Gut bacteria play key role in vaccination, study finds

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The bacteria that live in the human gut may play an important role in immune response to vaccines and infection by wild-type enteric organisms, according to two recent studies resulting from a collaborative effort between the University of Maryland School of Medicine Institute for Genome Sciences and the Center for Vaccine Development.

The first study, published online in *PLOS ONE*, examines the impact of an oral typhoid vaccination on the microbiota, or populations of bacteria, in the human gut. The second study, also published online in *PLOS ONE*, looks in monkeys at the impact in the gut microbiota of vaccines against *Shigella*, as well as exposure to wild-type *Shigella*, another group of bacteria that, like *S.* Typhi, gain access to the host via the oral route. These studies find that higher diversity in the gut microbiota, i.e., more types of bacteria in the gut, affect the characteristics and magnitude of the immune responses to the vaccines and, in the case of exposure to wild-type *Shigella*, appear to be more resistant to infection. This research provides a window into how vaccines and resistance to enteric pathogens work. It also helps scientists understand more about how the "good" bacteria in the body affect human health, a growing area of research known as the human microbiome.

"Our research raises the intriguing possibility that the gut microbiota may play an important role in response to vaccines and susceptibility to enteric pathogens, or bacteria that affect the intestinal tract," says the senior author on both papers, Claire M. Fraser, Ph.D., Professor of the Departments of Medicine and Microbiology and Immunology and

director of the Institute for Genome Sciences (IGS) at the University of Maryland School of Medicine. "The results are preliminary and more research is needed. In future studies, we plan to expand the subject pool and add metagenomic analysis. Metagenomics, also known as community or environmental genomics, will allow us to look at the function of the gut microbiota and how it is changing under various vaccination schedules. This research provides a fascinating window into the human microbiome, and how the bacteria in our bodies impact our health. Both *S.* Typhi and *Shigella* are still devastating to populations in certain parts of the world. We hope that this work might one day help to provide relief to those areas that still suffer from these diseases."

The first study analyzed the impact of an oral typhoid vaccination with an attenuated *Salmonella enterica* serovar Typhi (*S.* Typhi) on the human gut microbiota. While typhoid is not considered endemic in Western countries today, it is estimated that there are over 20 million illnesses associated with typhoid worldwide, particularly in south-central and south-east Asia. Scientists at the Center for Vaccine Development and other institutions have long been working to develop an improved oral vaccine to prevent the disease. Differences in the effectiveness of experimental vaccines have been attributed to heterogeneous immunogenicity among subjects, host genetics, nutrition, socioeconomic status and other factors. Researching the impact of the composition of intestinal microbiota is a new approach made possible by state-of-the-art advances in high-throughput sequencing technologies. The cutting edge facilities at the University of Maryland Institute for Genome Sciences generate huge quantities of data far more quickly than older technology. Similarly, advanced instrumentation and immunological techniques at the Center for Vaccine Development have, and continue to provide significant insights into the immune responses that are likely to correlate with protection.

The typhoid study involved an interdisciplinary team of scientists:

experts in infectious diseases, enteric pathogens, microbiology, immunology and genomic analysis. The team found preliminary evidence that the gut microbiota might play a role in how individuals respond to vaccination. The study is noteworthy for its longitudinal analysis, and tracking data across ten discrete time points (pre- to 56 days post-immunization). The scientists found that more diversity in the gut microbiota may enable more robust immune responses to the vaccine.

The second study, also led by this interdisciplinary team at the University of Maryland School of Medicine, similarly found evidence that the diversity of the gut microbiota was related to responsiveness and protection against *Shigella dysenteriae 1*. The research examined cynomolgus macaques that had been immunized with attenuated *Shigella* vaccines and/or challenged with wild-type *S. dysenteriae 1*. The scientists found that those animals that showed high diversity in their gut microbiota were more resistant to *Shigella* infection than those with lower diversity.

"These studies were performed to evaluate the hypothesis that the gut microbiota composition may impact the response to vaccination or exposure to enteric pathogens in humans and non-human primates. Salmonella and *Shigella* were chosen because of their great importance to Public Health. Since they gain access to the host when they are ingested, we would expect many factors in the gut microenvironment, including the presence of a defined microbiota, to play a key role in the immune response to vaccination and resistance to infection," says Marcelo B. Sztein, MD, Professor in the Departments of Pediatrics, Medicine and Microbiology and Immunology and Associate Director for Immunologic Studies at the Center for Vaccine Development, University of Maryland School of Medicine. "This area will continue to be a target for our research as we try to learn more about these pathogens, how they affect the body and how we can prevent infection with these sometimes

deadly illnesses."

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"The interdisciplinary expertise here at the School of Medicine allows us new approaches to complex medical challenges, such as determining the correlations between vaccinations, commensals and enteric pathogens," says E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs at the University of Maryland and the John Z. and Akiko K. Bowers Distinguished Professor and dean of the University of Maryland School of Medicine. "Dr. Fraser and Dr. Sztein are leaders in their fields, and this research was made possible by rare, highly advanced technology available at the Institute for Genome Sciences, the Center for Vaccine Development and the Department of Pathology. We expect more groundbreaking discoveries from these research scientists, paving the way for the treatment and prevention of deadly diseases throughout the world."

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