

INFECTIOUS DISEASES VS. CLINICAL RESEARCHERS: WHO IS WINNING?

*“They were running hand in hand,
and the Queen went so fast that it was
all she could do to keep up with her . . .
The most curious part of the thing
was, that the trees and the other
things around them never seemed to
change their places at all.”*

- Lewis Carroll *Through the Looking Glass* 1871

The American biologist Leigh Van Valen (1973) first proposed the metaphor of Lewis Carroll’s the Red Queen as an evolutionary observation. The Red Queen runs hard but never gets anywhere because everything else in the landscape is also running: “It takes all the running you can do to keep in place!”

We are now beginning to understand how the challenges of the Red Queen apply to the development of innovative new drugs and diagnostics for infectious diseases. The rate of selection of resistant organisms from antimicrobial pressures, climate shifts, commercial air travel, greater population densities, and an increasing community of patients immunosuppressed from aging or a multitude of diseases and/or their treatments seem to outpace our current arsenal of infectious disease therapeutics and diagnostics and risk a global public health disaster.

Since the publication of “Through the Looking Glass,” we have seen amazing strides in the field of infectious diseases and examples where we were able to keep up with the speed of an ever-changing environment and reminders that the global setting of infectious diseases can quickly accelerate in ways that we can barely comprehend. We have witnessed

the eradication of smallpox and are in the final stages of eradication of polio. We have seen the “Golden Age of Antibiotics” and now the emergence of multi-drug resistant organisms. Successes in managing mother-to-child transmission of HIV are coupled with continued, staggering statistics that reemphasize the fitness of the virus. Pandemic influenza and the potential of bioterrorism remain a real and constant fear. Lower respiratory infections, diarrheal diseases, HIV/AIDS, and tuberculosis continue to rank among the top 10 causes of death. In low income countries, lung infections, diarrheal diseases, HIV/AIDS, tuberculosis, and malaria are key factors in explaining why less than one in five of all people reach the age of 70 and more than a third of all deaths are among children under 15 [World Health Organization. Available at <http://www.who.int/mediacentre/factsheets/fs310/en/index.html>].



The accelerated events of the last several decades prove that our guard against infectious and communicable diseases cannot be let down. However, in the past decade, the development of new antibacterial agents has been decreasing dramatically [Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:155-164.]. The expenses and difficulties in designing appropriate clinical trials, offset by the relatively small market size for antibiotics compared to other therapeutics and compounded by regulatory requirements that seem to evolve as quickly as the pathogens, are



major hurdles to the development of new infectious diseases therapeutics and diagnostics. Historical controlled trials are useful only if the clinical setting, including treatment and supportive care, has remained relatively unchanged and the strain of pathogen that is being evaluated has not evolved excessively and still has similar characteristics, antibiotic susceptibility patterns, and virulence factors to the strain in the historical study. For pathogens that can rapidly adapt to environmental pressures such as *Staphylococcus aureus* that can divide as quickly as every 30 minutes (and in which the rate of methicillin resistance has increased from 2% in 1974 to 22% in 1995 to 63% in 2004), *Mycobacterium tuberculosis* which can go from a streptomycin resistant rate of 2% to over 80% within three or four months [Mandell, G. L.; Petri Jr, W. A. Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, Ninth Edition, International Edition pp. 1155-1174. J.G. Hardman, L.E. Limbird (eds) 1996], and viruses that can mutate even faster (3×10^{-5} mutations per base per replication cycle for HIV), historical controlled studies may be a challenge. Noninferiority trials with more stringent margins of noninferiority often face the challenge of comparing an agent to a comparator that first became available in an era before widespread use of placebo controlled studies and whose efficacy rate is itself unclear. Ethical concerns of superiority studies versus placebo or delaying effective therapy until the pathogen is confirmed are becoming progressively more demanding as the time to first dose of the antimicrobial is becoming an important performance indicator in many institutions.

To be innovative and succeed against a landscape of infectious diseases that seems to overtake the discovery of new agents and diagnostics, infectious diseases programs and studies must also evolve dynamically. By utilizing extensive population modeling from databases of similar antimicrobial agents against target pathogens or from nonclinical models of infection, companies can effectively optimize study drug dose and timepoints, even before a study begins. Adaptive trial designs can enable real time analysis of the study data and further validate such model's goodness of fit in such a way to reduce the number of patients required to reach meaningful clinical endpoints. Ongoing active antimicrobial surveillance programs are crucial to manage the added

complexity of international enrollment that may arise from variations in the availability and capability of local microbiology laboratories, variations in standard of care, or differences among the quality and reliability of data. Innovative point of care testing to rapidly identify specific target pathogens combined with confirmatory molecular epidemiology techniques is necessary to properly manage the broadened scope of antimicrobial research. An integrative, dynamic, multidisciplinary approach is fundamental to withstand the tug and pull of the current operational and regulatory environment of global infectious diseases research, the balance of risk and benefit to the patient, as well as the mechanistic issues of the therapeutic agent, the diagnostic tests, and the organism. Adaptability and novel ways of thinking about infectious diseases programs and studies are required for survival.

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