Luring bacteria into an evolutionary trap to reduce treatment resistance

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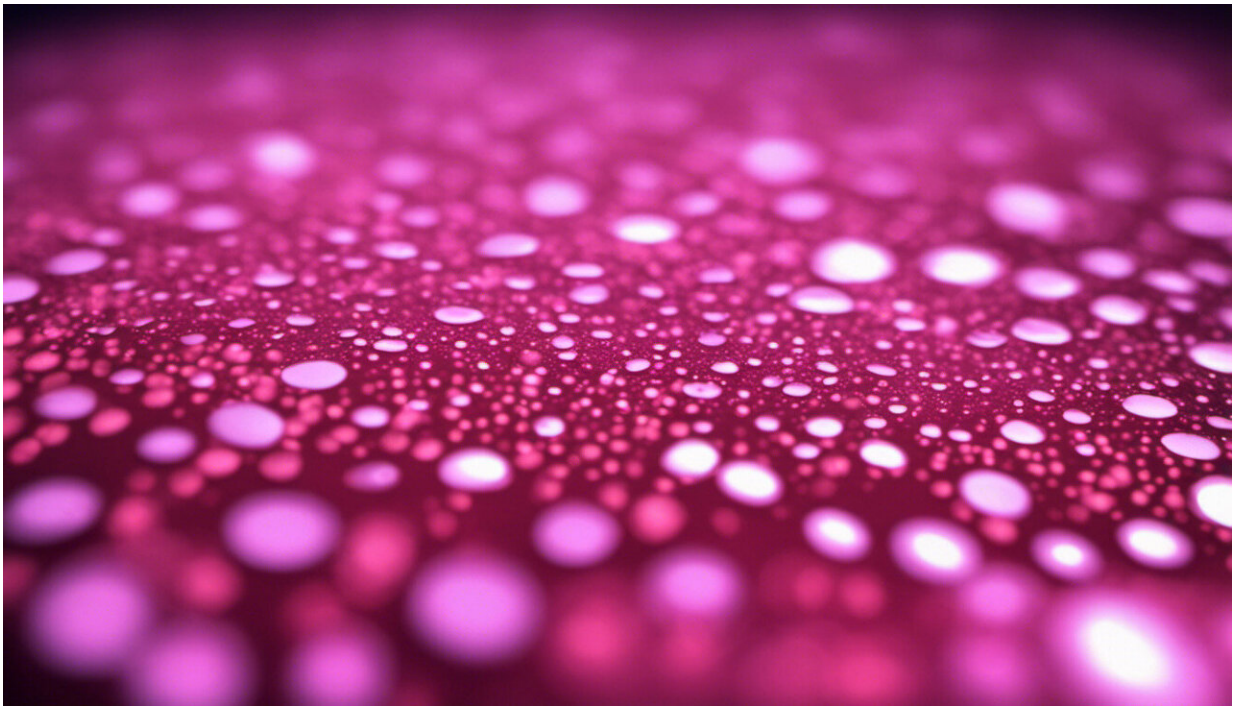

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Researchers at ETH Zurich and the University of Basel have developed a vaccine that protects animals from Salmonella. These bacteria often escape the effects of vaccination by genetically modifying their protective coat. The researchers have succeeded in manipulating this process to lure the bacteria into an evolutionary trap.

Developing vaccines against bacteria is in many cases much more difficult than vaccines against viruses. Like virtually all pathogens, bacteria are able to sidestep a vaccine's effectiveness by modifying their genes. For many pathogens, such genetic adaptations under selective pressure from vaccination will cause their virulence or fitness to decrease. This lets the pathogens escape the effects of vaccination, but at the price of becoming less transmissible or causing less damage. Some pathogens, however, including many bacteria, are extremely good at changing in ways that allow them to escape the effects of vaccination while remaining highly infectious.

For scientists looking to develop vaccines, this kind of immune evasion has been a fundamental problem for decades. If they set out to develop vaccines against bacterial pathogens, often they will notice that these quickly become ineffective.

Weaponising immune evasion

Now, however, researchers at ETH Zurich and the University of Basel have exploited precisely this mechanism to come up with an effective vaccine against bacteria. They succeeded in developing a Salmonella vaccine that, instead of trying to outright kill intestinal bacteria, rather guides their evolution in the gut to make them a weaker pathogen.

"This allowed us to show that immune evasion is not only a major challenge in vaccine development, but that it can in fact be put to good use in both human and veterinary medicine," explains ETH Professor Emma Slack. "We can use it to drive the evolution of pathogenic microorganisms in a certain direction—in our case, a dead end." Slack led the study, which involved many researchers from different groups at ETH Zurich and other institutions, together with ETH Professor Wolf-Dietrich Hardt and Médéric Diard, Professor at the University of Basel's Biozentrum.

Combination vaccine leads to the goal

In their study, the researchers inoculated mice with a series of slightly different vaccines against Salmonella typhimurium, and observed how the Salmonella in the animals' guts modified their genes to escape the vaccines' effects. This let the scientists identify the full spectrum of possible immune evasion mutations in Salmonella typhimurium. Subsequently, the researchers produced a combination vaccine from four Salmonella strains that covered the bacteria's full spectrum of genetic evasion options.

A surprising immune evasion was driven by this combined vaccine, causing an important Salmonella sugar coating on the surface to atrophy. While the affected bacteria were still able to multiply in the animals' guts, they were largely unable to infect body tissues and cause disease. This is because the sugar coating is part of the bacteria's protective coating that shields them from the host's defenses as well as from viruses that often infect and kill the bacteria. In tests on mice, the scientists were able to show that their new vaccine was more effective at preventing Salmonella infections than existing vaccines approved for use in pigs and chickens.

The scientists now plan to use the same principle to develop vaccines against other microorganisms—for example, against antimicrobial-resistant bacterial strains. In addition, it ought to be possible to use the approach in biotechnology and bring about specific modifications in microorganisms by exerting selective pressure through vaccines.

More information: Médéric Diard et al, A rationally designed oral vaccine induces immunoglobulin A in the murine gut that directs the evolution of attenuated Salmonella variants, *Nature Microbiology* (2021). DOI: 10.1038/s41564-021-00911-1

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