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Review

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

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ABSTRACT

Background: Within-host models describe the dynamics of immune cells when encountering a pathogen, and how these dynamics can lead to an individual-specific immune response. This systematic review aims to summarize which within-host methodology has been used to study and quantify antibody kinetics after infection or vaccination. In particular, we focus on data-driven and theory-driven mechanistic models.
Materials: PubMed and Web of Science databases were used to identify eligible papers published until May 2022. Eligible publications included those studying mathematical models that measure antibody kinetics as the primary outcome (ranging from phenomenological to mechanistic models).
Results: We identified 78 eligible publications, of which 8 relied on an Ordinary Differential Equations (ODEs)-based modelling approach to describe antibody kinetics after vaccination, and 12 studies used such models in the context of humoral immunity induced by natural infection. Mechanistic modeling studies were summarized in terms of type of study, sample size, measurements collected, antibody half-life, compartments and parameters included, inferential or analytical method, and model selection.
Conclusions: Despite the importance of investigating antibody kinetics and underlying mechanisms of (waning of) the humoral immunity, few publications explicitly account for this in a mathematical model. In particular, most research focuses on phenomenological rather than mechanistic models. The limited information on the age groups or other risk factors that might impact antibody kinetics, as well as a lack of experimental or observational data remain important concerns regarding the interpretation of mathematical modeling results. We reviewed the similarities between the kinetics following vaccination and infection, emphasising that it may be worth translating some features from one setting to another. However, we also stress that some biological mechanisms need to be distinguished. We found that data-driven mechanistic models tend to be more simplistic, and theory-driven approaches lack representative data to validate model results.

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1. Introduction

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 surveillance and intervention strategies in the context of infectious diseases [1,2]. In general, the immune response consists of innate and adaptive immune systems. The innate immune system is active from birth and provides a specific response to pathogens, whereas the adaptive or acquired immune system produces specific cells and molecules to protect the body against invaders. Within the adaptive immune response, we can distinguish between two types of immunity, dependent on the functions of B- and *T*-cells. Serum antibodies produced by B-cells and plasma cells induce humoral immunity. More specifically, with the assistance of helper *T*-cells, B-cells differentiate into long-living (in the bone marrow) plasma cells that can produce antibodies against a specific antigen. Antibodies can bind to antigens and neutralize them or cause lysis. On the other hand, cell-mediated or cellular immunity is orchestrated by activated T lymphocytes, which recognize infected cells and achieve cell lysis [3]. Both cellular and humoral immune responses are essential to generate short- and long-term immunity in the host.

Within-host kinetics refers to dynamics of immune cells and antibodies in individuals (or animals) which are linked to specific biological mechanisms and for which the extent and evolution with time since infection or vaccination are potentially individual-specific. To facilitate both individual- and population-based perspectives, within-host models often allow for the specification of individual-level effects or individual-specific parameters reflecting differences in terms of individual immune responses on top of model parameters that are shared among individuals [4,5]. The dynamics of immune cells, for instance, describe the life cycle of the immune response and covers all different mechanisms by which a microorganism triggers the activation of long- and short-term immune cells to defeat micro-organisms [4,6]. Furthermore, for many (viral) diseases, there is considerable uncertainty regarding the immune response, e.g., how long do antibodies persist and protect individuals against (re)infection, and whether immunity against certain pathogens is long-lasting (or potentially lifelong). On top of that, age (and other factors) might impact the dynamics of the immune response [2], and waning of the humoral immune response may differ when induced by natural infection or vaccination. It is worth noting that upon exposure, infection history might play a role in protection against new infections. For example, in case of SARS-CoV-2 infection, an individual's immune state is activated, possibly impacted by pre-existing antibodies, otherwise known as immunoglobulins (i.e., IgG, IgM, and IgA antibodies) to other coronaviruses or previous infections with other variants, leading to differential severity of the disease [7,11]. Within the set of antibodies, different temporal dynamics are encountered, in particular, IgG antibodies tend to peak last [7,8]. Moreover, one can hypothesize that vaccinated individuals develop a similar immune response, however, history of exposure or infection may also be a fundamental factor contributing to individual heterogeneity in antibody production and persistence after vaccination. Within-host modeling approaches can be based on a set of mathematical (differential) equations describing the evolution of specific quantities over time. As such, we will distinguish between mathematical models, or so-called mechanistic models, and purely statistical models, referred to as phenomenological models in this manuscript. For example, Leuridan et al. [36] investigated several phenomenological models, such as the exponential decay, or a Gompertz model, to study the antibody decay and quantify the association between the covariates and the antibody response. Note that in general, phenomenological models can be parametric, semi-parametric or non-parametric in nature. We stress the importance of mechanistic models, since they have a biological or physical meaning, thereby explaining interactions between different model components through time, or time and space, whereas phenomenological models try to quantify the association between an independent variable and observed dependent variables or covariates.

Mathematical models are typically expressed in terms of a system of mathematical equations describing the evolution or flow of subjects, individuals, substances, etc. over time or between different compartments or subpopulations. Such mechanistic models are often formulated based on a system of partial differential equations (PDEs) which, under certain conditions, can simplify to a set of ordinary differential equations (ODEs). For example, one of the simplest models found in this review, defined boosting of antibody production followed by a simple exponential decay of antibodies [6]. Next to deterministic models, having a unique solution for the set of ODEs, stochastic models describe the change in variables relying on stochastic processes and probability distributions for transition probabilities. Next to deterministic and stochastic models, subject-specific approaches relying on the specification of random effects are possible thereby accounting for individual variability in antibody kinetics [9].

During this review we classified the selected mechanistic models into data-driven or theory-driven approaches, where the first represent models that are fitted to observed data (i.e., combining mathematical and statistical modeling techniques) and the latter solely investigating properties of a model (e.g., the impact of varying a specific model parameter) without contrasting it with observed data.

When studying antibody kinetics with phenomenological models, one focuses on relationships between covariates and antibody kinetics, without necessarily capturing the underlying biological mechanisms that are responsible for such associations. As an alternative to phenomenological approaches, within-host models offer an elegant way of describing antibody kinetics in terms of such mechanisms. More specifically, as it is important to consider different immune cells that are responsible for antibody production, within-host models are well-suited to describe processes responsible for antibody kinetics and to unravel how specific components of the immune system interact. Consequently, having more knowledge about antibody kinetics may help to solve one of the many

logistic issues of vaccination strategies and prevention of future outbreaks.

This review aims at presenting a comprehensive overview of the different within-host modeling approaches used to describe antibody kinetics, including the dynamics of humoral immune responses and other biological mechanisms. Moreover, in doing so we study approaches for vaccine-induced immunity and immunity induced by natural infection separately.

2. Methods

A protocol for the study described in this manuscript has been published in PROSPERO, CRD42022309251 [12]. The search strategy and eligible publications retrieved from the search are summarized according to the PRISMA guidelines [13].

2.1. Eligibility criteria

Studies including healthy participants that took part in a vaccination trial and were followed up over time, and studies including individuals that were infected by a specific pathogen were considered eligible for inclusion. Therefore, both observational and experimental studies were identified. For the latter, open-label, single-blind, or double-blind, Phase I, Phase II and Phase III randomized controlled trials were considered.

Publications were excluded when immunogenicity dynamics were studied under a drug therapy intervention to inhibit the viral load of the virus. Moreover, we did not include publications of studies conducted in animals or that included in-vitro experimental data.

Although the focus is on the study of different models in the context of within-host kinetics, eligibility criteria are formulated in terms of study design and endpoints being related to antibody evolution over time. For the ‘‘data-driven” approaches, the choice of different models to study within-host kinetics is largely determined by the availability of longitudinal data on the evolution of immune cells and antibodies. For theory-driven approaches, no explicit link to a specific data structure is required for inclusion, though focus should be on within-host kinetics. Therefore, the eligibility criteria reported on in Section 2.1 are primarily of importance regarding data-driven approaches described below. Studies that did not accommodate antibody change over time were considered not eligible for inclusion into this review.

2.2. Search procedure

The keywords of the search string were defined based on keywords used in papers from experts on the field of within-host mathematical modeling. Consequently, a search of potential eligible papers was conducted by using the keywords *‘within-host mathematical model’* or *‘infectious disease mathematical model’*. Through synonyms of the aforementioned keywords we developed the query to find literature in this systematic review: (‘‘Mathematical Model” OR ‘‘Longitudinal data analysis”) AND (‘‘Within-host” OR ‘‘Individual estimate” OR ‘‘Individual-specific”) AND (‘‘Antibody Dynamic” OR ‘‘Antibody Persistence” OR ‘‘immunity waning” OR ‘‘dynamics of immune cells”). PubMed and Web of Science databases were screened to identify relevant literature in English up to May 2022. In addition, EndNote was used to discard duplicate papers and manage references of publications that were retrieved. Lastly, a citation search was performed from the retrieved papers to amplify the literature in this field.

2.3. Outcome

The primary outcome of interest was a mathematical model looking at antibody kinetics. Furthermore, other biological mechanisms that may interact with antibody production were gathered, such as humoral cells, age, time of exposure, and other biological phenomena.

2.4. Selection process

One reviewer (IGF) assessed the selected papers based on abstract and title. Publications that met the eligibility criteria were included in the review. We were not able to assess the risk of bias, since the outcomes in the retrieved studies varied. Furthermore, the type of study was at times hard to classify, as the description of the study design and data were either incomplete or absent. In case of disagreement, senior authors (BO, SA, NH) were consulted to make a final decision on the inclusion or exclusion of a paper. The full-texts of eligible publications were screened in the second round of the literature review.

2.5. Data collection process

We collected information about the pathogen being studied, type of data, study design (how many groups were included in the trial), the number of measurements, and research question. Furthermore, we summarized only the methodology on mechanistic models, i.e., their compartments and parameters, as well as the type of outcome, type of mechanistic model, method of inference or analytical analysis, and model selection. An overview of the collected data from the eligible publications is presented in Table 1 and 2 for dynamics after vaccination and natural infection, respectively.

3. Results

The aim of this systematic review is to collect and unravel which mechanistic approaches have been used in literature to study antibody kinetics. Therefore, we studied data-driven and theory-driven approaches, where the latter approaches usually having no data to support the models and thus not requiring statistical techniques to estimate their parameters.

Fig. 1 shows a flow chart is presented describing each retrieval decision during the search. In total, 78 unique publications were identified and included. Following the flow chart, selected papers were classified in different categories, as provided by Fig. 2. In particular, whereas 25 studies focused on vaccine-induced immunity only 14 papers considered immune dynamics after natural infection. These 39 publications were retrieved based on our query (see Fig. 2). Once the papers obtained from the query were screened, a citation search for the retrieved papers was conducted. A total of 7 studies on ODE-based modelling and 32 studies in which a phenomenological model was used, were retrieved for which the classification is presented in Fig. 2. These ODE-based mathematical models that were not found in the original query [14–19], used more refined keywords such as *T*-cell responses, antibody-producing cells, or vaccine strategies, which were not precisely defined in our search string.

Despite the importance of studying antibody kinetics using a mechanistic model, only 20 publications out of a total of 1592 papers accounted for this. Within the group of mechanistic models, we focus on 8 studies related to vaccine-induced immunity, and 12 studies investigating dynamics after natural infection, as described in Fig. 2. In addition to the mechanistic models, in the context of vaccine-induced antibody kinetics there were 49 studies on phe-

Table 1
Mathematical models in the context of vaccine-induced immunity.

Author and Year	Pathogen	Antibody half-life	Sample size	Data points	Method	Hierarchical vs non-hierarchical	Compartments	Inference/Analytical analysis	Model selection
Pasin et al., 2019	Ebola	24 days after vaccination. Confidence interval (CI) (22,26)	59 participants in each study (UK, Kenya, East Africa)	A baseline measurement and 7 days after the first dose are collected in all groups. Depending on the group, blood samples are collected either on days 29, 36, 50, 180, 240, and 360, or on days 29, 57, 64, 78, 180, 240, and 360	Data-driven ODE-based	Hierarchical	Short-lived and long-lived plasma cells yielding to antibody production	Likelihood-based coupled with MCMC samples	Nonpenalized loglikelihood based cross-validation criterion (LCVa)/ Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)
Andraud et al., 2012	Hepatitis A	17.5 to 26 days	289 in the first group and 113 in the second group	1,12, 18, 24, 30, 36, 42, 48, 50, 66, 78, 90, 102, 114 and 126 months in the first group and 1, 6, 12, 18, 30, 42, 54, 66, 78, 90, 102 and 114 in the second group	Data-driven ODE-based	Hierarchical	Short-lived and long-lived plasma cells yielding to antibody production	Likelihood-based coupled with MCMC samples	AIC
Keersmaekers et al., 2019	Varicella	–	155	Baseline measurement, and 1 and 12 months after vaccination for B-cells. For *T*-cells baseline measurement, 1, 2, 3, and 12 months after vaccination were collected	Data-driven ODE-based	Hierarchical	B and T cells Dynamics with further contrast between short-living and long-living B and T cells	Likelihood-based couples with MCMC samples	AIC
Author and Year	Pathogen	Antibody half-life	Sample size	Data points	Method	Hierarchical vs non-hierarchical	Compartments	Inference/ Analytical analysis	Model selection
Berbers et al., 2013 [20]	Pertussis	–	178. A third sample was collected on 113 out of 178 participants	Before vaccination, 4–6 weeks post vaccination, and 2 years after for a sample of 13 participants	Data-driven ODE-based	Hierarchical	Production and decay of antibodies	Bayesian hierarchi cal frame work	–
Bonin et al., 2020	Yellow fever	–	We refer to the reader to go to Tables 6–9	First scenario: Before vaccination, 30–45 days, 1–5 years, 5–9 years, 10 years post vaccination. Second scenario: 5–9 years and 10 years after vaccination, 30–45 days, 1–5 years, 5–9 years, and 10 years post booster. For more details, we refer to the reader to go to references 3, 19–25 of this paper	Theory- driven ODE-based	Non-hierarchical	Vaccine virus, Antigen- presenting cells (APCs), CD4+ and CD8+ T cells, short and long-lived plasma cells, memory B cells, and antibodies	–	Comparison of the solution of the model with the experimental data
Bonin et al., 2018	Yellow fever	–	Data from Martins et al. [40] 900	Before vaccination, 3 to 7 days after vaccination, and 30 days after vaccination. Some of the participants were retested 10 months after the vaccine	Theory- driven ODE-based	Non-hierarchical	Vaccine virus, APCs, CD8+ T cells, short-lived and long-lived plasma cells, memory B cells and antibodies	–	Comparison of the solution of the model with the experimental data
Bonin et al., 2017	Yellow fever	–	Kay et al. [43] N = 30; [42] N = 824	Kay et al. [43] collected data before vaccination and on day 21, also 26 subjects provided a third serum sample at month 8. In the second study, the authors did not explicitly specified but there was a follow-up period of 141 months [42]	Theory-driven ODE-based	Non-Hierarchical	Vaccine virus and CD4+ T cells, short-lived and long-lived plasma cells, B cells and antibodies	–	Comparison of the solution of the model with the experimental data
Balelli et al., 2020	Ebola	23.9 days after vaccination. CI (22,26)	177	Days 1, 8, 29, 36, 50, 180, 240, and 360 for group receiving the second dose at day 29th, and for the group receiving the second dose at day 57th samples were collected at days 1, 8, 29, 57, 64, 78, 180, 240, and 360	Theory-driven ODE-based	Hierarchical	Vaccine antigen, memory B cells, short-lived and long-lived cells, and specific antibodies	Studied structural identifiability for the model calibration	–

Table 2
Mathematical models in the context of natural infection immunity.

Author and Year	Pathogen	Antibody half-life	Sample size	Data points	Method	Hierarchical vs non-hierarchical	Compartments	Inference/ Analytical analysis	Model selection
Teunis et al., 2016	Pertussis	–	121 (Versteegh et al. [14])	Measure after 3 months of symptom onset and after a year of infection	Data-driven ODE-based	Hierarchical	Multiple compartments where antibodies are produced and then interact with antigens	Bayesian hierarchical framework	–
de Graaf et al., 2014	Pertussis	727 days	121	Measurements were taken at the baseline, and then patients were followed up for 10 years and sera was taken at irregular intervals	Data-driven ODE-based	Hierarchical	Pathogen concentration which interact with the immune or antibody level	Bayesian hierarchical framework using Markov Chain Monte Carlo (MCMC)	–
White et al., 2014	Malaria	Depending on the antigen different estimates are observed. Ghanian children range from (7–56) Model 1, (13–37) Model 2, (11–26) Model 3. Gambian children (32–176) Model 1, (8–16) Model 2, and (3–18) Model 3	151; 124	at birth; 2, 4, and 6 weeks after birth and then every 4 weeks up to 2 years in group 1. Every-two weeks up to three months in group 2	Data-driven ODE-based	Hierarchical	Model 1: Antibodies interact with antigens. Model 2: Plasma cells yield to antibodies. Model 3: Short-lived and long-lived plasma cells yield to antibodies	Bayesian hierarchical framework	–

Author and Year	Pathogen	Antibody half-life	Sample size	Data points	Method	Hierarchical vs non-hierarchical	Compartments	Inference/ Analytical analysis	Model selection
Sasmal et al., 2019	Dengue virus	–	–	–	Theory-driven ODE-based	Non-hierarchical	Healthy cells, infected cells, dengue secondary virus, *T*-cells, cytokines, B-cells, homogeneous antibody after secondary infection, antibody specific for the secondary infection, memory cells, and the heterogeneous antibody	Stability And equilibria of the model is studied	–
Alshaikh et al., 2021	HIV-HTLV co–infection	–	–	One measurement	Theory-driven ODE-based	Non-hierarchical	CD4+T cells, HIV-infected cells, HTLV- infected cells, free HIV particles, and antibodies	Stability and endemic equilib rium criteria are studied	–
Versteegh et al., 2015	Pertussis	–	121	Measure after 3 months of symptom onset and after a year of infection	Data-driven ODE-based	Hierarchical	Pathogen concetration and antibody production	Bayesian hierarchical framework	–

Author and Year	Pathogen	Antibody half-life	Sample size	Data points	Method	Hierarchical vs non-hierarchical	Compartments	Inference/ Analytical analysis	Model selection
Mehra et al., 2021 [35]	Malaria	3, 6 months to a year	–	One measurement	Theory- driven ODE-based	Hierarchical	Antibody response produced by mosquito bites	–	–
Gujarati and Ambika, 2014	Dengue virus	–	68 (34 first infected, and 34 re-infected)	One measurement	Theory- driven ODE-based	Non-hierarchical	Healthy cells, infected cells, dengue virus particles, lymphocytes and neutralizing antibodies	Stability of the equilibrium state is studied	Comparison between the solution of the model and the observed data
Nikin-Beers and Ciupe, 2015	Dengue virus	–	103	–	Theory- driven and data-driven ODE-based	Non-hierarchical	Uninfected monocytes, infected monocytes, dengue virus, resting and activated B lymphocytes, plasma cells, and antibodies	Model's equilibria and stability	–
Nowak et al., 2000	None in particular	–	–	One measurement	Theory- driven ODE-based	Non-hierarchical	Uninfected cells, infected cells, free virus particles, and neutralizing antibodies	–	–

Author and Year	Pathogen	Antibody half-life	Sample size	Data points	Method	Hierarchical vs non-hierarchical	Compartments	Inference/ Analytical analysis	Model selection
Sebayang et al. 2021	Dengue	–	–	–	Theory-driven ODE-based	Non-hierarchical	Susceptible cells, infected cells, virus concentration, second type of susceptible cells, antigen-presenting cells, IgM, IgG, *Cm*, and Cg which are IgM and IgGs clearing the ongoing infection respectively	Numerical simula tions and sensitivity analysis	–
Anam et al. 2022	Dengue	–	–	–	Theory-driven ODE-based	Non-hierarchical	Susceptible cells, infected cells, virus concentration, second type of susceptible cells, antigen-presenting cells, IgM, IgG, *Cm*, and Cg which are IgM and IgGs clearing the ongoing infection respectively	Numerical simula tions and sensitivity analysis	–

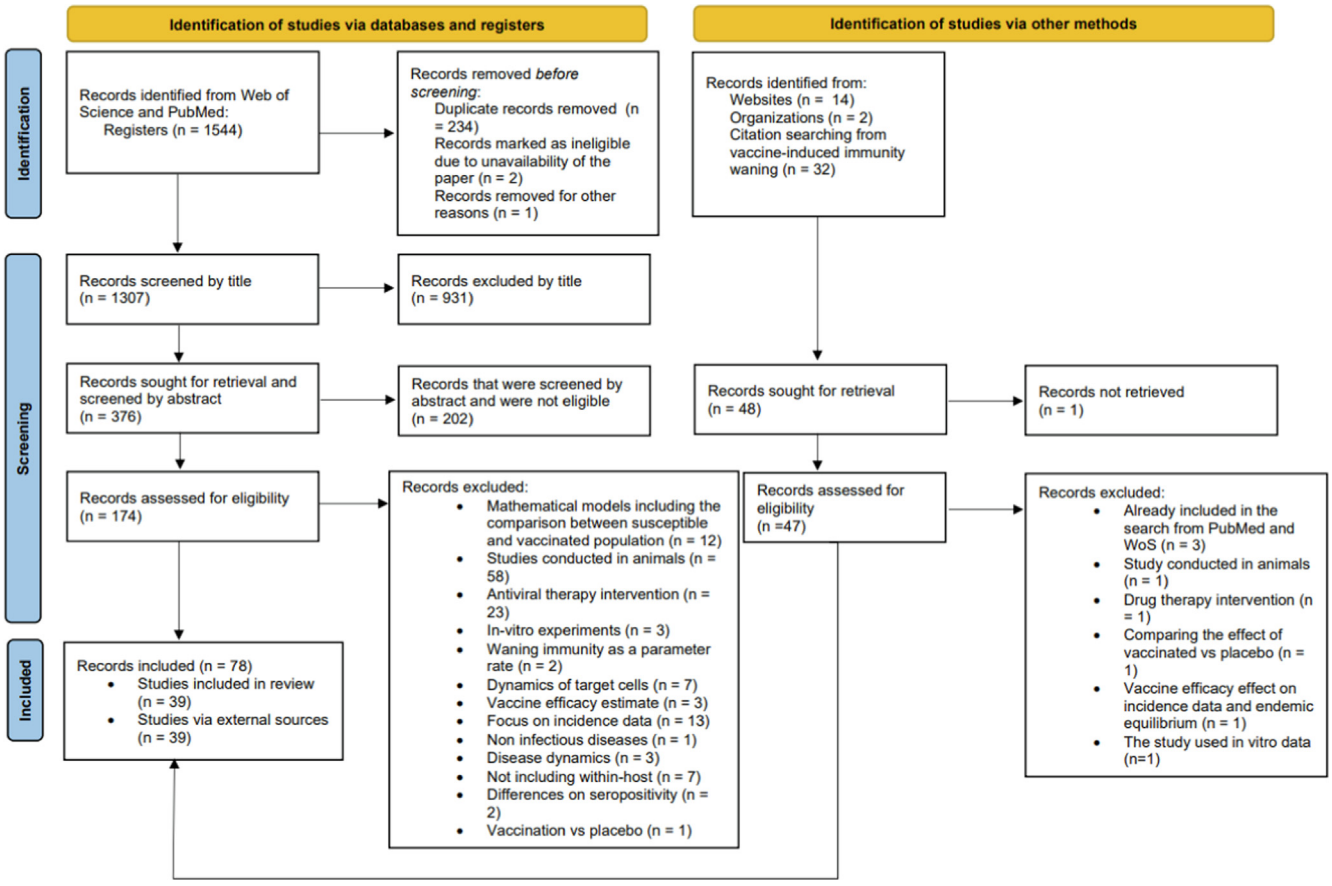

Fig. 1. PRISMA flow diagram for systematic reviews which includes searches of registers and other sources. The left columns represented the screening procedure of the search string used in PubMed and WoS, describing the reason why some studies were discarded in each round. The right column represents the screening procedure through citation search and the studies that were collected by author's name prior to the reports found in the left hand side by the query.

nomenological models, such as Hens et al. [19] in which a linear mixed effect model (LMM) was used. In contrast, we did not find an extensive literature on phenomenological approaches in the context of natural infection, as depicted in Fig. 2.

The results obtained on mechanistic models are presented in Tables 1 and 2. We studied separately vaccine-induced and natural infection settings as the biological mechanisms could potentially differ between one and other. These tables obtain several different pathogens, e.g., the Ebola virus [22,23], the yellow fever virus [24–26], HIV [27], and the Dengue virus [28,29] among others. Some of the retrieved papers did not refer to a specific pathogen [15].

It is apparent from these tables that in vaccine trials, a higher frequency of sampling is observed, with samples taken before and after the prime dose. Study designs typically consist of yearly measurements, with more samples taken during the first year after vaccination. Sampling frequency when studying antibody kinetics after natural infection was found to be different, with generally a longer follow-up period for individuals, though with sampling times mostly within the first six months after infection. In some cases, data collection is found to show a seasonal pattern as, for example, viral respiratory pathogens show higher circulation in winter, while this pattern may be different for other pathogens as they are influenced by environmental factors, for example [21].

The estimated half-life of antibodies is of great importance in data-driven mechanistic models as it governs the waning process, whereas for theory-driven mechanistic models the parameter is fixed to a value obtained from available literature [30]. We found IgG antibody half-life values after vaccination, such as Pasin et al. [22] of 24 days (95 %) CI: [21, 26] for Ebola virus. Similarly, Andraud et al. [5] reported a 95 % CI of [17.5, 26] days for Hepatitis A. In contrast, White et al. [6] provided a wide range of plausible antibody half-lives depending on the model, study population, and antigen of malaria.

In this systematic review we distinguished between theory-driven (11), and data-driven (8) approaches, except for one mixed-methods approach [17] for which the authors reported the theoretical model and stability criteria, while some parameters were estimated. However, the type of inference was not defined in the manuscript. Theory-driven approaches typically study more complex dynamics that translate into multiple compartments and various interconnections between them. Importantly, as these approaches are not data-driven, the realism behind these more complicated structures is not necessarily verifiable based on available data. For example, Balelli et al. [18] emphasized and added a specific memory B cell component. The memory B cell component was used to evaluate the magnitude of the immunological memory response induced by a booster dose. Alternatively, the following papers shared similarities in describing dynamics of the humoral response while starting from a population of susceptible cells. For instance, Alshaikh et al. [27] studied the activation of antibodies under (co)infection with HIV and HTLV. Sasmal et al. [31] described a (re)infection flow produced after the first infection while accounting for antibodies that are homogeneous with respect to primary infection, but heterogeneous to secondary infection with another serotype. Similarly, Nikin-Beers et al. [17] studied a secondary Dengue virus infection to determine the role of antibodies in inducing severe disease. By accounting for this, the authors emphasized the role of long-lived plasma cells after first infection.

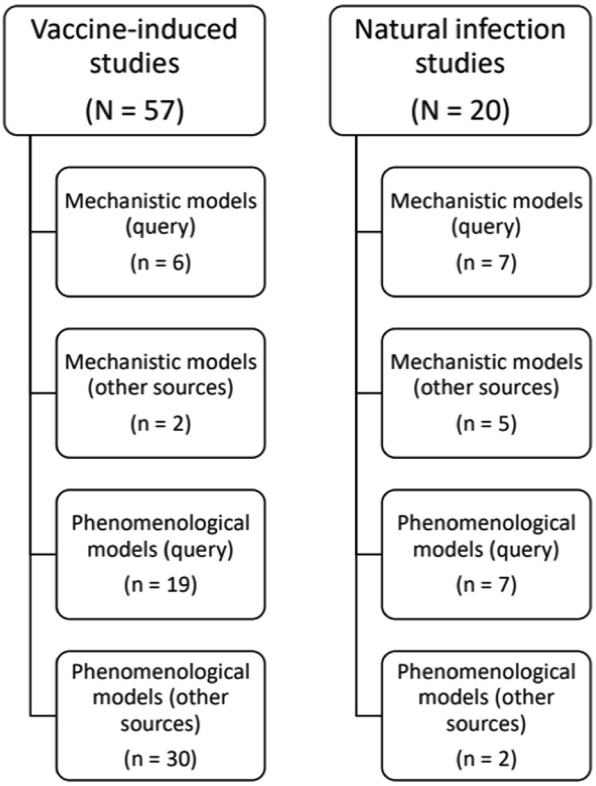

Fig. 2. Classification of the selected studies in the systematic review, differentiating between the source of immunity, type of model and finding source.

Several of the data-driven mechanistic approaches retrieved in our search focused on populations of short- and long-lived plasma cells [5,6,22,32]. The differential equations describing transitions among these populations differ between studies of vaccination and natural infection. To further clarify, Keersmaekers et al. [32] accounted for two vaccine doses relying on two smooth functions describing the proliferation rates in long-lived cells. In contrast, Pasin et al. [22] studied the proliferation of antibodies in relation to binary explanatory variables, indicating when the visit after the prime-boost occurred. On the other hand, White et al. [6] analysed the antibody titres per antigen, and when a boost of these titres occurred, these authors assumed an exposure of that specific antigen, which may not have coincided with the virus detection methods.

With respect to the types of statistical models that have been studied to infer the parameters of the mechanistic models, results show that both linear and non-linear mixed-effects models have been considered. Likelihood-based methods with Bayesian principles have relied on the estimation of their parameters through a mixed-effects approach, while fully Bayesian approaches have shown more variation in how these parameters were estimated.

Model comparison for data-driven models was often done using AIC [5,22,32] and less often using LCVa or BIC [22]. Nonetheless, White et al. [6] concluded that the model comparison was at times challenging to evaluate, given the number of random effects and parameters of the models in a Bayesian framework.

4. Discussion

Our review revealed that the literature about within-host models that study antibody kinetics is rather scarce and that more research in this direction is warranted.

The first question in this review sought to determine which mechanistic models have been used in literature and which biological processes were integrated into their core equations. As it was mentioned in the introduction section, we distinguish throughout the review between data-driven and theory-driven models, with the latter often studying much more complex dynamics. On the question of theory-driven mechanistic approaches, we note that they typically study processes starting from a population of susceptible cells, followed by infected cells, *T*-cell and B-cell activation, to neutralising antibody production.

One of the recommendations we wish to make is to pay more attention in future modelling work to the difference in proliferation rate of the virus in the context of natural infection or vaccination, since in the latter case the virus is unable to proliferate itself. In contrast, data-driven approaches typically study the interaction between pathogen concentration and antibody production site, or the dynamics of short- and long-lived plasma cells and antibodies.

There were several noteworthy findings regarding the parameters of these mechanistic models. Bonin et al. [24,25] included a pre-existing innate immune response in one of the parameters of the model, defined as the homeostasis rate. White et al. [6] studied the impact of maternal immunity and malaria protection and therefore integrated a parameter specifying maternal immunity. Andraud et al. [5] formulated different hypotheses of the parameters, such as the lifespan of antibodies being relatively short in comparison to plasma cells, which allowed the authors to work under different solutions of the model.

Regarding the inference used in data-driven mechanistic models, we found that most often fully Bayesian or likelihood methods coupled with MCMC sampling were used. The latter approach is a rather particular way to do inference for dealing with the inherent complexity of fitting such models to data. Specific software like NIMROD or Monolix has been developed and used relying on MLE and maximum a posteriori (MAP) approaches [5,22,32]. For this reason, it is not straightforward to strictly classify data-driven approaches as purely frequentist or Bayesian.

The different studies use different software with different options, for example in terms of the number of iterations, making it hard to compare modelling approaches. For example, in fully Bayesian approaches, Teunis et al. [33] used 10^6 MCMC iterations in JAGS, while White et al. [6] ran 200 million MCMC iterations though for the latter no specific software was reported.

Another interesting finding in these data-driven approaches, especially in fully Bayesian approaches, was the difficulty to come up with an accurate model comparison. According to Gelman et al. [34] the Watanabe-Akaike information criteria (WAIC) using cross-validation may be the preferred choice, since it adds a correction for the effective number of parameters to adjust for overfitting, and it may have fewer stability problems than the AIC and the Deviance Information Criterion (DIC). However, most of the models presented in this review used AIC and at times BIC or LCVa.

As was pointed out in the introduction to this paper, mathematical models are classified into mechanistic models and phenomenological models. We could in this review distinguish between parametric, semi-parametric and non-parametric phenomenological approaches. A well-known example of parametric approaches is the LMM, as can be illustrated in the work by Bovier et al. [37] assuming that the log-antibody titres and random effects follow a normal distribution. In contrast, non-parametric models do not make any assumptions and allow the estimation of the parameters to adapt to the pattern of the data. A classic example of non-parametric approaches can be illustrated in the work by Geistanger et al. [38], in which the authors used a local regression approach, not specifying any a priori shape when modelling IgA data.

Having discussed the nature of such phenomenological models, we now introduce which parametric assumptions have been used to study the relationship between the predictor and the response

variables. Results show that linear (linear regression, fractional models) to non-linear (exponential decay, power-law models) mixed approaches have been used. A useful example of linear models is the work by Hens et al. [19] which considered fractional polynomials with and without covariates and studied different degrees within these models to fit the data. Another well-known example of linear approaches by Aregay et al. [10] uses a linear mixed-effects model to estimate the subject-specific trajectories of HPV antibody titres over time. The model includes a fixed-effect quadratic polynomial to capture the overall trend of the antibody titres, as well as a random intercept and slope to account for the individual variability in the antibody responses. The distinction with non-linear approaches is further exemplified in studies such as Tiru et al. [39] and Leuridan et al. [36]. The first used the so-called catalytic model, which essentially represents a non-linear function of time, and the model parameters include the initial antibody level, the decay rate, and the plateau level. The second, used an exponential decay, generalized exponential decay, and a Gompertz model to study the antibody decay and quantify association with covariates.

Returning briefly to the subject of study design as mentioned in the results section, it is worth mentioning how required sample size, the timing of sampling, follow-up period, frequency, and from whom samples are taken may be crucial to inform within-host models [41]. Therefore it is essential to think carefully about the design of a study before it is implemented.

A limitation of this review is that more search strategies concerning data-driven mechanistic models, or using search terms such as antib* or vaccin*, could have been used. However, since plenty of publications had to be discarded, and the use of citation search did not increase the number of papers, we decided to adhere to the current query, as described in the protocol of the review, CDR42022309251 [12].

The strength of our study is that it focuses on mathematical models, and more specifically mechanistic models, synthesizing the types of populations that have been considered to study antibody kinetics, and its underlying hypotheses that motivated the model development. Within data-driven mechanistic models, our review gives an overview of which statistical approaches have been studied to infer their parameters from data. To the best of our knowledge, this review is the first one to focus on mechanistic models to study antibody kinetics. In future investigations, it might be possible to use and build on modelling techniques as found in this review.

5. Conclusions

This systematic review underlines that more research needs to be done in data-driven mechanistic approaches to study the waning of humoral immunity. Although the use of phenomenological models is widely used especially in the context of vaccination, these are limited to studying the association between antibody decay and its covariates. In addition, more research is needed on the methods of inference in data-driven mechanistic models, such as semi-parametric to full parametric tools, as well as incorporating more data and measurements to feed the model.

An important consideration for future modeling work, is that there exist differences between pathogens in terms of immune responses. Hence, some immune cells, times of antibody decay and exposure to different antigens are not directly comparable for all pathogens, which can lead to think about pathogen-specific compartments to describe the respective humoral immune response. However, an essential remark by de Graaf et al. [30], is that these models can not consider too many parameters, since that would lead to overfitting. Therefore, similarities exist between the compartments and parameters considered in different models.

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Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Irene Garcia-Fogeda reports financial support was provided by University of Antwerp. Niel Hens (NH) reports that the Universities of Antwerp and Hasselt have received funding for advisory boards and research projects of MSD, GSK, JnJ, Pfizer outside the proposed work. NH did not receive any personal remuneration.

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