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Mathematical Models of Antimicrobial Resistance: Overview of Trends and Research Gaps

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Antimicrobial resistance (AMR) occurs when microorganisms develop mechanisms that reduce the efficacy of antimicrobial agents [6]. Recognized by the World Health Organization (WHO) as one of the top 10 global threats and known as the "Silent Pandemic", AMR undermines the health of humans and animals, while also impacting the environment, food security, economic development, and social equality, requiring urgent action and effective management strategies [7].

Studies have projected that AMR could lead to up to 10 million annual deaths by 2050, with a 100 trillion economic burden [4, 5]. A 2019 review estimated 4.95 million associated with AMR deaths, 1.27 million directly attributable, particularly in low and middle-income countries (LMICs) [2]. Furthermore, a 2024 analysis predicted that without interventions, AMR could result in 1.91 million attributable deaths and 8.22 million associated deaths by 2050 [3].

Mathematical modeling is a crucial tool for predicting trends, understanding causal mechanisms, and assessing intervention strategies. This study reviews the literature on mathematical models for AMR, revealing trends and identifying research gaps that limit their applicability. Our goal is to provide an overview of mathematical modeling approaches to AMR, focusing on different types of models and their objectives (evolution, mortality, resistance, and impact of intervention). We reviewed the literature on the application of these models to AMR.

The review, based on 31 articles, showed that 20 studies used deterministic models, eight used stochastic models, two compared both, and one used both deterministic and agent-based models. Regarding the host, (15/31) did not specify a particular host, 13 focused on humans, and others on humans and animals. In terms of acquired resistance, 14 studies adopted a general approach, seven focused on the host, four on the community, two on hospitals, two in the laboratory, one study combines host and community and one both hospital and community.

In 29 studies, bacteria were the focus, one study examining viruses and another investigating both bacterial and viral pathogens. Regarding resistance mechanisms, 14 studies investigated mutations, six combined them with horizontal gene transfer (HGT), five HGT through conjugation, four consider general mechanisms, one HGT through both conjugation and transformation, and one focuses on gene regulation. Eighteen studies did not include pharmacokinetic/pharmacodynamic (PK/PD) parameters, six included both, six focused on PD and one on PK.

In Figure 1, various aspects of AMR are highlighted. Combined drug therapy was used in only four studies, in contrast to the predominant use of monotherapy (27 studies). Only three models (9.7%) considered the economic impact of AMR. More than half (18/31) included drug concentration in treatment scenarios. Two articles did not address resistance evolution. Cross-validation and empirical validation were performed in seven studies. Sensitivity analysis was incorporated into the 26 studies, while the immune response appeared in less than a quarter (6/31). The cost of fitness included in the studies 27, and four studies considered spatial dispersal.

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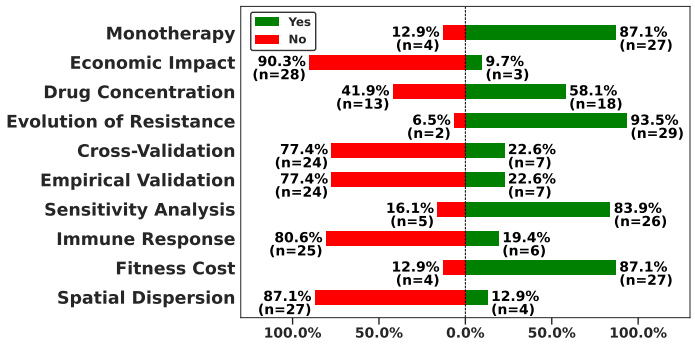

Figure 1: Distribution of model characteristics in the 31 reviewed articles. Source: Author.

We identified several relevant gaps during this review, including: deterministic models do not capture rare events, require stochastic models; combined therapy was rarely considered, despite its potential to prevent or delay resistance; fitness cost and PK/PD parameters were often omitted; the immune response is essential for AMR and treatment efficacy [1], but it is rarely addressed; factors such as economic impact and spatial dispersal need further exploration.

Future studies should consider models that capture biological uncertainties and rare resistance events, which can be addressed using stochastic modeling tools such as the Gillespie algorithm and Markov chains; include PK/PD and combined therapies to improve treatment predictions and delay resistance; consider economic factors to facilitate efficient allocation of resources and intervention planning; and incorporate immune response and spatial dispersal of pathogens, especially in LMICs. Collaboration between mathematicians, epidemiologists, and healthcare professionals is crucial to translate theoretical advances into effective public policies, particularly in LMICs.

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