

**WHO CARES ABOUT THE MOLECULAR POPULATION GENETICS OF THE *MYCOBACTERIUM*
TUBERCULOSIS COMPLEX: A HISTORICAL PERSPECTIVE**

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Investigation of the molecular population genetics of bacterial pathogens began in the 1970s and rose to prominence in the 1980s and 1990s. The field was started by investigators trained in eukaryotic population genetics and evolution who viewed bacteria as tractable experimental systems for addressing several questions of interest to evolutionary genetics. By the late 1980s and early 1990s the fundamental principles of bacterial population genetics had crystallized, namely that (i) the clone or cell line is the fundamental unit of virulence; (ii) there is considerable intraspecies variation in virulence; (iii) considerable intraspecies differences exist in allelic and gene content variation; (iii) many species have non-random disease- and host-specific genotype-phenotype relationships; and (iv) bacteria exhibit a diverse array of population structures, ranging from highly clonal to highly recombinational. Although analysis of the molecular population genetics of *Mycobacterium tuberculosis* (MTB) complex members has only been conducted for approximately 10 years, these studies have contributed important information to our understanding of the molecular evolutionary genetics of these organisms and host-pathogen interactions. The worldwide medical interest in these organisms has provided critical motivation to investigate the molecular population genetics and evolution of these organisms. Studies based on comparative gene sequencing, comparative genome analyses, high-throughput single nucleotide polymorphism analysis, and a variety of other genotyping methods have revealed that all of the fundamental principles of bacterial population genetics are recapitulated in the MTB complex. These analyses also have revealed that distinct MTB clonal lineages are distributed non-randomly on a global basis. Studies of comparative virulence assessment using a strain designated HN878 (Houston 878) and representing a distinct clone of MTB have been especially instructive in illustrating intraspecies variation in host-pathogen interactions, including virulence. In the aggregate, we will review key findings from molecular population genetic analysis of MTB complex organisms and use them to illustrate several reasons why mycobacteriologists should be interested in this area of investigation.