**Title:**

Multi-Strain Vaccination Strategies on Viral Genotype Networks

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**Abstract:**

We implement a novel approach for vaccine strain selection based on a genotype network of viral strains. Current strategies for selecting vaccine strains of multi-strain pathogens involve present and forecasted incidence of particular strains. Here we emphasize the effects of transcending immunity, and exploit the genetic similarity between strains to determine optimal strategies in the case of multi-strain vaccination. We employ a genetic algorithm (GA) to find optimal strategies in the *N* choose *k* search space of *k* vaccines on *N* strains, seeking to reduce the number of strains that may be reached in an outbreak. We tested the strategy on toy networks of varying size and structure, before searching optimal strategies for multiple real-world *Influenza A* (H3N2) genotype networks. This approach consistently reduced the mean expected outbreak size, with significant improvements on random searches. Evolved solutions were evaluated on *Influenza A virus* networks that grew beyond the time of solution computation, simulating the 6 month delay between strain selection and distribution. Despite ignorance toward future states of the genotype network, GA-evolved strategies consistently outperformed even the best random solutions after a year of novel strain emergence. Our approach suggests that knowledge of the genotype network can provide useful insight for vaccine strain selection.