Ad fontes!

THE GLOBAL TUBERCULOSIS (TB) control community is challenged by an ever increasing number of multidrug-resistant (MDR) and extensively-resistant (XDR) TB cases. Not long ago, acid-fast smear microscopy was satisfactory for initiating a standard regimen. Drug susceptibility surveillance studies were and still are a matter for the epidemiologists, conducted every few years. Today, drug susceptibility testing (DST) results are required in real time for guiding individual therapeutic drug regimens, especially in patients harboring drug-resistant TB strains. The World Health Organization’s recent policy statement concerning molecular line probe assays for rapid screening of patients at risk of MDR-TB is additional proof that faster turnaround times are necessary.

There are many reasons for determining the drug susceptibility of Mycobacterium tuberculosis: first, DST may be used in the research arena to screen new compounds or to develop a new testing protocol. Second, information from DST results is crucial in surveillance studies. Third, DST results are pivotal in planning wide-scale therapy trials. Fourth, familiar to the clinical bench worker, DST is performed to aid in identification of the species of mycobacterium. Fifth, and importantly, DST results are necessary to guide appropriate antimicrobial therapy in patient care. For these five different uses, the methodology, the compounds and the concentration tested may vary greatly.

In this issue, Kam and coauthors tested 378 isolates with three different methods against six non-first-line compounds. The critical concentration for each compound and method was calculated based on the greatest cumulative percentage difference between susceptible and resistant strains. While this is a very interesting approach, to thoroughly validate this new approach one would need additional clinical information, such as immune status. Furthermore, to prevent any bias in the study, it would be important for the strains to be shown to be genetically dissimilar through DNA fingerprinting.

In 2000, Drlica’s research team introduced a new concept in defining a drug concentration threshold above which bacterial cells require the presence of two or more resistance mutations for growth. The simultaneous occurrence of multiple mutations is a rare event relative to the number of cells present during infection; consequently, administration of the drug above the concentration threshold, called mutant prevention concentration (MPC), will severely restrict selection of resistant mutants. In their experiments, the MPC has been taken as the drug concentration that allows no mutant to be recovered from a susceptible population of more than $10^{10}$ cells. However, for the MPC to be therapeutically useful, it must be below the concentration achievable in serum. Clearly, more research studies need to be carried out to confirm this novel approach.

More recently, Schön and coworkers evaluated wild-type minimum inhibitory concentration (MIC) distributions for first-line anti-tuberculosis drugs, including pharmacokinetic and pharmacodynamic data as outlined by the European Committee of Antimicrobial Susceptibility Testing for setting clinical breakpoints. This is a big step in the right direction and begs the question as to how much longer the TB laboratory community will continue to apply different principles from general microbiology in the field of DST.

Similar to the Renaissance Humanism slogan Ad fontes, i.e., going back to the source of the Greek and Roman scholars, TB microbiologists need to go back to the clinical microbiology principles and embrace their principles for drug susceptibility testing—Ad fontes!

Sven E. Hoffner*
Max Salfinger†

* Swedish Institute for Infectious Disease Control
Solna, Sweden
† Florida Department of Health
Tallahassee, Florida, USA
e-mail: Max_Salfinger@dob.state.fl.us

References