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Yale researchers uncover typhoid's lethal secret

By Bill Hathaway

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Typhoid fever is one of the oldest documented diseases known to have afflicted mankind but what makes it so lethal has remained a mystery for centuries.

In a study appearing online July 10 in the journal Nature, Yale researchers offer an explanation of how the devastating disease marked by delirium and stupor still kills 200,000 people every year - and also suggests the basis of a future vaccine.

The culprit appears to be a powerful toxin possessed by *Salmonella typhi*, the bacterium that causes typhoid fever. Yale scientists for the first time describe the structure of the typhoid toxin and show that it causes disease in mice. The toxin helps explain why typhoid fever has such different symptoms than an infection by its close genetic cousin Salmonella, the common cause of food poisoning.

"What makes this so exciting for us is that vaccines and therapeutics that target toxins have an excellent track record of success," said Jorge Galan, the Lucille P. Markey Professor of Microbial Pathogenesis and senior author of the paper.

Typhoid fever is believed to have killed Athenian leader Pericles and a third of the population of the Greek city in 430 BC during the Peloponnesian War and has perplexed doctors ever since. Untreated, it kills up to 20% of those it infects, however many of those who survive remain carriers for life but show no symptoms. This fact explains why fever, illness and death followed from job to job the notorious carrier Mary Mallon, best known as Typhoid Mary. A cook for wealthy New England families, she is believed to have unwittingly infected several dozen people in the early 20th century.

Although the cause of typhoid fever has been known for over a century, what makes *Salmonella typhi* so deadly has remained a mystery. Galan and his team showed that the answer to this mystery may be typhoid toxin, a lethal toxin created from the merger of two separate and powerful toxins. The atomic structure of the toxin and its receptor reported in this

study, may pave the way to new life-saving therapeutics.

Jeongmin Song and Xiang Gao of Yale are co-authors of the study.

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