LETTER TO THE EDITOR

# Phage therapy: a potential breakthrough in Tuberculosis treatment

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To the Editor, Tuberculosis (TB) is the second leading cause of mortality worldwide from a single infectious agent[1]. According to the WHO, it has infected over 10.6 million people worldwide, leading to 1.30 million deaths in 2022[1]. Antibiotics are the primary treatment; however, multidrug-resistant (MDR), extremely drug-resistant (XXDR), extensively drug-resistant (XDR), and total drug-resistant (TDR) strains have emerged. These strains pose a great threat to the management of the disease in TB-endemic areas such as Pakistan, India, Indonesia, Bangladesh, Philippines, China, Nigeria, and the Democratic Republic of Congo, which contributes to more than two-thirds of the emerging cases.[1] Moreover, the prevalence of multidrug-resistant or rifampicin-resistant tuberculosis was 3.3% among newly diagnosed cases and 17% among already treated individuals, affecting nearly 0.41 million people in $2022_1$. All these factors are alarming for the development of novel therapeutic plans.

Recent studies have investigated Mycobacteriophages and their enzymes as potential therapeutic agents. These studies have effectively demonstrated the use of the five-phage cocktail in alleviating tuberculosis strains.[2] Similarly, the mycobacteriophage D29 liposomal form has shown its potent lytic activity against a model of tuberculous granulomas generated by human blood mononuclear cells in vitro, as well as on tuberculous infection in C57BL/6 mice.[3] Moreover, the LysB protein from the D29 mycobacteriophage has demonstrated its lytic action against drug-sensitive and drug-resistant isolates in extracellular and intracellular environments.[4]

These phages work without antagonizing the action of anti-tuberculosis drugs and effectively infect both isoniazid-sensitive and resistant strains.[2] They also show antibiotic synergy with rifampicin and thus can be used as a combination therapy to reduce further conversion into more resistant strains.[3] Furthermore, the simultaneous use of multiple strains of phages in phage cocktails was also found to increase efficacy and decrease bacterial potential for developing phage resistance.[2]

The antibiotic synergy, host specificity, and smaller number of doses compared with other drug treatments suggest Mycobacteriophages as a viable alternative for treating drug-resistant tuberculosis, however more evidence regarding the impact of human alveolar lining fluid components, the body's immune response, phage resistance, and possible dosages are needed. In particular, the lack of phage therapy regulations needs to be addressed before physicians can incorporate them into their regular treatment protocols.

To conclude we call for future research and clinical trials to evaluate the potential of Mycobacteriophages and their enzymes as adjuvants to shorten treatment durations and prevent the emergence of new resistant strains.

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**MAA**: Concept, methodology, project administration, validation, writing-original draft and final approval.

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