Antibiotics may increase susceptibility to sexually transmitted infections

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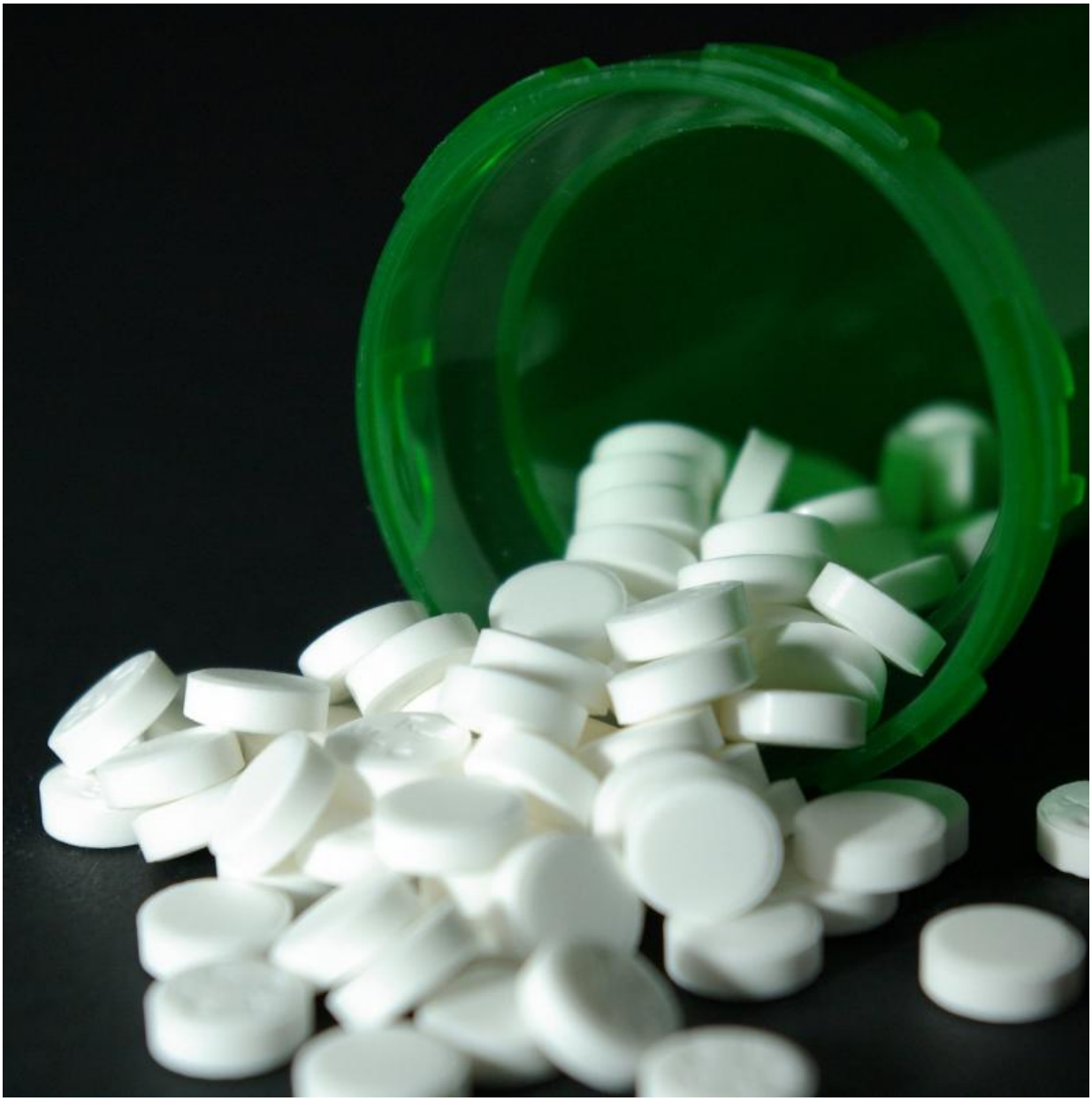

Pills. Credit: Public Domain

(Medical Xpress)—Commensal microbiota, populations of bacteria that inhabit the tissues of larger organisms, often have complex relationships with their hosts. Researchers have been aware for some time that commensal microbiota play a role in antiviral immunity by producing immune inductive signals that trigger inflammasome responses, among other things.

However, the role of dysbiosis on antiviral immunity hasn't been studied. Dysbiosis describes the loss of bacterial diversity within a microbiome, and the direct role that commensal microbiota play in antiviral immunity suggests that such loss would facilitate viral infections. Recently, a collaborative of Korean and Japanese scientists conducted a study into the effects of antibiotic-induced dysbiosis on antiviral immunity, and have published their results in the *Proceedings of the National Academy of Sciences*.

The researchers investigated the mechanisms of commensal microbial immunity on the genital mucosa by treating mice with antibiotics for four weeks and then exposing them to HSV-2. A control group received placebo. They report that the antibiotics caused dysbiosis within the vaginal microbiota, and resulted in a dramatic increase in innate immune response—specifically, they noted increases in an alarmin called IL-33, which blocked effector T cells from migrating into the vaginal tissues and secreting antiviral cytokines.

Antibiotic-treated mice succumbed to HSV-2 infection dramatically faster than control mice. They exhibited more severe pathology and all mice treated with antibiotics prior to viral exposure died within 11 days

of infection. "Taking these data together, we find that depletion of commensal bacteria results in a severe defect in antiviral protection following mucosal HSV-2 infection," the researchers write.

By analyzing stool and vaginal washes from both groups of mice, they determined that antibiotic treatment induced an imbalance in the microbial composition of the vaginal mucosa. Further, they were able to determine that no single species of bacteria was responsible for the antiviral immunity effects of the commensal microbiome; rather, it was the imbalance of the microbiotic population that accounted for the effects.

Proteomic analysis revealed changes in the abundance of certain vaginal wash proteins; the researchers hypothesize that factors driven by inflammatory damage of epithelial cells during antibiotic treatment modulate local immunity. Further, an innate immune cytokine, IL-33, is a big contributor to the impairment of antiviral immunity to mucosal HSV-2 infection. They corroborated the role of IL-33 in a supporting experiment in which they injected mice with recombinant IL-33 for eight days before viral infection. These mice died much faster than control mice.

The authors write, "Our present study demonstrates that inhibitory signals induced by the depletion of commensal microbiota also affect antiviral immunity. Taken together, our findings provide a unique insight into the role of commensal bacteria in maintaining the integrity of surface barrier epithelial cells by preventing pathogenic bacteria colonization, thereby supporting a micro-environment conducive to antiviral defense."

They note that their results are clinically relevant, with implications regarding the use of oral antibiotics and increased susceptibility to sexually transmitted infections, as well as other infectious viruses.

More information: Dysbiosis-induced IL-33 contributes to impaired antiviral immunity in the genital mucosa, *PNAS* 2016 ; published ahead of print January 25, 2016, DOI: 10.1073/pnas.1518589113

Abstract

Commensal microbiota are well known to play an important role in antiviral immunity by providing immune inductive signals; however, the consequence of dysbiosis on antiviral immunity remains unclear. We demonstrate that dysbiosis caused by oral antibiotic treatment directly impairs antiviral immunity following viral infection of the vaginal mucosa. Antibiotic-treated mice succumbed to mucosal herpes simplex virus type 2 infection more rapidly than water-fed mice, and also showed delayed viral clearance at the site of infection. However, innate immune responses, including type I IFN and proinflammatory cytokine production at infection sites, as well as induction of virus-specific CD4 and CD8 T-cell responses in draining lymph nodes, were not impaired in antibiotic-treated mice. By screening the factors controlling antiviral immunity, we found that IL-33, an alarmin released in response to tissue damage, was secreted from vaginal epithelium after the depletion of commensal microbiota. This cytokine suppresses local antiviral immunity by blocking the migration of effector T cells to the vaginal tissue, thereby inhibiting the production of IFN-γ, a critical cytokine for antiviral defense, at local infection sites. These findings provide insight into the mechanisms of homeostasis maintained by commensal bacteria, and reveal a deleterious consequence of dysbiosis in antiviral immune defense.