Within-host modeling to measure dynamics of antibody responses after natural infection or vaccination: A systematic review

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Background

Understanding the mechanisms of **within-host kinetics** of the humoral (and cellular) immune response to a viral, parasite, or bacterial infection is crucial to foresee better intervention strategies in the context of infectious diseases.
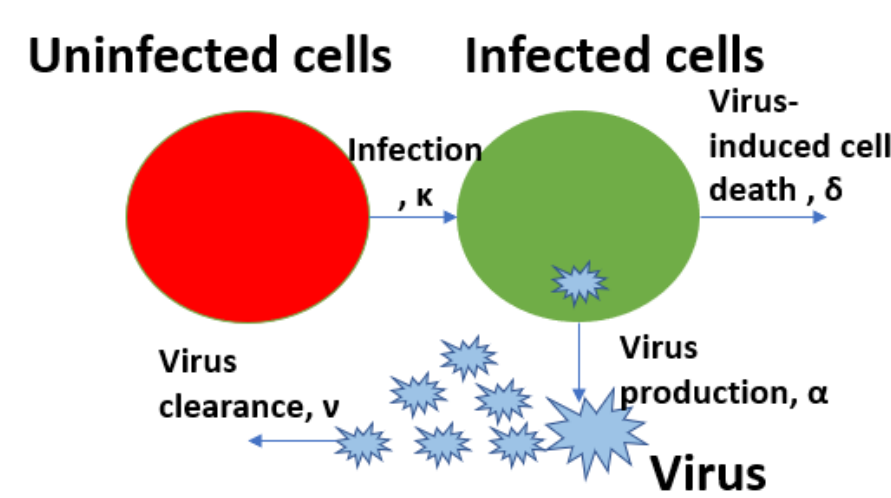

Figure 1: Flow describing the dynamics of uninfected cells, infected cells, and infectious virus [4]
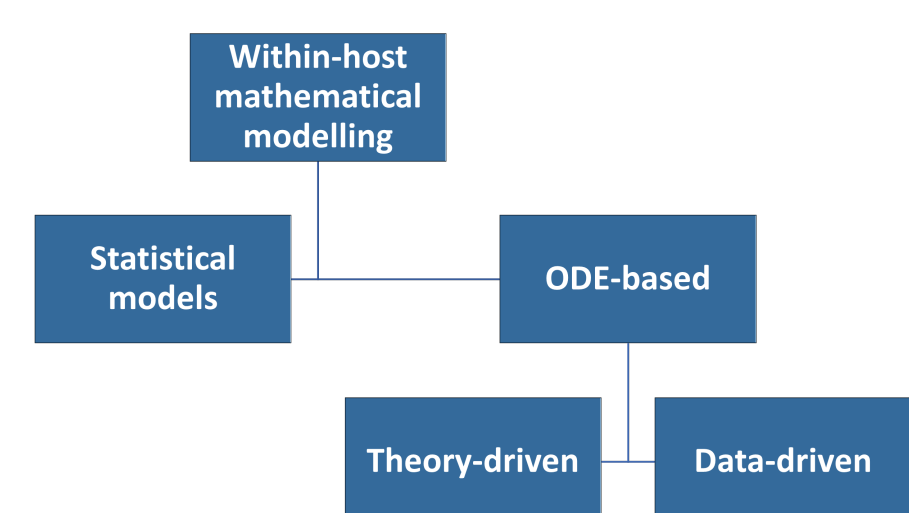
Objectives

Fig. 2: Classification of the within-host mathematical models

To identify within-host **mechanistic modeling approaches to study humoral immunity processes** after vaccination or natural infection. This is crucial to unravel the specific components of the immune system and their dynamics.
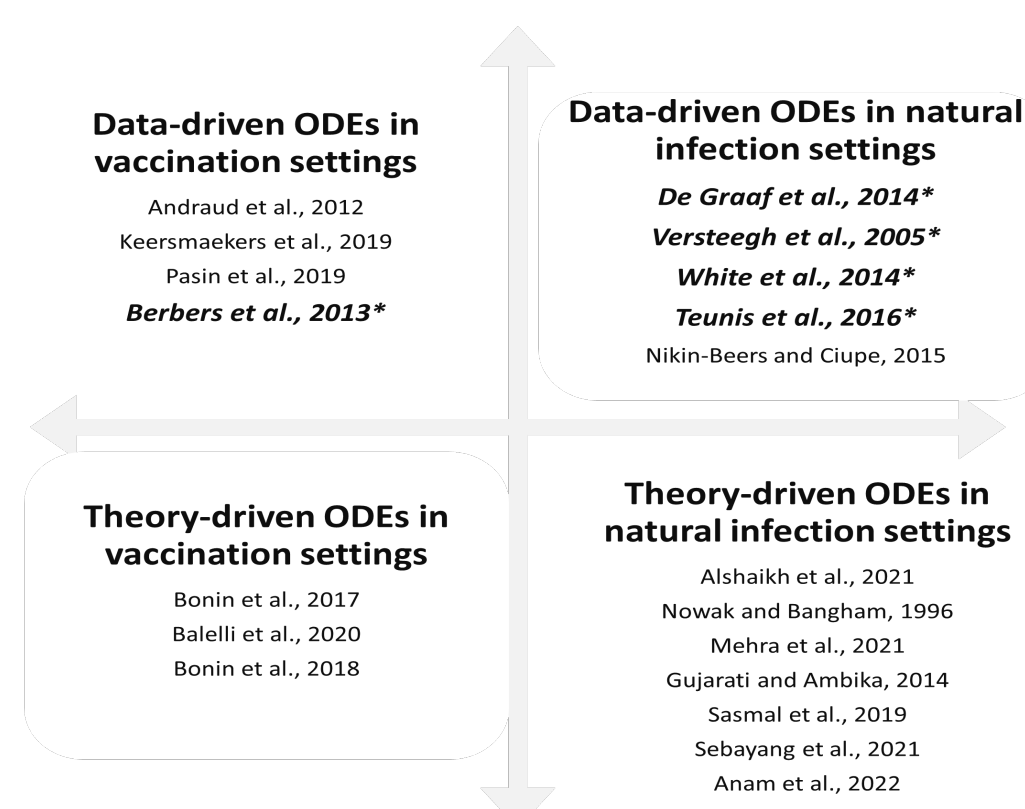
Methodology

The search strategy of our **systematic review** and eligibility criteria are summarized as follows:
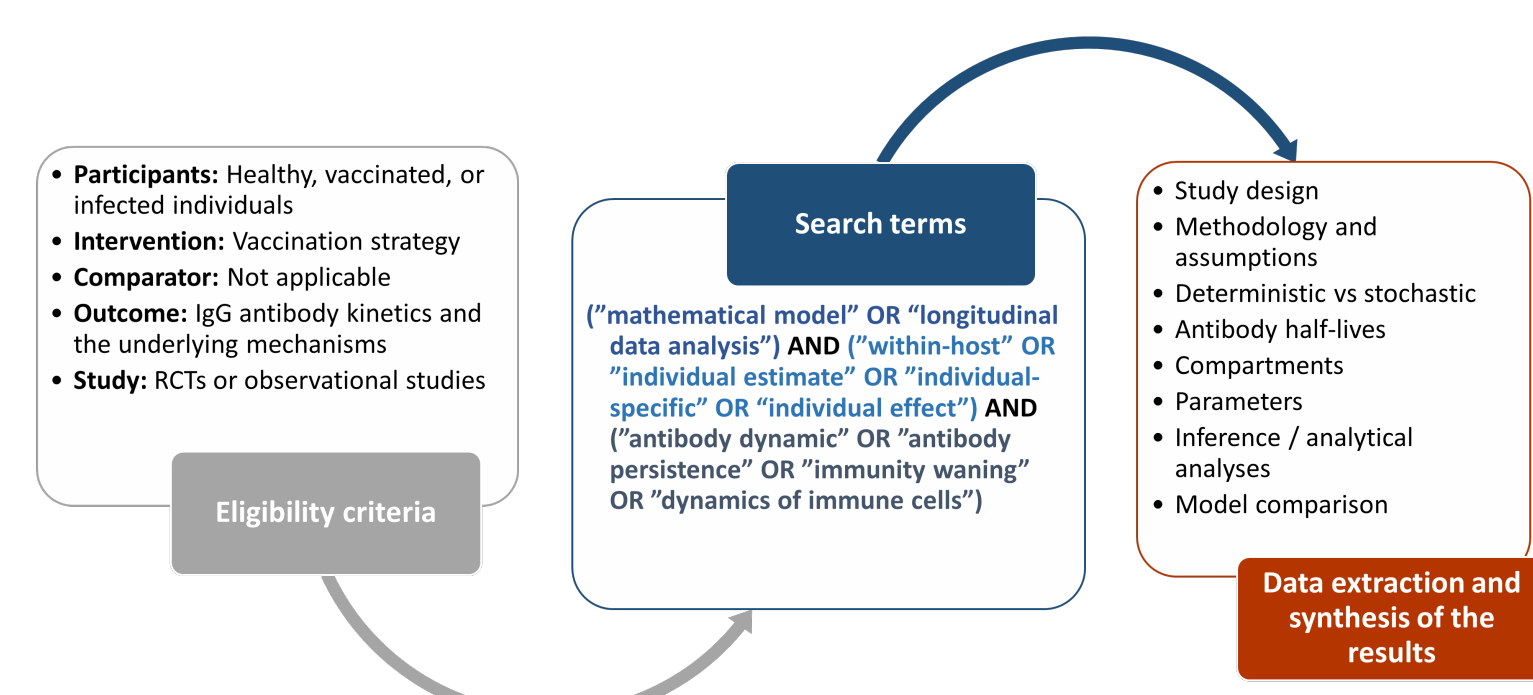
Results

To date, only 20 publications out of 77 have relied on mechanistic models to study the dynamics of humoral immunity.

* Refers to which studies have used Bayesian approaches

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How have Bayesian methods been applied in the parameter estimation of such models?

Vaccine-induced setting: Berbers et al., [5]

Estimation of the model parameters and prediction of the **peak antibody concentrations together with half-time antibody values** were performed using Hierarchical Bayesian methods and Monte Carlo Markov Chain (MCMC).

- **Simple exponential decay**
- **Parametric distributions** for the antibody growth and decay (e.g., Gamma, Inverse gamma).
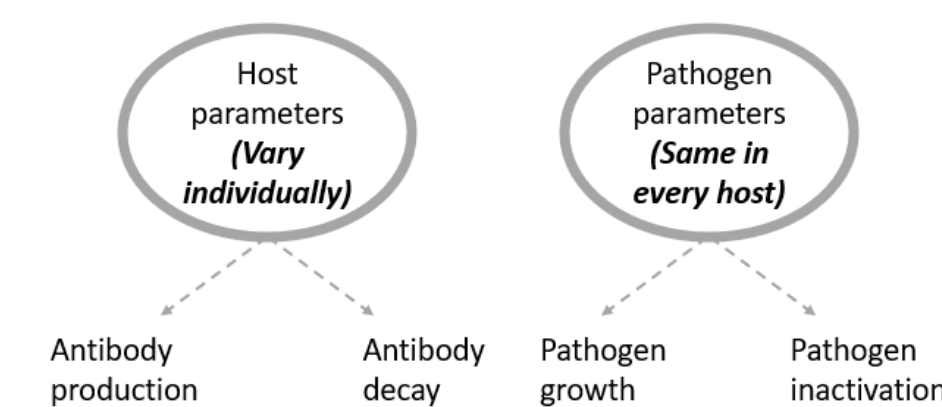
Natural infection setting: White et al., [2]

White et al., [2] studied the impact of maternal immunity on Malaria infections in children.
MCMC iteration using a random walk Metropolis-Hastings algorithm (Model 1):

1. Local parameter (n)
   - $\vec{\theta^{n'}} = [d_m^{n'}, d_a^{n'}, A_m^n, \theta_1^n...\theta_N^n]$
   - $L_{mix}^n(\theta_n'|D_n)$
   - Accept probability $min = \left\{1, \frac{L_{mix}^n(\theta_n'|D_n)}{L_{mix}^n(\theta_n|D_n)}\right\}$

2. Nuisance parameter (n)
   - $\vec{\theta^{n'}} = [d_m^n, d_a^n, A_m^{n'}, \theta_1^{n'}...\theta_N^{n'}]$
   - $L_{mix}^n(\theta_n'|D_n)$
   - Accept probability $min = \left\{1, \frac{L_{mix}^n(\theta_n'|D_n)}{L_{mix}^n(\theta_n|D_n)}\right\}$

3. Global parameter
   - $\vec{\theta} = [d_m', d_a', \sigma_m', \sigma_a', \sigma_{obs}', \theta^1...\theta^N]$
   - Calculate the total likelihood $L_{TOTAL}(\theta'|D_n)$ and update the prior $P(\theta')$
   - Accept probability $min = \left\{1, \frac{L_{TOTAL}(\theta'|D)*P(\theta')}{L_{TOTAL}(\theta|D)*P(\theta)}\right\}$

Truncated normally distributed measurement error
200 million MCMC iterations computed with acceptance rates using Robins-Munro algorithm.

Natural infection setting: Teunis et al., [6]

Teunis et al, [6] extended the work by de Graaf et al., [7] defining multiple antibody production sites defined as c_k below.

Infection and waning immunity process respectively

$$b'(t) = \mu_0 * b(t) - \Sigma c_k * y_k(t) \qquad b(t) = 0$$
$$y_k'(t) = \mu_k * y_k(t) \qquad y_k'(t) = -w_k^* * y_k(t)$$

What functions are studied?
$$\begin{cases} \text{Non-exponential decay} \\ \text{Bi-exponential decay} \\ \text{Power functions} \end{cases}$$

All models used 3 chains and 10^6 iterations. A multivariate normal prior was chosen for the different model parameters, and a Wishart distribution for the random effects.

Findings

1. COMPARTMENTS
   - **Data-driven approaches:** Typically study the interaction between pathogen growth with antibody production, or the dynamics between short- and long-living cells with antibodies.
   - **Theory-driven approaches:** Typically study more complicated processes, starting from susceptible cells population to neutralizing antibody production.

2. PARAMETERS
   - **Data-driven approaches:** Linear, non-linear mixed approaches. **Exponential decay**, bi-exponential, power functions. Smoothing functions and binary functions represent normally the time of vaccination.
   - **Theory-driven approaches:** Simulation approaches to generate the parameters (e.g., Poisson or Binomial distributions).

3. INFERENCE/ANALYTICAL ANALYSES
   - **Data-driven approaches:** Use of Maximum likelihood estimation (MLE) and Bayesian hierarchical approaches with Monte Carlo Markov Chain (MCMC).
   - **Theory-driven approaches:** Model's equilibria and stability.

4. COVARIATES
   Study groups are widely studied. However, there is a **lack of information on geographical background**, surveillance systems, and age.

5. MODEL COMPARISON
   - **Data-driven approaches:** Difficulties in Bayesian approaches due to the number of parameters and complexity of the models. WAIC (Watanabe-Akaike information criteria) for future modelling work. AIC (Akaike information criteria) within MLE [3].
   - **Theory-driven approaches:** Comparison to simulated data.

6. SOFTWARE IN BAYESIAN METHODS
   - Monolix, JAGS.

Conclusion

- More research is needed on the **methods of inference** in data-driven mechanistic models, such as semi-parametric to full parametric tools.
- Biological mechanisms must be distinguished in vaccination or natural infection settings.
- There is not a lot of software that can perform ODEs with Bayesian hierarchical approaches.

Acknowledgments

References

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