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Nonlinear mixed models and related approaches in infectious disease modeling: A systematic and critical review

Olaiya Mathilde Adéoti [a], Schadrac Agbla [b], Aliou Diop [c], Romain Glèlè Kakaï [a, *]

[a] Laboratoire de Biomathématiques et d'Estimations Forestières, University of Abomey-Calavi, Cotonou, Benin
[b] Department of Health Data Science, University of Liverpool, Liverpool United Kingdom
[c] Laboratoire d'Etude et de Recherche en Statistique et Developpement, Gaston Berger University, Saint-Louis Senegal

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ABSTRACT

The level of surveillance and preparedness against epidemics varies across countries, resulting in different responses to outbreaks. When conducting an in-depth analysis of microinfection dynamics, one must account for the substantial heterogeneity across countries. However, many commonly used statistical model specifications lack the flexibility needed for sound and accurate analysis and prediction in such contexts. Nonlinear mixed effects models (NLMMs) constitute a specific statistical tool that can overcome these significant challenges. While compartmental models are well-established in infectious disease modeling and have seen significant advancements, Nonlinear Mixed Models (NLMMs) offer a flexible approach for handling heterogeneous and unbalanced repeated measures data, often with less computational effort than some individual-level compartmental modeling techniques. This study provides an overview of their current use and offers a solid foundation for developing guidelines that may help improve their implementation in real-world situations. Relevant scientific databases in the *Research4life* Access initiative programs were used to search for papers dealing with key aspects of NLMMs in infectious disease modeling (IDM). From an initial list of 3641 papers, 124 were finally included and used for this systematic and critical review spanning the last two decades, following the PRISMA guidelines. NLMMs have evolved rapidly in the last decade, especially in IDM, with most publications dating from 2017 to 2021 (83.33%). The routine use of normality assumption appeared inappropriate for IDM, leading to a wealth of literature on NLMMs with non-normal errors and random effects under various estimation methods. We noticed that NLMMs have attracted much attention for the latest known epidemics worldwide (COVID-19, Ebola, Dengue and Lassa) with the robustness and reliability of relaxed propositions of the normality assumption. A case study of the application of COVID-19 data helped to highlight NLMMs' performance in modeling infectious diseases. Out of this study, estimation methods, assumptions, and random terms specification in NLMMs are key aspects requiring particular attention for their application in IDM.

* Corresponding author.
E-mail addresses: mathildeadeoti@yahoo.fr (O.M. Adéoti), schadrac.agbla@gmail.com (S. Agbla), aliou.diop@ugb.edu.sn (A. Diop), romain.glelekakai@uac.bj (R. Glèlè Kakaï).

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1. Introduction

In recent years, there has been an increased interest in statistical modeling of infectious diseases (ID) based on reported cumulative cases (Büyüktahtakı et al., 2018; Lee, Hu, Chen, Huang, & Hsueh, 2020; Nishiura et al., 2006; Paul & Held, 2011; Tovissodé et al., 2020, 2021). These models capture the behaviour of outbreaks and enable the estimation of critical epidemiological parameters.

From the review by Gnanvi et al. (Gnanvi, Salako, Kotanmi, & Kakaï, 2021), and Tang et al. (Tang et al., 2020), the first and most used approaches related to epidemic modeling are compartmental models, which are a type of mathematical model used by epidemiologists to simulate infectious disease epidemics for over a century. Compartmental models divide a population into mutually exclusive compartments that denote disease status and provide a set of differential equations that define the flow of the population between compartments (Brauer, Castillo-Chavez, & Castillo-Chavez, 2012). Traditionally, they are named after their compartments, with examples including the SIR (susceptible-infectious-recovered) model (Kermack & McKendrick, 1927) and the classic SEIR (Susceptible-Exposed-Infectious-Recovered) model. Other technical extensions to this basic SIR model, as well as mechanical extensions such as modifications to the three-compartment SIR model to account for additional components or disease mechanisms, have been developed and widely discussed (Tang et al., 2020). Moreover, all these mechanistic models are of great interest in analyzing infection dynamics for large populations, such as countries or states, where most model parameters may be assumed to be homogeneous and represent the entire population. Such a macro-modeling approach is particularly valuable in the early phase of a disease outbreak when health administrations aim to develop nationwide macro-intervention protocols. Even during the COVID-19 epidemic, numerous research works have proposed the generalized susceptible, exposed, infectious, removed model to predict the inflexion point for the growth curve (Peng, Yang, Zhang, Zhuge, & Hong, 2020). Additionally, Yang et al. (Yang et al., 2020) modified the proposed model and considered public health interventions in predicting the trend of COVID-19 in China. Liu et al. (Liu, Magal, Seydi, & Webb, 2020) proposed a differential equation prediction model to identify the influence of public policies on the number of patients, while Li et al. (Li, Feng, & Quan, 2020) used a symmetrical function and a long-tail asymmetric function to analyze daily infections and deaths in Hubei and other places in China. However, a major limitation of these works is that researchers are typically confined to analyzing data from a single country, thereby neglecting the global nature of the pandemic.

As the epidemic evolves, surveillance data becomes abundant and attains higher resolution at the community level. Researchers, in turn, are increasingly interested in estimating the average behaviour of the disease for entire regions while highlighting specific nuances for different countries. In such circumstances, a macro-model becomes unsuitable for an in-depth analysis of micro-infection dynamics due to substantial heterogeneity across local communities. It's worth noting that most existing macro-mechanistic models for the spread of infectious diseases are based on the assumption that the system is homogeneous in space. This assumption holds that if the population vulnerable to the infectious disease is well-mixed, human interventions will be uniform across different spatial locations. However, this scenario is only realistic in certain situations. Substantial heterogeneity in urbanization, ethnic distribution, political views, governance, and economic composition among different subgroups of individuals distributed over geographical locations influences the spread of infectious diseases.

Infectious disease outbreak data (reported cumulative cases) are often collected within countries or regions. Similarly shaped profiles with different decay patterns, unexplained variation among repeated measurements within each country or region, skewness, outliers, or skewed heavy-tailed noises are some inherent features possibly embodied within response variables (Schumacher, Ferreira, Prates, Lachos, & Lachos, 2021). Countries that experienced an outbreak earlier will likely have more data than their counterparts within the same region. To be prepared, and due to data scarcity, countries that have not yet reached the peak of the outbreak tend to utilize existing data from countries within their region to model the average pattern and make inferences about the epidemic. Moreover, the level of surveillance and preparedness against outbreaks varies across countries, influencing different countries' responses to epidemics, which, in turn, may affect epidemiological parameters. Thus, modeling should consider the variability across and within countries when estimating the dynamic spread of diseases over different countries. Significant extensions of infectious disease models, incorporating spatial heterogeneity across various geographical locations into modeling and analysis, have greatly impacted epidemiological research. The recent development involves integrating classical spatial cellular automata (CA) (Von Neumann Burks et al., 1966) with temporal multi-compartment models, leading to an important class of spatio-temporal multi-compartment models. This system has been well-studied and is widely discussed, with various propositions highlighted in the latest review by Tang et al. (Tang et al., 2020), showcasing its usefulness in predicting local infection risk. Moreover, various individual-level modeling techniques are available. Individual-level models are applied to infectious epidemic data to enhance the understanding of the spatio-temporal dynamics of infectious diseases. These models, which are flexible and intuitively parameterized under a Bayesian framework via Markov chain Monte Carlo (MCMC) methods, can be challenging to implement due to intense computational requirements, especially when calculating the full posterior for large or moderately large susceptible populations or in the presence of missing data. (Deardon et al., 2010).

The onset of the disease occurs at different periods between and within countries or regions and at different stages of a pandemic from one country to another. Meanwhile, unless data integration is employed, combining data from different countries to elicit a solution with a unified view, estimation, or prediction may fail to capture some crucial changes in the shape of the infection trajectory due to a lack of knowledge about the other stages (Lee, Lei, & Mallick, 2020). Considering the

different stages of the spread of the disease is crucial information that should be used in modeling. Nonlinear mixed effects models (NLMMs) constitute a proposed methodology that accommodates the different stages of the diseases and borrows information from the different time series to provide a more robust and reliable fit and prediction.

In recent years, nonlinear mixed effects models have garnered significant attention in the statistical literature due to their flexibility in handling heterogeneous and unbalanced repeated measures data with less effort and time consumption than advanced compartmental/mechanist techniques. This versatility proves particularly valuable in various areas of investigation (Pinheiro, Bates, & Lindstrom, 1995), including epidemiology, especially in modeling infectious diseases. Rodríguez et al. (Rodríguez et al., 2017) emphasized the utility of a nonlinear mixed-effects model in infectious disease modeling for obtaining estimates of key epidemiological parameters, such as turning points. These estimates provide crucial information about the changing trends of the epidemic and can potentially indicate shifts in intervention and control strategies. Furthermore, the nonlinear mixed-effects model integrates information from within and between both individuals and countries or regions, outperforming individual-level models that only analyze data within single entities. (Lee, Lei, & Mallick, 2020). Li et al. (Li, Qian, & Huggins, 2003) modelled diseases with heterogeneous rates by allowing for household heterogeneity, assuming that the probability of avoiding infection varies randomly in a chain binomial model known to describe outbreaks of infectious diseases in households. Similarly, Davis et al. (Davis, Waller, & Haber, 2006) considered heterogeneity in transmission probabilities by including household-specific random effects when estimating vaccine efficacy based on outbreak household data. Zeger and Karim (Zeger & Karim, 1991) and Lin and Zhang (Lin & Zhang, 1999) used a generalized linear (additive) mixed model (GLMM) to analyze longitudinal data on respiratory infection in Indonesian children. Paul and Held (Paul & Held, 2011) introduced random effects into the model discussed in Held et al. (Held, Höhle, & Hofmann, 2005) and later extended in Paul et al. (Paul, Held, & Toschke, 2008), where the counts (number of cases of a specific disease) are assumed to follow a Poisson distribution to accommodate heterogeneous disease transmission and incidence levels.

Recent advancements by Schumacher et al. (Schumacher, Ferreira, et al., 2021), Zeitoun et al. (Zeitoun et al., 2020), and Kaimann and Tanneberg (Kaimann & Tanneberg, 2021) have introduced a novel class of Nonlinear Mixed Effects Models (NLMMs) for efficient parameter estimation in infectious disease modeling. This includes essential parameters such as infection rate, reproduction number, peak time, peak size, and more, with specific applications to the COVID-19 pandemic. Zeitoun et al. (Zeitoun et al., 2020) utilized NLMMs to assess the association between participants in a national election and the epidemic spread of COVID-19 in France. Conversely, Kaimann and Tanneberg (Kaimann & Tanneberg, 2021) employed NLMMs to analyze the relationship between measures taken against the COVID-19 pandemic and the cumulative number of confirmed COVID-19 cases.

Despite the increasing use of NLMMs, a review of their development trends, estimation methods, and key specifications has not yet been conducted. NLMMs remain under-explored in the context of infectious disease dynamic modeling. A clear discussion about the advantages or challenges of using such an approach to handle infectious diseases is necessary to provide an overview of the current use state and offer a solid foundation for developing guidelines that may help improve its implementation. In this paper, we conducted a systematic and critical review of studies published between January 1, 2000, and December 30, 2021, on NLMMs related to infectious diseases. The aim is to (i) summarise the current state of the use of NLMMs in infectious disease modeling and computational advances, (ii) assess model-building specifications (non-linear function, random effects and error distributions, estimation methods, etc.) for robust infectious disease modeling, and (iii) discuss the advantages or limits of using NLMMs to handle infectious disease dynamics.

2. Overview on nonlinear mixed effects models

2.1. Theoretical framework

For general forms illustration, let n denote the number of subjects and n_i represent the number of measurements on the i^{th} subject. It's worth noting that in particular cases of infectious disease modeling, the subjects typically refer to countries or areas within a country. For notational convenience, let x_{ij} $(i = 1, 2, \ldots, n; j = 1, 2, \ldots, n_i)$ be a vector incorporating independent variables, $\phi_{ij} = (\phi_{1ij}, \ldots, \phi_{sij})^\top$; $\beta = (\beta_1; \ldots; \beta_p)^\top$. The NLMMs model can be written as (Lindstrom & Bates, 1990):

$$\boldsymbol{y}_i = \mu_i(t_{ij}; \boldsymbol{\phi}_{ij}) + \boldsymbol{\epsilon}_i \quad ; \quad \boldsymbol{\phi}_{ij} = d(x_{ij}; \boldsymbol{\beta}; b_i), \tag{2.1}$$

where the subscript i is the subject index; $\boldsymbol{y}_i = (y_{i1}; \ldots; y_{in_i})^\top$, with y_{ij} being the response value for individual i at time t_{ij}; $\mu_i(t_{ij}; \boldsymbol{\phi}_{ij}) = (\mu(t_{i1}; \boldsymbol{\phi}_{i1})^\top; \ldots; \mu(t_{in_i}; \boldsymbol{\phi}_{in_i}))^\top$, with $\mu(.)$ being a nonlinear known function, $\boldsymbol{\epsilon}_i = (\epsilon_{i1}, \ldots, \epsilon_{in_i})^\top$ is a random error vector, $d(.)$ is an $s-$ *dimensional* linear function generally expressed as $d(x_{ij}; \beta; \boldsymbol{b}_i) = \boldsymbol{A}_i\beta + \boldsymbol{B}_i\boldsymbol{b}_i$ with $\boldsymbol{A}_i$ and $\boldsymbol{B}_i$, design matrices, $\boldsymbol{\beta}$ is a p-dimensional locator vector of fixed-effects, $\boldsymbol{b}_i = (b_{1i}; \ldots; b_{qi})^\top$ is a q-dimensional vector $(q \leq s)$ of random-effects (assumed mutually independent across subjects and independent of the within-subject errors $\boldsymbol{\epsilon}_i$) associated with the i^{th} subject. Nonlinear mixed-effects models have been proposed for analyzing various complex longitudinal data, including epidemic data. Examples include dengue outbreak data (Rodríguez et al., 2017), HIV viral dynamics (Wu, Liu, & Hu, 2010), and the spread of COVID-19 (Lee, Lei, & Mallick, 2020). However, it is often assumed that both random errors and random effects follow a normal distribution. This assumption may not always yield reliable results, especially when the data exhibit excessive skewness and heavy-tailedness. This is particularly pertinent in the case of infectious disease cases/death data (Schumacher, Ferreira, et al., 2021) or viral load dynamics (Huang & Dagne, 2010; Huang, Dagne, Zhou, & Wang, 2015).

2.2. Fitting NLMMs with non-normal errors and random effects

Let $\boldsymbol{\theta}$ be a vector of the model parameters, then classical inference on the parameter vector $\boldsymbol{\theta}$ is based on the marginal distribution for $\boldsymbol{Y} = (\boldsymbol{y}_1^\top; \ldots; \boldsymbol{y}_n^\top)$. Thus, the integrated likelihood of (2.1) with random errors and random effects distribution specification does not have, in general, a closed-form expression because the model function is not linear in the random effects. The model 2.1 can be viewed as a hierarchical model that, in some ways, generalizes both the linear mixed effects model and the usual nonlinear model for independent data (Pinheiro et al., 1995). In the first stage, the j^{th} observation on the i^{th} cluster is modelled as:

$$y_{ij} = \mu_i(t_{ij}; \boldsymbol{\phi}_{ij}) + \epsilon_{ij} \quad ; \quad i = 1, \ldots, n; j = 1, \ldots, n_i, \tag{2.2}$$

where ϵ_{ij} is a normally distributed noise term, while in the second stage, the cluster-specific parameter vector is modelled as

$$\boldsymbol{\phi}_{ij} = d(x_{ij}; \beta; \boldsymbol{b}_i) \quad ; \quad \boldsymbol{b}_i \sim \mathcal{N}(0, \boldsymbol{D}), \tag{2.3}$$

with β, a p-dimensional vector of fixed population parameters, $\boldsymbol{b}_i$ a q-dimensional random effect vector associated with the i^{th} cluster and $\boldsymbol{D}$ is a general variance-covariance matrix. It is further assumed that observations made on different clusters are independent and that the $\boldsymbol{\epsilon}_i$ follow a $\mathcal{N}(0; \sigma^2 \boldsymbol{I}_{n_i})$ distribution and are independent of the b_i.

The systematic review shows that the most common distributions used for random terms were Normal distributions for both residuals and random effects (Fig. 1). However, such assumptions would be unrealistic or too restrictive when dealing with epidemic data. Epidemiological, particularly infectious disease data, exhibit skewness, outliers, or heavy-tailed behaviour (Lachos, Bandyopadhyay, & Dey, 2011; Schumacher, Ferreira, et al., 2021). Therefore, several works have identified situations where the routine use of the normality assumption appeared inappropriate (see, e.g., Litière et al. (Litière et al., 2007), Huang (Huang, 2009), Schumacher et al. (Schumacher, Ferreira, et al., 2021)). Being aware of the weakness of this specification in some cases of complex longitudinal data, other types of distributions (smooth and flexible) have been considered in the development of NLMMs.

Many alternatives to the normality assumptions involve more flexible distribution assumptions for random effects and residual errors. These alternatives include nonparametric (Agresti, Caffo, & Ohman-Strickland, 2004), semi-nonparametric (SNP) (Chen, Zhang, & Davidian, 2002; Zhang & Davidian, 2001), and copula-type distributions (Liu & Yu, 2008; Nelson et al., 2006), as well as parametric options (Dempster, Laird, & Rubin, 1977; McCulloch & Neuhaus, 2011; Meza, Osorio, & De la Cruz, 2012; Tovissodé, 2017).

Within parametric approaches, more flexible distributions, including the normal distribution are particularly interesting because they can be used to test significant departures from normality. The most general fully parametric existing approach for NLMMs only accounts for kurtosis using a scale mixture of normal (SMN) distributions (De la Cruz, 2014; Meza et al., 2012; Russo & Silva, 2013). In this elliptical subclass, the SMN distributions include heavy-tailed multivariate distributions such as Student-t, the contaminated normal, and slash. Let $\boldsymbol{\kappa}$ be the mixture variable associated to Y_{ij}, with cdf $H_\kappa(\cdot|\boldsymbol{\nu})$ and pdf $h_\kappa(\cdot|\boldsymbol{\nu})$. Likewise, let $\boldsymbol{\tau}$ be the mixture variable associated to $\boldsymbol{b}_i$, with cdf $H_\tau(\cdot|\boldsymbol{\nu}_b)$ and pdf $h_\tau(\cdot|\boldsymbol{\nu}_b)$. Under a mixed-effects design with n subjects and n_i measurements for the ith subject, the SMN-NLMM is given for the jth outcome Y_{ij} ($i = 1, \ldots, n$; $j = 1, \ldots, n_i$) as Meza et al. (Meza et al., 2012):

$$(\boldsymbol{Y}_i|\boldsymbol{\phi}_i) \overset{ind}{\sim} SMN_{ni}(\xi_i, \omega^2, \nu), \boldsymbol{b}_i \overset{ind}{\sim} SMN_q(\boldsymbol{\xi}_b, \boldsymbol{\Omega}_b, \nu_b), \tag{2.4}$$

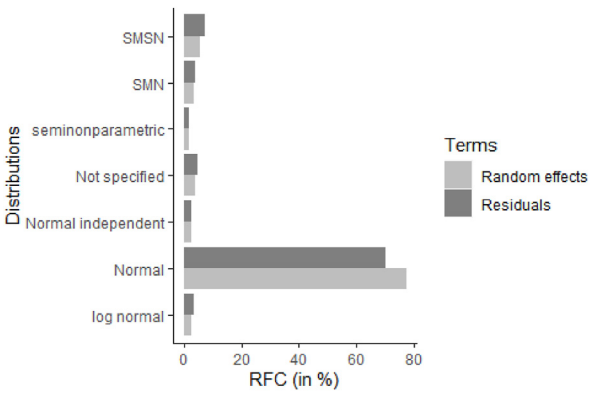

Fig. 1. Random terms distribution specification in NLMMs.

where $\boldsymbol{\phi}_i = \boldsymbol{A}_i\boldsymbol{\beta} + \boldsymbol{B}_i\boldsymbol{b}_i$, $\boldsymbol{A}_i$ and $\boldsymbol{B}_i$ are design matrices (subject-specific covariates), $\boldsymbol{\beta}$ is a p-vector of fixed (population) effects, the q-vector of random effects $\boldsymbol{b}_i$ and ξ_{ij}, ω^2, ξ_b and $\boldsymbol{\Omega}_b$ are unique distribution parameters such that $E\{Y_{ij}|\mathbf{x}_{ij}, \boldsymbol{\phi}_i\} = \mu_{ij}$ with $\mu_{ij} = \mu(\mathbf{x}_{ij}|\boldsymbol{\phi}_i)$, $Var\{Y_{ij}|\mathbf{x}_{ij}, \boldsymbol{\phi}_i\} = \sigma^2$, $E\{\boldsymbol{b}_i\} = \boldsymbol{0}$, and $Var\{\boldsymbol{b}_i\} = \boldsymbol{\Gamma}_b$. Using the stochastic representation $\boldsymbol{Y} \overset{d}{=} \boldsymbol{\mu} + \kappa^{-1/2}\boldsymbol{Z}$ with $\boldsymbol{Z}$, independent of the mixture variable $\kappa \sim H(\nu)$, and ν a scalar or vector-valued parameter, a hierarchical form of (2.4) is:

$$(\boldsymbol{Y}_i|\boldsymbol{\phi}_i, \kappa_i) \overset{ind}{\sim} N_{ni}(\mu_i(t_i;\boldsymbol{\phi}_i), \kappa_i^{-1}\omega^2), \quad \omega^2 = \sigma^2\boldsymbol{I}_{n_i} \tag{2.5a}$$

$$\boldsymbol{b}_i \overset{ind}{\sim} N_q(\boldsymbol{\xi}_b, \tau_i^{-1}\boldsymbol{\Omega}_b). \tag{2.5b}$$

This approach provides a simple way to identify and control outliers at the residuals and random effects levels (Meza et al., 2012). Skewness is, however, often present in data from many application fields, including epidemiology, where skewed variables are generated naturally or follow truncation/censoring processes (see, e.g., Urban et al. (Urban, Bürger, & Bolnick, 2013)). Skew normal nonlinear regression models have been developed by Cancho et al. (Cancho, Lachos, & Ortega, 2010) and Xie et al. (Xie, Wei, & Lin, 2009) using the skew-normal distribution (Azzalini, 2005). This approach gained more attention in the last decade, especially in modeling viral load dynamics (Huang and Dagne, 2010, 2012, 2013; Huang et al., 2015; Lachos, Castro, & Dey, 2013). Taking $n_i \times n_i$ skewness diagonal matrix $\boldsymbol{\Delta}_i = diag(\delta_{i_1}, \ldots, \delta_{i_{ni}})$ and $\boldsymbol{\delta}_i = (\delta_{i_1}, \ldots, \delta_{i_{n_i}})^\top$, $\boldsymbol{\Delta}_b = diag(\delta_{b_1}, \ldots, \delta_{b_q})$ and $\boldsymbol{\delta}_b = (\delta_{b_1}, \ldots, \delta_{b_q})^\top$, a Skew normal nonlinear mixed-effects model can be written as a hierarchical model as follows:

$$\boldsymbol{y}_i = \mu_i(t_{ij};\boldsymbol{\phi}_{ij}) + \boldsymbol{\epsilon}_i \quad ; \quad (\boldsymbol{\epsilon}_i) \overset{ind}{\sim} SN_{ni}(-\sqrt{2/\pi}\,\delta_i, \sigma^2\boldsymbol{I}_{n_i}, \boldsymbol{\Delta}_i), \tag{2.6a}$$

$$\boldsymbol{\phi}_{ij} = d(x_{ij};\boldsymbol{\beta};\boldsymbol{b}_i) \quad ; \quad \boldsymbol{b}_i \overset{ind}{\sim} SN_q(-\sqrt{2/\pi}\,\boldsymbol{\delta}_b, \boldsymbol{\Gamma}, \boldsymbol{\Delta}_b). \tag{2.6b}$$

In real-world data analysis with possible sample size variation, it is generally considered $\delta_{i_1} = \cdots = \delta_{i_{n_i}} = \delta_e$, then $\boldsymbol{\Delta}_i = \delta_e I_{n_i}$ and $\boldsymbol{\delta}_i = \delta_e \boldsymbol{1}_{n_i}$, where $\boldsymbol{1}_{n_i} = (1, \ldots, 1)^\top$. Subsequently, nonlinear regression models with residual errors distributed as a scale mixture of skew-normal distributions (SMSN) were introduced by Garay et al. (Garay, Lachos, & Abanto-Valle, 2011) and are known for being more computationally advanced, taking advantage of the EM algorithm (Meza et al., 2012; Schumacher, Dey, & Lachos, 2021; Tovissodé, 2017). The resulting models allow for the consideration of both skewness and kurtosis in the data by introducing a few parameters to the traditional regression model. The latest developments in this area include some important specifications following Tovissodé (Tovissodé, 2017). Let $\lambda \in \mathbb{R}$ and $\boldsymbol{\lambda}_b \in \mathbb{R}^q$, the shape parameters of the response Y_{ij} and the q-vector of random effects $\boldsymbol{b}_i$, respectively and let us denote the moments of the mixture variables as $\kappa_{e_t} = E\{\kappa^{-t/2}\}$ and $\tau_{e_t} = E\{\boldsymbol{\tau}^{-t/2}\}$ $(t = 1, 2)$, all assumed finite. Under a mixed effects design with n subjects and n_i measurements for the ith subject, the SMSN-NLMM is given for the jth outcome Y_{ij} $(i = 1, \ldots, n; j = 1, \ldots, n_i)$ as:

$$(Y_{ij}|x_{ij}, \boldsymbol{\phi}_i) \overset{ind}{\sim} SMSN_1(\xi_{ij}, \omega^2, \lambda, \nu), \boldsymbol{b}_i \overset{ind}{\sim} SMSN_q(\boldsymbol{\xi}_b, \boldsymbol{\Omega}_b, \boldsymbol{\lambda}_b, \boldsymbol{\nu}_b), \tag{2.7}$$

with $\boldsymbol{\phi}_i$, $\boldsymbol{\beta}$, $\boldsymbol{b}_i$, ξ_{ij}, ω^2, ξ_b and $\boldsymbol{\Omega}_b$ as defined above. A hierarchical representation of the random vector $\boldsymbol{z}$ following scale mixture of skew-normal distributions denoted $SMSN_q(\boldsymbol{\mu}, \boldsymbol{\Lambda}, \boldsymbol{\lambda}, \boldsymbol{\nu})$ is $(\boldsymbol{z}|\boldsymbol{\kappa}) \sim SN_q(\boldsymbol{\mu}, \boldsymbol{\Lambda}, \boldsymbol{\lambda})$ and then a convenient stochastic representation for $\boldsymbol{z}$ is (Tovissodé, 2017):

$$(\boldsymbol{z}|\boldsymbol{\kappa}, \boldsymbol{T}_0) \sim N_q\Big(\boldsymbol{\mu} + \boldsymbol{T}_0\boldsymbol{\kappa}^{-1/2}\boldsymbol{\Lambda}^{1/2}\boldsymbol{\delta}, \boldsymbol{\kappa}^{-1}\Big(\boldsymbol{\Lambda} - \boldsymbol{\Lambda}^{1/2}\boldsymbol{\delta}\boldsymbol{\delta}^\top\boldsymbol{\Lambda}^{1/2}\Big)\Big), \tag{2.8}$$

where $\boldsymbol{\kappa} \sim H_\kappa(\nu)$ and $\boldsymbol{T}_0 \sim HN(0, 1)$. The mean and the variance of this SMSN vector $\mathbf{z}$ are

$$E\{\boldsymbol{z}\} = \boldsymbol{\mu} + c\kappa_{e1}\boldsymbol{\delta}_0 \quad \text{and} \quad Var\{\boldsymbol{z}\} = \kappa_{e2}\boldsymbol{\Lambda} - c^2\kappa_{e1}^2\boldsymbol{\delta}_0\boldsymbol{\delta}_0{}^\top\boldsymbol{\Lambda}^{1/2}, \tag{2.9}$$

where $c = \sqrt{\frac{2}{\pi}}$ and $\boldsymbol{\delta}_0 = (1 + \boldsymbol{\lambda}^\top\boldsymbol{\lambda})^{-1/2}\boldsymbol{\Lambda}^{1/2}\boldsymbol{\lambda}$.

Using 2.9 on 2.7, relationships between parameters of the specified distributions, the expectation of the response and the residual variance and the variance-covariance matrix of random effects are (Tovissodé, 2017):

$$\xi_{ij} = \mu_{ij} + c\kappa_{e1}\delta_e \quad \text{and} \quad \omega^2 = \kappa_{e2}^{-1}(\sigma^2 + c^2\kappa_{e1}^2\delta_e^2) \tag{2.10}$$

$$\boldsymbol{\xi}_b = -c\tau_{e1}\boldsymbol{\delta}_b \quad \text{and} \quad \boldsymbol{\Omega}_b = \tau_{e2}^{-1}(\boldsymbol{\Gamma}_b + c^2\tau_{e1}^2\boldsymbol{\delta}_b\boldsymbol{\delta}_b{}^\top), \tag{2.11}$$

with $\delta_e = \omega\lambda(1 + \lambda^2)^{-1/2}$; $\boldsymbol{\delta}_b = (1 + \boldsymbol{\lambda}_b^\top\boldsymbol{\lambda}_b)^{-1/2}\boldsymbol{\Omega}_b^{1/2}\boldsymbol{\lambda}_b$. Using the stochastic representation 2.8, a hierarchical form of (2.7) is:

$$(Y_{ij}|\boldsymbol{\phi}_i, \kappa_{ij}, t_{ij}) \overset{ind}{\sim} N_1\left(\mu_{ij} + \left(t_{ij}\kappa_{ij}^{-1/2} - c\kappa_{e_1}\right)\delta_e, \kappa_{ij}^{-1}\overset{-}{\omega}^2\right), \tag{2.12a}$$

$$\kappa_{ij} \overset{ind}{\sim} H_\kappa(\nu) \quad \text{and} \quad t_{ij} \overset{ind}{\sim} HN(0,1), \tag{2.12b}$$

$$(\boldsymbol{b}_i|\tau_i, u_i) \overset{ind}{\sim} N_q\left(\left(u_i\tau_i^{-1/2} - c\tau_{e_1}\right)\boldsymbol{\delta}_b, \tau_i^{-1}\overset{-}{\boldsymbol{\Omega}}_b\right), \tag{2.12c}$$

$$\tau_i \overset{ind}{\sim} H_\tau(\nu_b) \quad \text{and} \quad u_i \overset{ind}{\sim} HN(0,1), \tag{2.12d}$$

where $\overset{-}{\omega}^2 = \omega^2 - \delta_e^2$ and $\overset{-}{\boldsymbol{\Omega}}_b = \boldsymbol{\Omega}_b - \boldsymbol{\delta}_b\boldsymbol{\delta}_b^\top$.

Based on this latest class of scale mixtures of skew-normal distributions, Schumacher et al. (Schumacher, Ferreira, et al., 2021) formulated a robust nonlinear mixed-effects model for modeling COVID-19 death data. These models are particularly valuable in infectious disease data, addressing inherent features such as similarly-shaped profiles with different decay patterns, unexplained variation among repeated measurements within each country, and the presence of skewness, outliers, or skew-heavy-tailed noises within response variables.

2.3. Parameter estimations in NLMMs

The integrated likelihood of NLMMs (2.1) with random errors and random effects distribution specification does not have, in general, a closed-form expression because the model function is not linear in the random effects (Kerioui et al., 2020). Consequently, the model lacks a direct analytical expression for the likelihood function, resulting in a wealth of literature on approaches for approximating the observed data likelihood to perform inference for the population parameters. These methods include first-order approximations (Sheiner & Beal, 1983), first-order conditional methods (Lindstrom & Bates, 1990), Gaussian quadrature (Davidian & Gallant, 1993), adaptive Gaussian quadrature (Rabe-Hesketh, Skrondal, & Pickles, 2004), Laplace approximations (Beal & Sheiner, 1985), Markov chain Monte Carlo (MCMC) (Spiegelhalter, Best, Carlin, & Van der Linde, 2014), Monte Carlo integration (Wakefield, Smith, Racine-Poon, & Gelfand, 1994), and importance sampling (Geweke, 1989).

In the normal case, various approximations of the integrated likelihood of (2.1) have been proposed to render the numerical optimization of the likelihood function tractable. These approximations often rely on the first-order Taylor series expansion of the response function around the conditional mode of the random effects, as introduced by Lindstrom and Bates (Lindstrom & Bates, 1990). Additionally, Pereira and Russo (Pereira & Russo, 2019) proposed an EM-type algorithm, combining elements of the EM algorithm (Dempster et al., 1977) and the Newton-Raphson algorithms. Utilizing a first-order Taylor expansion of the response as a function of both $\boldsymbol{\beta}$ and $\boldsymbol{b}_i$, Schumacher et al. (Schumacher, Dey, & Lachos, 2021) derived an approximate scale mixture of skewed normal (SMSN) marginal distribution for the response, effectively transforming the NLMM into an approximate linear mixed-effects model. They further proposed an EM algorithm, extending common linearization-based estimation procedures (Lin & Wang, 2017; Lindstrom & Bates, 1990; Matos, Prates, Chen, & Lachos, 2013; Pinheiro & Bates, 1995) to SMSN-NLMMs. These approximation methods generally perform well when the variability of random effects is small, and the number of subject-specific measurements (n_i) is large. However, they may result in considerable errors when these conditions are violated, such as in cases of sparse data or large variability in random effects (Davidian & Giltinan, 1995; Lindstrom & Bates, 1990; Meza et al., 2012; Pinheiro & Bates, 1995). Due to the involvement of intractable integrals in the *E-step* of the EM algorithm for NLMMs, various approximations, like the SAEM (Delyon, Lavielle, & Moulines, 1999), have been developed. The SAEM has proven to be very efficient in computing NLMM parameters (Kuhn & Lavielle, 2004; Meza et al., 2012). Moreover, the *M-step* of the EM algorithm is also often tricky when estimating NLMMs, requiring nonlinear optimization techniques (Wang, 2015). In such instances, the Expectation Conditional Maximization (ECM) algorithm of Meng and Rubin (Meng & Rubin, 1993) allows to break off the *M-step* in several simpler Conditional Maximization (CM) steps. This consists of updating a set of parameters with explicit and/or more straightforward updates given fixed values of the rest. However, ML-type estimation may be complicated by the high-dimensional integrals in the likelihood function if normality and linearity assumptions do not hold. Likewise, the asymptotic theory of maximum likelihood estimation may not apply to moderate-size (censored) data (Lachos et al., 2011). For instance, the Bayesian paradigm was proposed and recommended to be robust to data sparsity and large variability of random effects. Some Bayesian propositions in the context of heavy-tailed NLMMs models of epidemic data have been proposed Lachos et al. (Lachos et al., 2011, 2013), Huang and Dagne (Huang and Dagne, 2010, 2012, 2013), Huang et al. (Huang et al., 2015) and their high performance was known in all the cases.

2.4. Motivations for choosing NLMMs

Infectious disease counts from surveillance systems are typically observed in several administrative geographical areas. Meanwhile, the analysis of such complex longitudinal data required particular attention relatively to some inherent features like similarly-shaped profiles with different decay patterns; unexplained variation among repeated measurements within each area possibly viewed as clustered data as taking on the same country or area at roughly the same time. In recent years, Nonlinear mixed effects models (NLMMs) have been proposed for modeling many complex longitudinal data (Lindstrom & Bates, 1990; Wu et al., 2010). Paul and Held (Paul & Held, 2011) has extended the model from the early works of Held et al. (Held et al., 2005) and Paul et al. (Paul et al., 2008) for the analysis of multiple time series of infectious disease counts to account for different incidence levels or varying disease transmission via possibly correlated random effects. They have considered the monthly cases of meningococcal disease caused by the Neisseria meningitidis bacterium in 94 departments of France in one hand and the weekly number of laboratory confirmed influenza cases in 140 administrative districts in Southern Germany. With the evidence of geographical heterogeneity within France in meningococcal disease incidence and seasonal waves spreading of the influenza incidence, the predictive performance has improved as existing heterogeneity is accounted for.

Note that the data are not available at an individual level but are aggregated and often also subject to under-reporting and reporting delays, which may give rise to over-dispersion and blurred dependencies (Paul & Held, 2011). Several studies have proposed NLMMs to deal with heterogeneous disease transmission and incidence levels in wide range of epidemics such as influenza (Lee et al., 2009; Wang et al., 2020), hospital-acquired infections (Duval et al., 2018), HIV/AIDS (Dinh, Chowell, & Rothenberg, 2018), and SARS-CoV-2 (Chong et al., 2021; Lee, Lei, & Mallick, 2020). Nonlinear mixed effects models (NLMMs), derived from dynamic mechanism characterized by a system of differential equations, are often used to model the viral load trajectories as well as to quantify inter-subject and intra-subject variations in viral load measurements (Huang & Dagne, 2010). As in their study of single dengue outbreaks analysis based on the reported cumulative cases, the interest lays on estimating the average behavior of a health area in the population and the variability among and within health areas, Rodríguez et al. (Rodríguez et al., 2017) have developed and applied a nonlinear mixed-effects model instead of the methodologies performed for each area separately. For such circumstances, the NLMMs approach is highly recommended because the areas are regarded as sample from a population and it does not ignore variability among and within areas.

For the latest COVID-19 dynamic, NLMMs have been applied by Kaimann and Tanneberg (Kaimann & Tanneberg, 2021) as integrating information from different subjects to increase the predictive power for the individual (Lee, Lei, & Mallick, 2020) and allowing the estimation of within and among groups variation. An additional key advantage of NLMMs highlighted by the authors was the ability to account for nonlinearity. Nonlinear mixed-effects models have since been successfully applied to analyze the relationship between measures taken against the COVID-19 pandemic and the cumulative number of confirmed COVID-19 cases. Lee et al. (Lee, Lei, & Mallick, 2020) demonstrated the advantage of NLMMs due to their predictive accuracy and ability to integrate data from multiple countries, compared to individual country-based COVID-19 spread models. Schumacher et al. (Schumacher, Ferreira, et al., 2021) explained that the different stages of disease spread are crucial information that should be incorporated into modeling. In their study of COVID-19 death data, they introduced a new NLMM methodology that jointly accounts for the different stages of the disease and leverages information from multiple time series to provide a more robust and reliable fit and prediction.

3. Nonlinear mixed effects models: a systematic review

3.1. Methods

A systematic search of originally published articles on NLMMs in infectious diseases modeling from January 2000 to December 2021 was conducted using the *Research4life* Access initiative programs, such as *HINARI* (www.who.int/hinari) and *AGORA* (www.fao.org/agora). Relevant scientific databases in these programs, such as "PubMed," "Scopus," and "Google Scholar," were used to search for papers dealing with NLMMs in infectious diseases modeling. The outcomes of the search queries were initially examined to determine their relevance by reading their titles and abstracts, after which full texts were downloaded for further scrutiny. From an initial list of 3,641 papers, 124 were finally included in the review. The selection of papers for the study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as illustrated in Fig. 2.

The contents of these retrieved papers were meticulously examined to eliminate duplicates. Commentaries, purely descriptive studies, letters, and all articles on applied NLMMs in fields other than infectious disease modeling were excluded. Additionally, all pharmacokinetics-pharmacodynamics studies were excluded as they did not align with the study scope criteria. A list of relevant information and basic characteristics of the studies related to NLMMs analysis with applications to infectious disease modeling was extracted from the selected papers. This included: (1) characteristics of the papers, (2) estimation methods used, (3) inferential issues, (4) model performance assessment and validation, (5) infectious disease of interest, the study aspects (spread out or viral load (Huang et al., 2015) dynamic), the considered cluster level, and the geographical area from which the data originated. The count and relative citation frequency ($RFC = 100 \times$ *Number of citations*/*Sample size* with $0\% \leq RFC \leq 100\%$; the closer its value is to 100, the stronger the trend) were calculated for trend evaluation and illustrated using the bar plots or scatter plots built as appropriate in the ggplot2 package (Wickham, Chang, & Wickham,

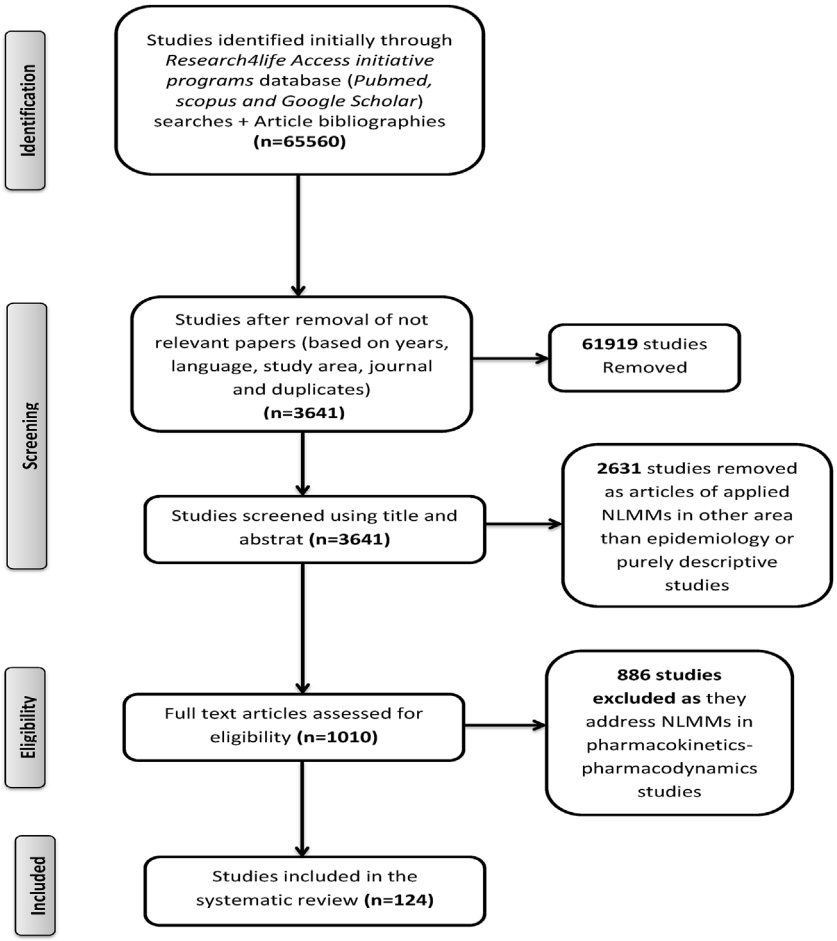

Fig. 2. Flow diagram of the identification process for the reports included in this review.

2016, pp. 1–189) in R software (RCore, 2019). Relationships between various variables collected were investigated through a factorial correspondence (CA) analysis using the FactoMineR package (Lê et al., 2008) of R software. A critical analysis was conducted on the advantages and limitations of existing estimation methods, random term distribution specifications, model assessment, and software implementation.

3.2. Characteristics of the selected papers

The distribution of publications across journals revealed the Journal of Pharmacokinetic-Pharmacodynamic leads with 12.1% of included papers, followed by Statistics in Medicine (11.3%), Computational Statistics and Data Analysis (7.3%), and the Journal of Applied Statistics (Table 2 in Annexe). Research areas within NLMMs also exhibit distinct trends. Nearly a third (32.5%) of papers delve primarily into computational and estimation methods development (Fig. 3). Notably, out of the 124 papers reviewed, 19.4% (24 papers) directly tackle infectious disease outbreak dynamics or viral load dynamics through NLMM applications. Furthermore, 22.5% of the papers propose modeling methods tailored to specific infectious diseases like dengue, Ebola, Lassa, influenza, and COVID-19. Other frequent themes include heterogeneity issues (12.6%), random term distribution specification (8.9%), model assessment (4.1%), and advanced programming (3.3 Papers on modeling highlighted, in some cases, identifiability, autocorrelation, and covariate inclusion issues. Some studies focusing on the Bayesian approach investigated the sensitivity of estimations to the prior specification.

3.3. NLMMs and computational advances over the last two decades

NLMMs have undergone significant development since the beginning of the 21st century. To gain a clear view of this development, we depict data from all selected theoretical papers focusing on epidemic case studies (Theoretical_NLMMs) alongside data from applied NLMMs found in published infectious disease studies (Applied_NLMMs). Fig. 4A summarizes the

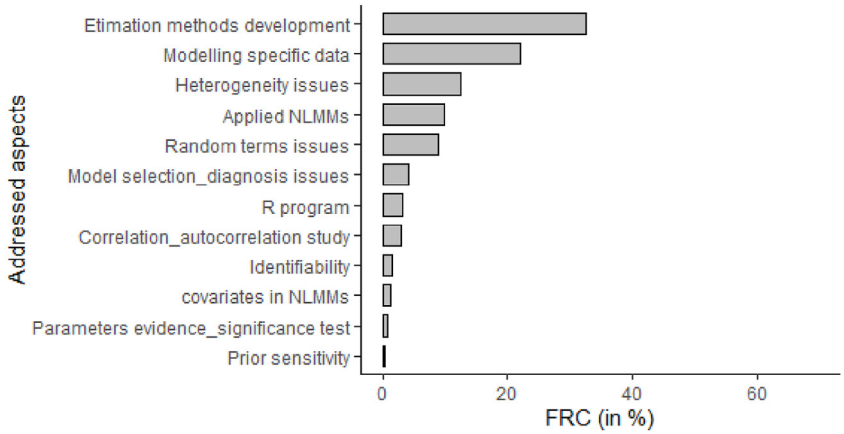

Fig. 3. Technical aspects addressed in NLMMs studies in the last two decades.

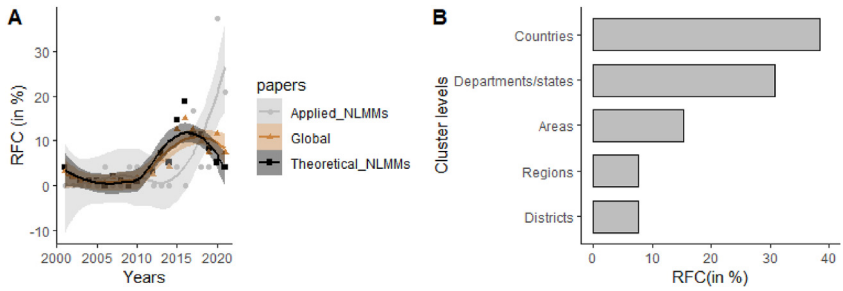

Fig. 4. Evolution of NLMMs development and application over time for the last two decades (A) and the usual cluster levels of epidemic spread out data (B).

evolution of NLMMs over time and shows that the last decade was when NLMMs development and applications evolved rapidly. Most publications date back from 2017 to 2021 (83.33%). This increasing focus on NLMMs, especially in infectious diseases modeling, over the last decade is likely due to the last world-known pandemics of Ebola and COVID-19 outbreaks in 2014 and 2020, respectively. In addition, at the cluster level (Fig. 4B) of infectious disease cases data from the selected papers, regions, countries, departments or states, districts, and areas of the country are considered, but they are usually aggregated at

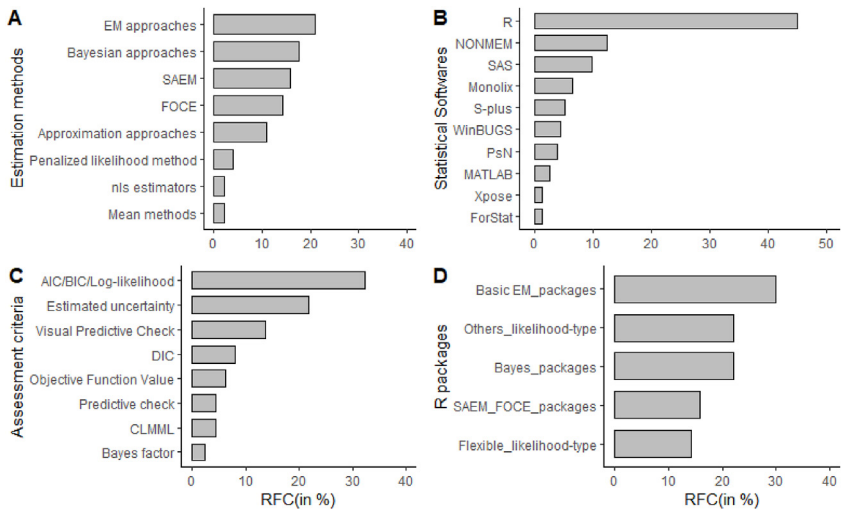

Fig. 5. NLMMs Computational advances from the last two decades.

the country level. This finding highlights a practical issue of data recording as it is generally aggregated by country, obscuring important information on the country for deep analysis.

The most used software for computation and analysis is R (Fig. 5B). The attraction to this statistical software is the availability and free access to some key packages (Fig. 5D) developed for NLMMs in various application areas. The most used R packages in NLMMs are “nlme” for the maximum likelihood approach, “R2winBUGS” and “rstan/brms” for the Bayesian method, “saemix” for the SAEM method and “nlmixr” for FOCE or SAEM.

In nonlinear-mixed effects modeling, the selection of the nonlinear mean structure and the type of random effects structure is critical. Additionally, another crucial step in the model-building of mixed-effects models is deciding which of the coefficients in the model need random effects to account for their between-areas variation and which can be treated as purely fixed effects (Rodríguez et al., 2017). Therefore, care should be taken in choosing the nonlinear link function for specific data. The axis system of the correspondence analysis depicted in Fig. 6A shows which type of infectious disease data for which nonlinear function while Fig. 6B shows the growth models as nonlinear function in analyzing ID dynamic data. Specifically, the result shows that growth models (as Logistic or derivative of logistic model Richards or Gompertz model) are potentially considered nonlinear mean functions in infectious disease spread out dynamic modeling. In contrast, the Exponential or bi-exponential function is the most used link function in viral load dynamic study (Fig. 6A).

A- Estimation methods in NLMMs; B- Statistical Softwares in NLMMs; C- Assessment criteria in NLMMs; D- Proposed R packages for NLMMs; with FOCE: First-Order with Conditional Estimation; nls: Nonlinear Least Squares; CLMML: Compound Laplace-Metropolis Marginal Likelihood; DIC: Deviance Information Criteria; Basic EM_packages:nlme, nlmeODE, nlm, nlmer, lme4; Bayes_packages:rstan/brms, R2WinBUGS, R2Cuba, R2jags; SAEM_FOCE_packages: saemix, nlmixr; Flexible_likelihood-type: sn, mixsmsn, etc.; Others_likelihood-type: others packages.

Model assessment criteria play a pivotal role in selecting and comparing models across various modelling approaches. Within the NLMM framework, diverse criteria have been employed, with the Akaike Information Criteria (AIC) or Bayesian Information Criteria (BIC) being the most commonly considered in likelihood-type approaches (Fig. 5C). However, it is important to note that these criteria may pose challenges in the presence of random effects (Paul & Held, 2011). For Bayesian analysis methods, selection and comparison commonly leverage: Posterior model probabilities, Watanabe-Akaike Information Criterion (WAIC) (Watanabe & Opper, 2010), leave-one-out cross-validation, Bayes factor (Carlin & Louis, 2000), posterior predictive checks (Gelman et al., 2013), log pseudo marginal likelihood (LPML), and Deviance Information Criteria (DIC) (Spiegelhalter, Best, Carlin, & Van Der Linde, 2002). Simulation-based studies often consider additional model selection approaches such as estimated uncertainty (mean square errors, bias, coverage rate). However, certain methods require more precise definitions, while others lack automation or the ability to be condensed into a single, easily interpretable numerical summary (Guo & Carlin, 2004). Using a complexity measure for the effective number of parameters based on an information-theoretic argument, some authors prefer DIC to others. For example, in a complex hierarchical model with the specification of its dimensionality somewhat arbitrary, in which neither AIC nor BIC is applicable, Huang and Dagne (Huang & Dagne, 2010) has referred to the DIC approach for comparison. However, as with other model selection criteria, DIC is not intended to identify the ‘correct’ model but rather as a method for comparing a collection of alternative formulations. Unfortunately, while this DIC (Spiegelhalter et al., 2002) can be computed, Plummer (Plummer, 2008) has shown that it tends to prefer overly complex models in situations with many random effects. For instance, Paul and Held (Paul & Held, 2011) proposed the comparison of successive one-step-ahead forecasts with the observed data as an alternative in such a situation. The latter was then considered a more natural approach for model selection in time series models than classical model choice criteria. Thus, for the particular case of infectious disease models with the specification of different flexible distributions for the random error and random effects, care must be taken in the choice of selection criteria to understand how the assumption of different flexible distributions contributes to epidemic breakout or viral load responses and parameter estimation compared to that of the Normal distribution for random error and/or random effects.

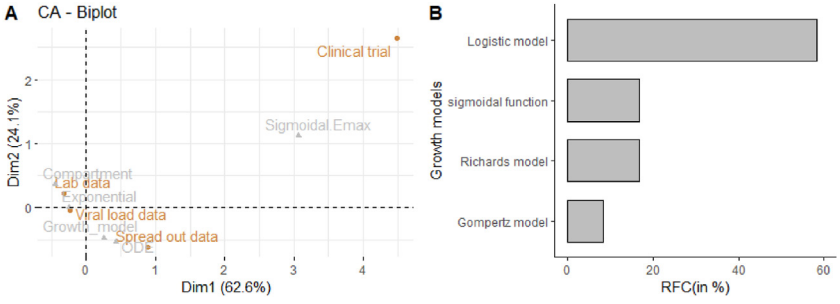

Fig. 6. Nonlinear mean functions in NLMMs; with A: Axis system of the correspondence analysis showing the relationship between nonlinear mean functions and ID data types; B: Usual growth models in NLMMs of ID data.

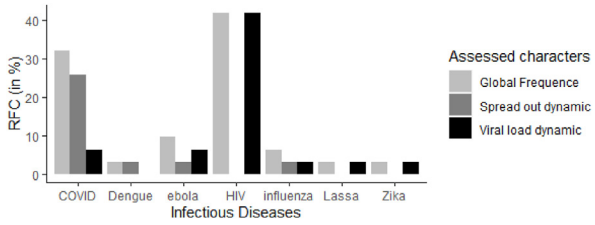

Fig. 7. Infectious Diseases modeling based on NLMMs.

3.4. Use of NLMMs in infectious disease modeling

About 20% of the selected papers mainly applied NLMMs to infectious disease modeling (Fig. 3). From this systematic review, NLMMs are essentially used for the viral load data and infectious diseases pandemic spread out (Fig. 7). The identified infectious diseases with at least a paper modeling their spread out or viral load through NLMMs are COVID-19, HIV, influenza, Dengue, Ebola, Lassa and Zika epidemics. The use of nonlinear mixed models in infectious disease modeling dates back over a decade but has gained much attention for the last world-known pandemics (COVID-19, Ebola, dengue, and Lassa). Therefore, apart from its widely known application in pharmacokinetic-pharmacodynamic studies, NLMMs were mainly used for infectious diseases' viral load dynamics, especially in the case of HIV (Huang & Dagne, 2010; Huang et al., 2015; Wu et al., 2010). It is essentially applied in the current COVID-19, dengue, influenza and Ebola pandemic spread out dynamic modeling. Some key examples are Rodríguez et al. (Rodríguez et al., 2017) for Dengue outbreak data modeling, Kaimann and Tanneberg (Kaimann & Tanneberg, 2021) in analyzing the relationship between the control measures and the cumulated number of confirmed COVID-19 cases and Schumacher et al. (Schumacher, Ferreira, et al., 2021) for robust COVID-19 death data modeling.

4. Case study: COVID-19 dynamic

In this section, we seek practical evidence of non-homogeneous characteristics in infectious disease data and the necessity of considering flexible distributions when using NLMMs in infectious disease modeling. Schumacher et al. (Schumacher, Ferreira, et al., 2021) highlighted the challenges of underreporting, particularly in understanding the true contamination numbers of COVID-19 in the population due to varying testing capacities between countries. Meanwhile, studies using the number of deaths as a proxy measure for COVID-19 cases (Amaro, Dudouet, & Orce, 2021; Maugeri, Barchitta, Battiato, & Agodi, 2020; Ribeiro Bernardes et al., 2020) are less likely to be affected by detection biases. Similar to Schumacher et al. (Schumacher, Ferreira, et al., 2021), who focused on modeling COVID-19 death curves in some Latin American countries as the new epicentre of the disease, we considered the same dataset from January 22, 2020, to June 24, 2020 (https://github.com/CSSEGISandData/COVID-19/) from Johns Hopkins University through the Center for Systems Science and Engineering. Given that a mixed-effect framework borrows information from population-average effects, we included some countries from Europe and North America that are in a more advanced stage of their COVID-19 death curves. The considered countries are Peru, Mexico, Chile, Brazil, Colombia, Belgium, Italy, the USA, and the United Kingdom.

Firstly, we emphasized the varied stages and asymmetric structure of the reported data by plotting the number of deaths against days since the first death for different countries jointly. Subsequently, we conducted a comparative study of the considered approaches: the normal nonlinear mixed-effects model (N-NLMM) and the scale mixture of skew-normal nonlinear mixed-effects model (SMSN-NLMM) to showcase the performance of both models.

4.1. Models specifications

Refering to section 2, the NLMMs model is written as (Lindstrom & Bates, 1990): $\boldsymbol{y}_i = \mu_i(t_{ij}; \boldsymbol{\phi}_{ij}) + \boldsymbol{\epsilon}_i$; $\boldsymbol{\phi}_{ij} = d(x_{ij}; \boldsymbol{\beta}; b_i)$, where the subscript i is the subject index. The normal nonlinear mixed-effects model is the initial standard proposition of the nonlinear mixed-effects model (2.1), where residuals (ϵ_{ij}) and random effects (b_i) are assumed to be normally distributed. In contrast, the SMSN-NLMM is the proposition with random terms assumed to come from a scale mixture of skew-normal distribution, as developed in 2.7.

For this case of application, the intra-individual regression function is the derivative of the generalized logistic as defined:

$$\mu(x_{ij}; \phi_i) = \frac{\phi_1 \phi_{3i} \phi_4 exp\{-\phi_{3i} x_{ij}\}}{(\phi_{2i} + exp\{-\phi_{3i} x_{ij}\})^{\phi_4+1}} \tag{4.1}$$

In this equation, $\phi_{2i} = exp\{\beta_2 + b_{2i}\}$, $\phi_{3i} = exp\{\beta_3 + b_{3i}\}$, and $\phi_k = exp\{\beta_k\}$, for $k = 1; 4$, with the exponential transformation being used to ensure positiveness of the parameters; $x_{ij} = t_{ij}$ is the time of observation j $(1 \leq j \leq n_i)$ on individual i $(1 \leq i \leq n)$. In addition to the fact that in (4.1), random effects are included to enable a multivariate approach and borrow information

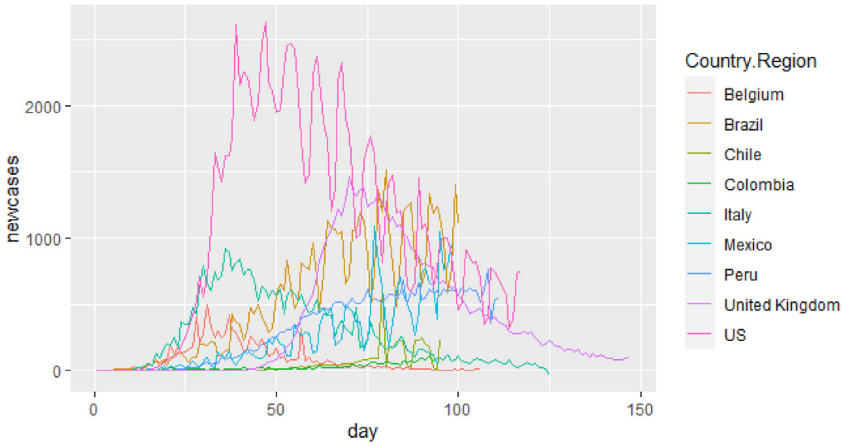

Fig. 8. Number of daily reported deaths since first death for the nine countries, until June 24th, 2020.

between the different time series, all nonlinear parameters are of interest for epidemic interpretations, where ϕ_3 control the infection rate, ϕ_4 is an asymmetry parameter, ϕ_1, ϕ_2 and ϕ_4 control the asymptote of the curve, given by $\phi_1 \frac{\phi_1}{\phi_2}^{\phi_4}$, with the peak occurring at time $t = -\frac{ln(\phi_2/\phi_4)}{\phi_3}$.

For numerical stability, the data have been standardized (linear transformation, $y_{ij} = z_{ij}/k_z$, where z_{ij} is the number of reported deaths for the i^{th} country and at the j^{th} day since first death, and k_z is chosen to be the sample standard deviation from the country data, which is the smallest one in the observed data).

4.2. Heterogeneity in infectious disease data

Fig. 8 illustrates the number of daily reported deaths since the first cases for the nine countries, with data clustered by country. The graph shows that the countries are at different stages of the COVID-19 pandemic. Based on these results, a possible extension to allow area-specific spread patterns of epidemics is interesting and necessary.

4.3. NLMMs and random term distributions

To demonstrate the impact of random term distribution when applying NLMMs to infectious disease data, we evaluated two propositions using the same data and considering different distributions. Rodríguez et al. (Rodríguez et al., 2017), Kaimann and Tanneberg (Kaimann & Tanneberg, 2021), and Lee et al. (Lee, Lei, & Mallick, 2020) used NLMMs for estimating epidemic spread curves by integrating global data and borrowing information, assuming normally distributed residuals and random effects. The second approach, proposed by Schumacher et al. (Schumacher, Ferreira, et al., 2021), formulates a nonlinear mixed-effects model based on the class of scale mixtures of skew-normal distributions for modeling COVID-19 dynamic data. The Shapiro-Wilk test was performed on standardized residuals when adjusting based on the "nlme" function of *nlme* package from R software (RCore, 2019). Fig. 9 highlights the non-normality of the standardized residuals. To further explore this non-normality across different countries, we conducted a Normality test per cluster (Table 1) and found no evidence of normality.

Fig. 10 displays the fitted curves for the N-NLMM model (blue line) and SMSN-NLMM model (red line), along with observed data (Number of daily reported deaths from the first death for the nine countries, until the June 24, 2020, in black) per country. It shows the usefulness of NLMMs in infectious disease modeling and confirms the importance of random terms

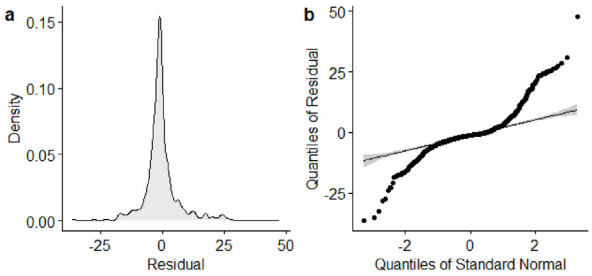

Fig. 9. The density curve and Q-Q plot of standardized number of deaths residuals reported in COVID-19 outbreak study: (a) Density curve; (b) Q-Q plot.

Table 1
Results of normality test per country.

Countries	statistics	p-values
Belgium	0.864	2.020×10^{-08}
Brazil	blue0.971	0.030
Chile	0.544	1.109×10^{-15}
Colombia	0.881	3.768×10^{-07}
Italy	0.972	0.011
Mexico	0.856	2.761×10^{-08}
Peru	0.961	0.003
United Kingdom	0.930	1.256×10^{-06}
US	0.977	0.048

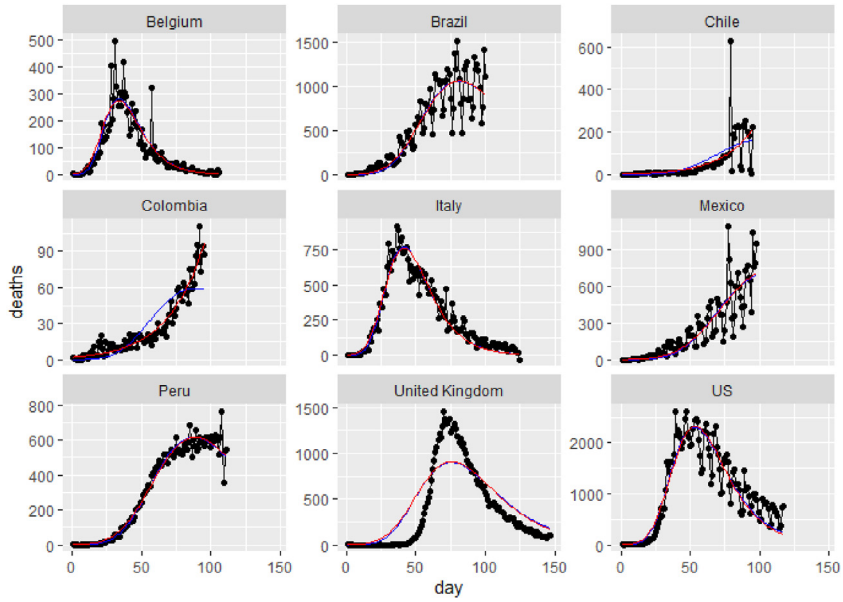

Fig. 10. Fitted curve for the N-NLMM model (blue line), SMSN-NLMM model (red line), along with real data (black) per country.

in the models' performance. The proposition using a flexible distribution (SMSN-NLMM) is better suited for this data, which exhibits skewness and outliers (Table 1), than the N-NLMM where residuals and random effects are assumed to be normally distributed.

5. Discussion

5.1. Heterogeneity issues in infectious diseases data

For the past two decades, infectious disease modeling has been one of the most crucial areas in epidemiology, contributing significantly to understanding the dynamics of epidemic outbreaks and predicting their future course. Most epidemic models, including the well-known SIR and its extensions (Gnanvi et al., 2021; Tang et al., 2020), are compartmental models—a mathematical approach that epidemiologists have used for over a century. While highly useful for analyzing infection dynamics in large populations, such as countries or states, the SIR-type model is most applicable when model parameters can be assumed to be homogeneous, representing the entire population. This model is particularly valuable in the early phases of a disease outbreak when health administrations aim to develop nationwide macro-interventions. However, with the spread of advanced infectious diseases showing substantial heterogeneity in factors like urbanization, ethnic distribution, political views, governance, and economic composition across different subgroups of individuals in various geographical locations, it becomes crucial to explore more advanced modeling approaches.

One possible extension is to employ the Partial Differential Equations (PDEs) approach, as proposed by Murray et al. (Murray, Stanley, & Brown, 1986), to allow for area-specific spread patterns of epidemics. However, this approach was criticized for its ignorance of the fact that infectious diseases spread through person-to-person interactions rather than a continuous population (Mollison, 1991). Instead, a General Cellular Automaton (CA), a micromodel that mimics an interactive

particle system as discussed by Tang et al. (Tang et al., 2020), was suggested as more suitable for modeling spatially varying infection dynamics. Originating in the works of Von Neumann et al. (Von Neumann Burks et al., 1966) and Ulam et al. (Ulam et al., 1962), the CA paradigm has been widely used in various applied fields, including modeling infectious diseases.

Furthermore, most existing models fail to account for potential cross-country or regional dependence on the disease spread. They also neglect the possibility of varying disease stages (e.g., early vs. advanced) across different countries (Schumacher, Ferreira, et al., 2021). From this study, we believe that the NLMM approach remains underutilized in the field of infectious disease modeling, particularly when aiming to estimate both the average disease behaviour within specific regions and the associated variability both between and within these regions.

Acknowledging the limitations of normality assumptions, which can be unreliable for data with skewness and heavy tails like COVID-19 cases and deaths, Schumacher et al. (Schumacher, Ferreira, et al., 2021) proposed a novel class of asymmetric NLMMs. This approach efficiently estimates parameters in infectious disease data analysis. In this model, random effects follow a scale mixture of skew-normal distributions (SMSN; Branco and Dey (Branco & Dey, 2001)), while random errors follow a symmetric scale mixture of normal distributions (SMN; Lange and Sinsheimer (Lange & Sinsheimer, 1993)). This novel approach, illustrated in (Fig. 10), presents an advanced alternative to the traditional normal distribution employed by Rodríguez et al. (Rodríguez et al., 2017).

The comparison of an individual nonlinear model for each area separately with a nonlinear mixed-effects model by Rodríguez et al. (Rodríguez et al., 2017) indicated that NLMMs are well-suited for modeling dengue outbreak data based on cumulative cases in different urban areas. Although underexplored in IDM, the method finds wide application in various epidemics, including influenza (Lee et al., 2009; Wang et al., 2020), hospital-acquired infections (Duval et al., 2018), HIV/AIDS (Dinh et al., 2018), and SARS-CoV-2 (Chong et al., 2021; Lee, Lei, & Mallick, 2020). Nonlinear mixed-effects models outperform individual models by pooling information from different areas, thereby enhancing the predictive power for each area individually (Lee, Lei, & Mallick, 2020). Similarly, Paul and Held (Paul & Held, 2011) discussed a non-linear model for analyzing multivariate time series of infectious disease counts, demonstrating that accounting for heterogeneity through random effects significantly improves predictive performance. In this field, methods for parameter estimation, random term specification, and statistical software tools for implementation and model comparison deserve further investigation, as they hold great promise for informing effective policy recommendations to control present and future infectious disease outbreaks across large spatial and temporal scales. Moreover, as the main advantage of NLMMs is modeling heterogeneity and flexibly handle unbalanced data, then it would be beneficial for further research to draw in depth comparisons to spatial compartmental models knowing that they have been playing a central role in modeling infectious disease dynamics.

5.2. Software implementation, algorithms/approaches and availability of packages

To make research findings transparent and to place resulting toolboxes into the hands of practitioners, an open-source software package must be a deliverable. This is so important, as the ease of implementation and numerical stability impact the choice of statistical models and methods for estimation and prediction. Statistical Software and relative packages for implementing NLMMs exist but need to be more comprehensive as the existing ones have one or more limits. The latest studies in NLMMs made available the possibility of implementing this statistical method in some of the most known statistical software, such as R and SAS, with this first mostly referred to in all fields of applied NLMMs. The SAS NLMIXED procedure, the R function nlme in the nlme package and the R function nlmer in the lme4 package are available and widely used for fitting nonlinear mixed-effects models and providing several different implementation variations. While types of software are available for fitting NLMMs models, concerns have been raised about the reliability of these procedures for fitting mixed-effects models (Stegmann, Jacobucci, Harring, & Grimm, 2018; Zhang & Gen, 2011). Markov chain Monte Carlo (MCMC) methods to perform estimation and prediction for state-space models is the most known approach in epidemic modeling. The SAEM has gained much attention in recent years and is also available through an R package “remix”, but further comparative studies are needed for its performance on others, especially Bayesian routine in complex longitudinal infectious diseases data as an extension of Schoemaker et al. (Schoemaker et al., 2019), Makowski and Lavielle (Makowski & Lavielle, 2006). It is worth noting the observed important interest in the Bayesian method while dealing with infectious disease modeling. The usefulness of Bayesian approaches for joint models, especially infectious diseases modeling (viral load dynamic), has known success with, notably, a dedicated tool that relies on a Gibbs Monte-Carlo by Markov Chains using BUG Software (R2WinBUGS package in R), but the computation cost was large (Kerioui et al., 2020). The performances of the Hamiltonian Monte-Carlo (HMC) algorithm implemented in Stan for inference in a nonlinear mixed model have been demonstrated in others. The No-U-Turn version of the Hamiltonian Monte-Carlo (HMC) algorithm would optimize the exploration of the target distribution by relying on Hamiltonian dynamics (Hoffman Gelman et al., 2014). It is theoretically proven that HMC can handle highly nonlinear estimation problems where Gibbs sampling could fail (Neal et al., 2011), and it has also been demonstrated to be faster than the combination of Gibbs and Metropolis-Hastings algorithms implemented in BUGS for providing efficient posterior distributions in case of complex models (Monnahan, Thorson, & Branch, 2017). In addition to “rstan” and “brms”, the R package “rstanarm” has been proposed with a previously compiled regression model using Stan (Gabry & Goodrich, 2017) for NLMMs implementation in the Bayesian framework. However, this extension is also limited to linear models for the longitudinal part. More research is still important in NLMMs program in R, especially when dealing with complex heterogeneous data exhibiting skewness, such as infectious disease dynamic data.

5.3. Open questions

A few open questions of great interest that motivate new methodological developments come out from this literature synthesis.

Q_1: Uncertainty in the estimation and prediction of different statistical methods: Are NLMMs the best-performing models for estimating key parameters in infectious diseases (R_0, peak, time-period ahead)?
Q_2: Uncertainty in estimating and predicting using different estimation methods in NLMMs: Is the Bayesian approach the best-performing method in estimating key parameters of infectious diseases (R_0, peak, $k-$ time ahead)?
Q_3: Modeling and forecasting epidemic outbreaks: Which epidemiological models are best for early predicting the epidemic peak and infected cases?
Q_4: What are the major countrywide covariates that cause infection trajectories of countries to behave differently in terms of the spread of the disease, providing evidence to explain the heterogeneity in the country-wise infection trajectories across a region?

6. Conclusion

Understanding the dynamics of the pandemic and predicting its future course is of utmost importance. Epidemic models have been pivotal in comprehending past and present infectious diseases. They will continue to be valued and enhanced to better understand infectious disease dynamics. The use of NLMMs in infectious disease modeling is of great significance, and further research is expected to enhance its performance in modeling infectious disease dynamics. NLMMs possess several inherent features that make them relevant modeling approaches for dynamic infectious diseases. They are among the top statistical methods for handling the substantial heterogeneity inherent in infectious disease transmission and intra-variability analysis. However, relatively few longitudinal data studies have included heterogeneity and skewness features. This synthesis on NLMMs can guide the selection of appropriate statistical methods for modeling future pandemic data.

Conflict of interest

As part of the submission of our manuscript entitled "*Nonlinear Mixed Models and related approaches in Infectious disease modeling: A systematic and critical review*" for consideration for publication in *Infectious disease modelling*, all the authors declare that they have no conflicts of interest.

CRediT authorship contribution statement

Olaiya Mathilde Adéoti: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Schadrac Agbla:** Writing – review & editing. **Aliou Diop:** Writing – review & editing. **Romain Glèlè Kakaï:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

Table 2
Journal of publication of studies in general

Journals	Effectifs	RFC (%)
J Pharmacokinet Pharmacodyn	15	12.10
Statistics in Medicine	14	11.29
NA (Preprint)	11	8.87
Computational Statistics and Data Analysis	9	7.26
Journal of Applied Statistics	9	7.26
AAPS Journal	6	4.84
Journal of Biopharmaceutical Statistics	5	4.03
Pharmaceut. Statist.	5	4.03
Journal of Agricultural, Biological, and Environmental Statistics	4	3.23
MULTIVARIATE BEHAVIORAL RESEARCH	4	3.23
PLOS ONE	3	2.42
Stat Comput	3	2.42
Statistical Methods in Medical Research	3	2.42
Biometrical Journal	2	1.61
Biostatistics	2	1.61

Table 2 (*continued*)

Journals	Effectifs	RFC (%)
Communications in Statistics?Simulation and Computation	2	1.61
Computer Methods and Programs in Biomedicine	2	1.61
CPT Pharmacometrics Syst Pharmacol.	2	1.61
Journal of the American Statistical Association	2	1.61
The International Biometric Society	2	1.61
American Society of Animal Science	1	0.81
Biological Sciences	1	0.81
BIOMETRICS	1	0.81
BIOPHYSICS AND MICROBIOLOGY	1	0.81
Bulletin of Mathematical Biology	1	0.81
Communications in Statistics?Theory and Methods	1	0.81
Eur J Drug Metab Pharmacokinet	1	0.81
European Journal of Operational Research	1	0.81
Journal of Multivariate Analysis	1	0.81
Journal of Statistical Computation and Simulation	1	0.81
Journal of Virology	1	0.81
Pharmaceutical Research	1	0.81
Pharmacometrics & Systems Pharmacology	1	0.81
PLOS COMPUTATIONAL BIOLOGY	1	0.81
Poultry Science Association	1	0.81
REVISTA INVESTIGACION OPERACIONAL	1	0.81
Statistics and Its Interface	1	0.81
Structural Equation Modeling: A Multidisciplinary Journal	1	0.81
The Journal of Infectious Diseases	1	0.81

Table 3
distribution of studies across countries

Countries	Effectifs	RFC (%)
USA	30	24.19
France	18	14.52
Sweden	13	10.48
Brazil	8	6.45
China	8	6.45
South Africa	7	5.65
Chile	5	4.03
Canada	3	2.42
Australia	2	1.61
Benin	2	1.61
California	2	1.61
Italy	2	1.61
London	2	1.61
NA	2	1.61
Switzerland	2	1.61
Taiwan	2	1.61
The Netherlands	2	1.61
Boston	1	0.81
Cuba	1	0.81
Denmark	1	0.81
Germany	1	0.81
Iran	1	0.81
Manchester-UK	1	0.81
Manhattan	1	0.81
Massachusetts	1	0.81
New York	1	0.81
New Zealand	1	0.81
Saudi Arabia	1	0.81
Sogang	1	0.81
Spain	1	0.81
Thailand	1	0.81

Table 4
Computational/Estimation methods advance in NLMMs

Estimation methods	Effectifs	RFC (%)
EM approach/M-estimation/MLE	37	21.02
Bayesian approaches	31	17.61
SAEM	26	14.77
FOCE	15	8.52
FOCEI	10	5.68
LIA	8	4.55
(adaptive) Gaussian quadrature approximation	7	3.98
penalized likelihood (splines) methodology	7	3.98
Approximation approach	4	2.27
nonlinear least squares estimators	4	2.27
mean imputation method	2	1.14
SAEM-pen (stochastic approximation EM-penalized)	2	1.14
two-step method	2	1.14
Bayesian-Random forest	1	0.57
Continuous Discrete Extended Kalman Filter	1	0.57
first-order linearization method (FO)	1	0.57
FOCE-Extended Kalman Filter	1	0.57
FOCE-Extended Least Squares	1	0.57
Gauss-Newton method	1	0.57
Huber's M-estimation	1	0.57
Hybrid Bayesian approach	1	0.57
LASSO-type method	1	0.57
MCPG:Monte-Carlo proximal-gradient	1	0.57
NonParametric Adaptive Grid, NPAG	1	0.57
nSCEBE: Simultaneous correction method of empirical Bayesian estimates	1	0.57
Ordinary Nonlinear Least Square Estimator (ONLS)	1	0.57
parametric power estimation	1	0.57
Robust linearized Gaussian likelihood	1	0.57
Robust Two-Stage Estimation	1	0.57
SAPG:stochastic approximation proximal-gradient	1	0.57
Simulated pseudo-maximum likelihood	1	0.57
stochastic expectation-maximization (StEM)	1	0.57
three-step multiple imputation method	1	0.57
truncated power basis functions (TPF-splines)	1	0.57

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