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*Letter to the Editor*

# Can Large Language Models Predicting Antimicrobial Resistance Genes Prevent the Spread of the Oral Resistome?

Pradeep Kumar Yadalam[1*], Raghavendra Vamsi Anegundi[1]

[1]Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai 600 077, India. pradeepkumar.sdc@saveetha.com (PKY); arvamsi2009@gmail.com (RVA)

***Corresponding author:** Pradeep Kumar Yadalam, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai 600 077, India. pradeepkumar.sdc@saveetha.com

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Antimicrobial resistance (AMR) is a major global health threat, causing over 1 million deaths annually.[1] Traditional methods are slow and limited, while whole-genome sequencing offers a more accurate method for determining AMR phenotypes. Two principal computational methods, rule-based catalog mapping and machine learning (ML), have been employed to predict AMR phenotypes from genomic data. A recent study evaluated the performance of four advanced ML algorithms, a baseline ML model, and the rule-based ResFinder tool in predicting AMR phenotypes across 78 species-antibiotic datasets.[2,3] The results revealed significant performance variations, with ML methods demonstrating superior accuracy for closely related strains and ResFinder exhibiting greater suitability for divergent genomes.

Given the escalating prevalence of AMR and the global dissemination of infectious diseases, such as COVID-19, accurate classification of antibiotic resistance genes (ARGs) is imperative. A recently proposed method fine-tunes nucleotide sequence and text language models using ARGs databases, enhancing performance with an augmentation technique based on large language models (LLMs) and ensemble method.[1] A tool predicts bacterial resistomes for *Escherichia coli* and *Pseudomonas aeruginosa* with deterministic and stochastic models. The deterministic model has 87% accuracy, 85% sensitivity, and 89% precision, while the stochastic model has 72% accuracy.[4] The stochastic model's lower accuracy may result from its reliance on probabilistic estimations, which can introduce variability compared to the deterministic model.

A systematic review was conducted to assess the antimicrobial efficacy of antibacterial-coated sutures in oral surgery, utilizing PubMed and Scopus databases for human clinical studies.[5] Five studies were identified, revealing a general trend toward lower bacterial retention with antibacterial-coated sutures compared to uncoated sutures. However, further research is imperative to substantiate these findings and evaluate their cost-effectiveness.

The oral microbiome serves as a reservoir for ARGs, with a higher prevalence observed in healthy individuals than in those with caries or periodontitis. *Actinomyces*, *Streptococcus*, *Veillonella*, *Corynebacterium*, *Neisseria*, and *Fusobacterium* constitute the core oral microbiome. Among the ARGs, *mefA*, *msrD*, *cfxA*, and *ermF* were found to be most prevalent in healthy individuals, while *tetQ*, *pgpB*, and *tet32* were more commonly associated with periodontitis.[5]

A comprehensive analysis of the oral microbiota revealed a diverse array of ARGs, with healthy oral conditions exhibiting the highest abundance. A recent study predicted the presence of 6,095 antibiotic resistance determinants (ARDs) in the human intestinal microbiota, highlighting the majority as distantly related to known ARDs and rarely shared with pathogens. The study further demonstrated a positive association between ARDs abundance and gene richness, independent of antibiotic exposure. Employing a machine learning model, the researchers accurately identified ARGs in both Gram-negative and Gram-positive bacteria, achieving classification accuracies ranging from 87% to 90%. Additionally, a standalone software tool was introduced to facilitate the identification of ARGs.[6] LLMs can predict ARGs, potentially preventing the spread of the oral resistome. They can identify patterns and predict the presence of ARGs, providing insights into public health interventions. LLMs can also help monitor the prevalence and distribution of ARGs, aiding personalized treatment and accelerating research. However, limitations include data quality, the complexity of resistance mechanisms, integration with other approaches, and ethical and privacy concerns.[1,5] LLMs should be integrated with traditional microbiological methods, public health policies, and education to combat ARGs effectively. While LLMs show promise in predicting ARGs, their potential to track resistance patterns in patients with periodontal disease, especially those undergoing non-surgical therapy and therapeutic mouthwash use, remains underexplored. A comprehensive approach involving healthcare professionals, policymakers, researchers, and the public is essential to slow the spread of resistant oral bacteria and preserve antibiotic effectiveness for future generations.

The limited availability of comprehensive datasets and the dynamic nature of the oral microbiome make predictions difficult. Longitudinal studies and data integration can overcome these issues. Guidelines for interpreting and integrating predictions into clinical practice are needed. Long short-term memory models can predict ARGs and peptides in the oral microbiome, enabling early detection and intervention. However, further research, collaboration, and standardized guidelines are needed to harness this approach and fully implement it in dental clinical practice.

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