

New mathematical model predicts more virulent microbes

Microbes and humans interact in myriad ways, sharing a long history. Many of the most successful microbes are those that inhabit but do not kill their host. Cheaters lose. Tuberculosis settles into the lungs. *Helicobacter pylori*, the microbe causing ulcers, burrows into the stomach where it thrives on acids. And *Salmonella typhi* takes up residence in the gallbladder. All of these organisms can persist in our bodies for decades. What explains their success?

A new mathematical model, devised by a microbiologist renowned for his study of *H. pylori* and a mathematician, provides the framework for understanding how persistent microbes obtain equilibrium with their human hosts. The multi-scale model, published in the October 18, 2007, issue of the journal *Nature*, is based on the idea that certain microbes and humans evolved together and along the way established complex strategies that enabled them to co-exist. These strategies are contingent in part on human population size.

The model helps explain the rules that govern the transmission of microbes and how they have operated in human history, says Martin J. Blaser, M.D., the Frederick King Professor and Chair of the Department of Medicine, and Professor of Microbiology at New York University School of Medicine. He and Denise Kirschner of the University of Michigan Medical School, Ann Arbor, are authors of the study. The model uses game theory, developed by Nobel prize-winning mathematician John Nash, the subject of the book and movie *A Beautiful Mind*, to describe a particular type of equilibrium.

The model can be used to better understand microbial responses to a changing human world, says Dr. Blaser. Based on their formulations, our biological future will probably be filled with some “pretty bad epidemics,” says Dr. Blaser. “Our model predicts that as effective population size increases and as immunodeficiency increases due to the spread of HIV infection, and an aging population, there will be more virulent organisms. This is bad news for us.”

Through the course of human evolution, Drs. Blaser and Kirschner propose that three classes of persistent microbes have evolved, each employing a different biological strategy to avoid being eliminated quickly by their human hosts. TB, *H. pylori*, and *Salmonella* are an example of each class. Any microbe that was “cheating” the system, in other words, tried to expand its territory in the body, wouldn’t survive because it would likely kill its host.

According to their theory, small populations select for certain kinds of microbial agents. More than 50,000 years ago, when humans lived as hunter-gatherers in small, isolated groups, the majority of microbes were transmitted within families or were those that would emerge late in life. Microbes that were not lethal were favored because there wasn’t a large reservoir of people to infect. Any microbe that killed off its hosts, wouldn’t have survived itself. *H. pylori* evolved during this time.

As population size increased and humans became less isolated, organisms that had perfected ways to hide in the body for decades, such as TB and *Salmonella typhi*, and then suddenly reactivate or get transmitted, evolved. These organisms could afford to induce more disease early in life because they had mechanisms to sustain themselves in human populations.

As even larger societies developed, more virulent organisms, such as measles, emerged because the population could permit the virus to spread. Our most recent epidemics, including influenza in the early 20th century and AIDS today, involve organisms that can kill millions because these highly virulent

organisms have a huge pool of people to infect, and still be transmitted.

“We did not make the laws of nature,” says Dr. Blaser. “Even though we may not like them, we need to understand them to better control infectious diseases.”

Source: New York University Medical Center and School of Medicine

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