How do we outsmart hypervirulent Salmonella strains that have an evolutionary edge over our immune systems?

New strains of *Salmonella* have developed a "Trojan Horse? stealth mechanism that allow them to become hypervirulent in a host body. How do we outsmart bacteria that have an evolutionary edge over our immune systems?

by sonia fernandez

*Salmonella* bacteria are some of the most ubiquitous and oldest-known microorganisms, infamous for countless outbreaks and engaged in a perpetual game of one-upsmanship with their hosts. The most common form of foodborne illness, *Salmonella* poisoning comes at a national expense of $14.6 billion a year, including time lost from work and health care.

UC Santa Barbara researchers Douglas Heithoff, Project Scientist, and Michael Mahan [2], Professor of Molecular, Cellular, and Developmental Biology [3], have invested
decades of extensive research into Salmonella. Their efforts are focused on a single-minded goal: beat them at the evolutionary arms race and prevent disease outbreaks before they make news headlines.

Mahan and Heithoff have recently made a startling discovery in their research: strains of ?hypervirulent? Salmonella enterica that are 100 times more capable of causing disease than the average strain of Salmonella.

Able to bypass conventional forms of detection, these naturally-occurring strains of Salmonella trick the host?s immune system to multiply at optimal efficiency, explained Mahan and Heithoff, who isolated the strains from diseased livestock. In an evolutionary leap that would impress the most experienced army commander, these strains have become experts in stealth mode combat on many surprising levels.

Douglas Heithoff (left) and Michael Mahan

?It basically alters the immune response in its favor,? said Heithoff. With the animal?s immune system unable to recognize them as a threat, they can make their way to target tissues in the body by hitching a ride with the host?s own macrophages ? a type of white blood cell that normally engulfs and digests harmful invaders. Inside the macrophage, the Salmonella multiply, then, like the ancient tale from Virgil?s Aeneid, emerge like Greek soldiers from the Trojan Horse to invade the body.

?Without a functioning immune system, the bacteria continue to replicate undeterred, causing more inflammation and tissue damage, resulting in accelerated disease manifestations and septic shock,? said Mahan. Organ failure and death may follow.

What makes these Salmonella strains particularly insidious is that they have evolved the ability to look and act just like their less-virulent cousins when outside of a host. With the implementation of a special laboratory culture media that mimics the host environment, Mahan and Heithoff were able to unmask these strains of Salmonella.

?What we think is that these strains have a heightened capacity to sense their surroundings and adapt very quickly,? said Heithoff. This trait allows them to conserve energy when there?s no food source and use it as needed.

?Outside their hosts they might switch to their less-virulent latent stage until the next host picks them up,? said Heithoff. ?This ability to quickly alter their gene expression determines how well the bacteria are going to survive.?

Salmonella?s survival instinct seems brilliant, if not sobering. The Trojan Horse act is
adaptation in action, and Mahan and Heithoff say scientists must stay one step ahead to prevent other strains, perhaps other pathogens, from evolving a hypervirulent state. The implications could overrun the global food industry?s current standard of prevention practices, and have a major detrimental impact on the public health system.

Among the researchers? counter-strategies is the development of a live, attenuated vaccine for livestock, which, the scientists say would reduce contamination and spread between the animals ? and to humans. The key to their research is developing stronger and smarter cross-protective vaccines that protect against several hundred strains of *Salmonella* at a time.

To date, Mahan and Heithoff have screened these *Salmonella* strains isolated only from livestock. What they haven?t found out yet is whether these *Salmonellae* have caused increased disease in humans, although, they say, that situation can?t be too far off.

?It is just another way nature wins ? by the maintenance of bugs that switch to combat mode only in the animal, but need to switch back to a latent state out of the animal to survive in the environment,? said Mahan. ?Other strains do this also, but hypervirulent strains do it in the extreme.?
Warning Signs

- Salmonella outbreaks from tainted food are now occurring with unprecedented regularity; a clear indicator of how fragile food safety has become.
- For every confirmed case of Salmonella food poisoning, there are roughly 30 that go unreported; meaning an outbreak of 250 individuals affects more than 7,500 people.
- Half of the antibiotics used in the U.S. are for livestock; multi-drug
resistant *Salmonella* strains have emerged because of chronic antibiotic exposure.

- *Salmonella* infections are responsible for up to 50% of bacteremia in young children and in patients with compromised host immunity in developing countries.

**Fighting Back**

- Recent advancements have resulted in the development of cross-protective vaccines that confer protection against several different strains simultaneously.
- In-water delivery of cross-protective vaccines shows considerable promise as a low-cost, low-stress method for livestock immunization.
- Knowing the molecular mechanism by which ?hypervirulent? *Salmonella* causes disease provides a means for the development of vaccines that stimulate potent immune responses to combat them.
- Developing cross-protective vaccines and understanding ?hypervirulent? *Salmonella* can also help researchers combat other drug-resistant infectious bacteria, such as *C. difficile* and *E. coli*.
- The FDA has recommended bar-code methods for source product identification; irradiation of post-harvest foods; and suspension of the use of antibiotics in animal feeds for growth promotion.
- Human bodies are 90% non-toxic bacteria and 10% mammalian cells. Understanding how we interact with these microbes is vital to disease prevention and maintenance of better health.