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MATHEMATICAL MODELS FOR PREDICTING THE SPREAD OF ANTIBIOTIC-RESISTANT BACTERIA

Khalid Saud Alanazi, Marwan Mohammed Al Qarni, Mohammed Hassan Mujarribi, Hassan Abdulraouf Abdulrhem Faris, Bader Obaid Alrashdi, Mohammed Omar Hakami, Faruq Omar Hakami, Hisham Abdullah Mujarribi, Abdullah Mohammed Abdullah Alqahtani, Hussain Ahmed Salman Alwadani, Hamdan Hamd Alyamy, Sami Ali Shaqarah, Nawaf Awid Alsaadi, Ghazi Muhammad Hayaz Al-Shehri

Abstract

Antimicrobial resistance is a worldwide health issue that requires the use of all available methods to manage it. Mathematical modeling is an important tool that allows us to better understand how antimicrobial resistance (AMR) develops and spreads. It also helps us to explore and suggest new ways to manage AMR. Ensuring the wide applicability of mathematical models is crucial, and this may be achieved by adhering to appropriate modeling practices. The aim of this work was to conduct a thorough systematic evaluation of existing models that examine the development and spread of antimicrobial resistance (AMR). Moreover, the research sought to uncover deficiencies in the information necessary for the development of practical models. The review conducted an extensive literature search and included 38 carefully chosen research. The chosen articles were analyzed using a modified version of established frameworks, and their quality was assessed according to the TRACE good modeling practice recommendations. None of the chosen articles met the TRACE standards. Our suggestion for future mathematical models is to: a) combine mechanistic modeling of biological processes, b) use stochastic modeling to account for uncertainty and unpredictability in the system, c) do sensitivity analysis and validate the model externally and internally. There are several mathematical models that describe the development and spread of antimicrobial resistance (AMR). Insufficient understanding of antibiotic resistance hinders the creation of effective mathematical models.

Keywords: Mathematical models, antimicrobial resistance, antibiotic bacterial, resistance, review.

1. Introduction

The discovery of antimicrobials in the field of medicine during the 1920s was widely seen as a miraculous occurrence. Subsequently, this therapy has led to the preservation of many lives. Nevertheless, historical evidence indicates that the implementation of any antimicrobial substance in human or veterinary medicine is promptly accompanied by the emergence of resistance to that substance [1]. The rise of antimicrobial resistance (AMR) poses a significant danger to our capacity to effectively treat prevalent infectious illnesses, leading to extended periods of sickness, impairment, and mortality [2]. The emergence of multidrug and pan-resistant organisms has become a global issue. Although it is difficult to accurately determine the precise costs of AMR, the genuine economic impact is significant [3]. In 2007, the expected economic impact of AMR in Europe was at least €1.5 billion, whereas in the US in 2000, it was estimated to be $55 billion (quoted from Gandra et al., 2014 [3]). Hence, it is crucial to restrict the occurrence and dissemination of antimicrobial resistance (AMR).

Antimicrobial resistance (AMR) is rapidly disseminating on a worldwide scale, affecting not only humans but also animals and the environment. Moreover, there is compelling evidence indicating the presence of a continuous flow of bacteria that are resistant to antimicrobials and carry antimicrobial resistance genes across these various compartments [4]. Studies have shown that AMR factors may persist in settings like sludge and wastewater treatment systems [5, 6], facilitating the spread of disease-causing bacteria and exacerbating the issue of AMR.

Mathematical models have a crucial role in aiding decision-making in the fields of medicine and public health [7]. They have contributed to enhancing our comprehension of the progression, origination, and dissemination of antimicrobial resistance (AMR) [7, 8]. Furthermore, they have the capability to detect deficiencies in our understanding and guide research towards acquiring crucial data on significant variables and mechanisms inside the simulated system. Nevertheless, in 2006, Opatowski et al. [7] conducted a study on mathematical models of antimicrobial resistance (AMR) and determined that significant enhancements were necessary for AMR models. These improvements should focus on including crucial aspects of pathogens, such as resistance mechanisms and inter-species cooperation. Regular assessment of published mathematical models is therefore vital for us to acknowledge advancements in AMR modeling. Identifying gaps in our understanding may help determine the priorities and provide appropriate hypotheses for future research in combating antimicrobial resistance (AMR).

Grimm et al. [9] revised the TRACE paradigm, which was first created in 2010, with the objective of formulating recommendations for generating valuable models. The TRACE paradigm has eight parts that, when adhered to, guarantee the clear communication of models upon publication. The elements of the model are as follows: Problem formulation, which involves clearly defining the objective and providing a description of the context in which the model is applied; Model description, which includes a written explanation of the model elements to enable readers to understand and replicate the model; Data evaluation, which involves

assessing the quality of the data used to parameterize the model; Conceptual model evaluation, which entails listing and explaining the most important design decisions made in developing the model; Implementation verification, which involves internally validating the model by testing for programming errors and assessing its performance; Model output verification, which entails externally validating the model by comparing its output with observations; Model analysis, which mainly involves conducting sensitivity analysis; Model output corroboration, which involves comparing the model output with data that were not used in creating the model. To get a comprehensive explanation of the TRACE components, please refer to the work of Grimm et al. [9].

Following the extensive and organized analysis of mathematical models from 1993 to 2006 undertaken by Temime et al. [10], many further reviews have been published [7, 8, 11]. However, the studies mentioned either focused on models that establish a connection between antibiotic usage and antimicrobial resistance (AMR) [11], or models that simulate AMR in populations consisting of people and bacteria, as well as in hospitals [7]. These reviews did not specifically include models that only focus on the dynamics of AMR inside individual hosts [8]. These systematic reviews did not analyze models of antimicrobial resistance (AMR) in connection to animal populations and the environment. Nonetheless, a thorough examination of mathematical models pertaining to antimicrobial resistance (AMR) should include models that encompass all relevant people and ecosystems, with the aim of addressing the AMR issue from a One-Health standpoint. By adopting this approach, researchers from diverse disciplines may use the knowledge and progress made in other subjects to their advantage.

The aim of this study was to evaluate the efficacy of mathematical and simulation models in predicting the development and spread of antimicrobial resistance (AMR) in people, animals, microbes, and the environment. Our objective was to identify deficiencies in the understanding required to develop effective models of antimicrobial resistance (AMR). The evaluation was conducted by a systematic review. The models that were presented were then condensed and contrasted using a modified version of frameworks that had been previously established [7, 8]. In addition, the strengths and limitations of the models were analyzed using the TRACE paradigm [9].

In a recent study, Heesterbeek et al. [25] examined the significance of mathematical modeling in understanding the spread of infectious diseases and its impact on public health. The authors stated that mathematical models may provide insights that can be used in public health strategies by incorporating fresh data.

2. Antimicrobial resistance (AMR)

Antimicrobial resistance (AMR) poses a significant risk to public health, and using mathematical modeling might be advantageous in combating this issue. It has the potential to play a significant role in understanding the dynamics of antimicrobial resistance (AMR), measuring the impact of influencing variables, and offering methods for its management and

prevention. Moreover, modeling might provide a chance to clarify any deficiencies in our understanding.

The examined publications exhibited a range of model structures and levels of complexity, spanning from basic deterministic models to sophisticated mechanistic models such as agent-based, individual, and nested models. Nevertheless, they often offered insufficient rationale for the selection of the model type and structure. Furthermore, most of the research primarily concentrated on modeling a solitary entity (Table 2), a singular strain of a pathogen (Table 5), assumed uniform blending (Table 4), and disregarded the presence of uncertainty and randomness in the progression and/or dissemination of antimicrobial resistance (Table 3). AMR is a complex issue that involves several components, such as external influences and interactions among different populations (microbiota, animal, and human populations), which might impact its emergence and transmission [26].

These factors of nonlinearity, heterogeneity, and stochasticity should be taken into account while developing mathematical models of AMR. Opatowski et al. [7] said that models should include the distinct properties of pathogens, such as the pathogen's resistance mechanism and the collaboration across species. They determined that this would result in significant enhancements of the models. However, in the 6 years after the publication of their study, only one work has provided a detailed description of a really nested model [27]. This model represents various bacterial strains inside individual organisms (pigs), which interact as a population with a diverse structure. Regrettably, this model has not undergone validation and so cannot facilitate the conversion of pathogens.

Moreover, a certain article [28] presented a framework to handle the intricate layers that exist inside the genetic makeup of cells, including the cellular environment, the host organism, and the host's environment. These models represent a desirable goal for the future, given the very intricate nature of the AMR issue and the need for a comprehensive understanding of its multi-level interactions. It would be very beneficial if the community could agree to use these standard models, allowing the extensive task of parameterizing these models to begin. In the future, we may use the knowledge and expertise of others instead of creating unique solutions for every individual challenge.

Stochastic processes in mechanistic modelling can accurately represent intricate and diverse structures and processes, as well as simultaneously model multiple pathogens/genes. This approach can also capture biological interactions that may impact antimicrobial resistance (AMR), such as the immune system, the effects of antibiotic dosing, the microbiome, and various factors that contribute to system variability. Furthermore, these models have the capability to provide valuable understanding of the time-dependent changes in antimicrobial resistance (AMR), both at the individual and community levels. According to Arepeva et al. [11], this family of models has an advantage over simpler models like deterministic differential equations.

Nine models used analytical solutions to address the modeled system, yielding comprehensive mathematical answers with a restricted assessment of the practical relevance of the results.

Indeed, only two articles [29, 30] made an effort to authenticate the models by using data. Analytical solutions are advantageous in circumventing the need for time-consuming and computationally costly simulations. However, considering the practical aspect, the significant intricacy of AMR and the restricted application of analytical solutions in real-world scenarios raise doubts about the effectiveness of this method in addressing and mitigating the AMR issue.

Models of AMR should ideally undergo validation using data. Nevertheless, a significant number of the published models depict theoretical scenarios in hospitals or communities without any corroborating evidence [31–35]. These models are only useful if a comparable hospital or setting can be found. If this is true, tests or observational investigations may be conducted to verify the accuracy of the models. Furthermore, there seems to be a deficiency in understanding the implementation of many standard parameters and their correlation with real-world scenarios.

3. Validation

Validation is a crucial aspect in the process of constructing a mathematical model. Validation may be categorized into two types: internal validation, which is performed to verify that the model is functioning as intended, and external validation, which is undertaken to evaluate the extent to which the model's outputs align with real-world observations. Out of the research conducted, only 13 of them included external validation of the models. Among these, ten studies relied on data while three studies relied on information from existing literature. The lack of validation in several published models (Table 5) may be attributed to insufficient useable data. Our understanding of the dynamics of antimicrobial resistance (AMR) inside a host, particularly in relation to genotypic AMR, is significantly lacking.

Curiously, all of the studies did not mention the conduction of internal validation. There are other techniques available for internal validation of models, including the rationalist approach, tracing method, and face validity [36]. Internal validation is crucial for guaranteeing that the code is devoid of mistakes, hence fulfilling the fifth criterion of the TRACE technique [9]. Internal validation may have been performed, even if it is not explicitly stated in the publication. However, it is crucial to provide a detailed explanation of the techniques and procedures used for internal validation to establish trust in the accuracy of the forecasts. Failure to validate the model might heighten the likelihood of inaccurate results and conclusions, hence diminishing the trust that the scientific community and decision makers have in the forecasts. It is necessary to perform and document rigorous internal validation of the models. Moreover, further investigation should be undertaken to gather data for the purpose of externally validating the models, therefore producing models that can provide reliable suggestions. There are mathematical publications that satisfy the TRACE requirements. An exemplary illustration of this may be found in the work of Foddai et al. [37].

Most of the publications primarily focused on modeling antimicrobial resistance (AMR) in connection to people. This was done either by directly modeling human populations (in hospitals or towns) or by studying microorganisms that directly affect human health. Only four animal-related simulations were done, as shown in Table 1. Animals can serve as a source of antimicrobial resistance (AMR) that can be transmitted to humans through various means such as meat consumption, use of animal waste as fertilizers, or direct contact. Therefore, it is important to focus on enhancing our knowledge of AMR dynamics in livestock production systems and the environment.

All the research included in this analysis consistently indicate that an escalation in antimicrobial use leads to a general rise in antimicrobial resistance (AMR). Several studies indicate that certain tactics result in comparatively lower rises in antimicrobial resistance (AMR), maybe attributed to the reduction of contact rates or the rotation of various types of antimicrobial agents [13, 15, 20, 27, 31–34]. One study showed a reduction in antimicrobial resistance (AMR) while using an antibacterial agent that bacteria had no resistance to [35]. Nevertheless, according to the scientists' findings, this characteristic is temporary and will decrease over time in direct proportion to the use of the medicine.

Several articles outline different approaches to attaining antimicrobial resistance (AMR), specifically focusing on AMR acquired in hospitals vs the community. These papers determine the parameter values at which the R0 (basic reproduction number, indicating the level of disease infectivity) exceeds 1. Nevertheless, there are no scientific articles that effectively align epidemiological data to establish parameters or verify the accuracy of their model. Several studies examining the epidemiological transmission of particular drug-resistant infections, such as MRSA, were not included in this review. Our focus is on the spread of resistance in general, rather than specific pathogens. When we say there are no statistics regarding epidemiological spread, we are referring to the transfer of resistance between bacteria in a real-life setting. There are several scientific articles that discuss the spread of in vitro studies [19, 58–61]. However, we maintain that these characteristics can only serve as a preliminary reference for estimating parameters in vivo, since the natural environment is far more intricate and competitive than a petri dish.

4. Summary

There are several mathematical models that describe the development and spread of antimicrobial resistance (AMR). Nevertheless, there is a dearth of understanding of the fundamental processes in operation, hence limiting the genuine efficacy of the formulated models. In addition, only a small number of models met the TRACE criterion. Future models of antimicrobial resistance (AMR) should aim to clarify the patterns and fluctuations in the incidence and spread of AMR. This will enable researchers to effectively understand and influence these patterns, with the goal of preventing and controlling AMR. Furthermore, it is crucial to prioritize research efforts towards generating data that can be used to parameterize and

test AMR models, enabling the extraction of meaningful insights from them. There is a need for more rigorous creation and testing of models, as well as a greater availability of experimental and observational data to enable the validation of these models.

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