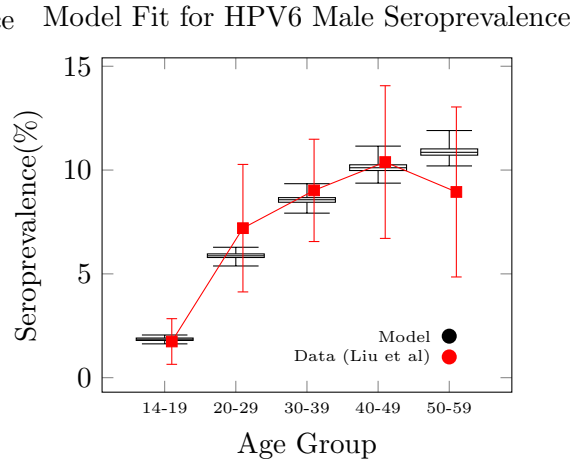


i: age, j: sexual activity level
k: sex, v: vaccination status

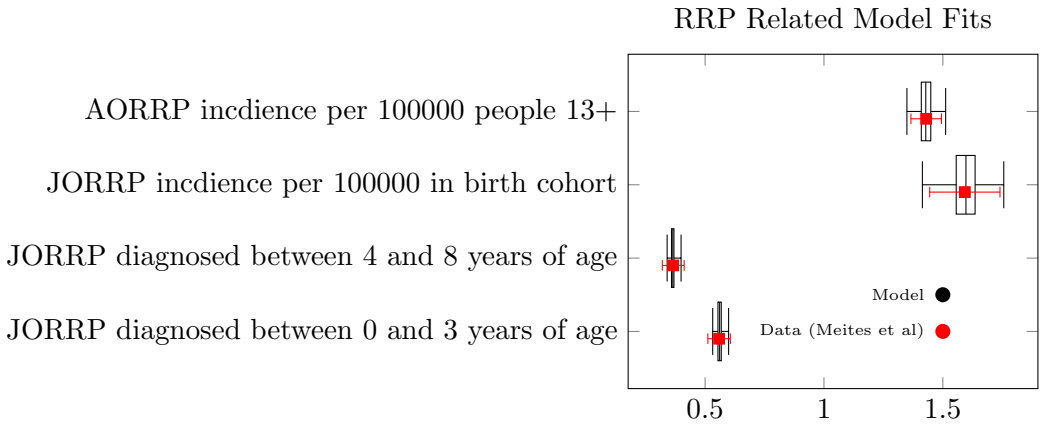
S	Susceptible
I	Infected
RRP	RRP Disease
R	Recovered without seroconversion
Rs	Recovered and seroconverted
λ	Infection rate
ρ	Progression to RRP
ε	Fraction of infections that seroconvert
γ_{hpv}	Clearance rate of HPV infection
γ_{rrp}	Clearance rate of RRP
ψ	Degree of protection against reinfection without seroconversion
ψs	Degree of protection against reinfection with seroconversion

Model Calibration





Model Calibration



Model Validation