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New insights could lead to a better pneumococcal vaccine

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Discovery of a new, previously unknown mechanism of immunity suggests that there may be a better way to protect vulnerable children and adults against Streptococcus pneumoniae (pneumococcal) infection, say researchers at Children's Hospital Boston and Harvard School of Public Health (HSPH). The findings, published in the open-access journal *PLoS Pathogens* on September 19, may aid the development of novel pneumococcal vaccines. (The current vaccine, Prevnar, is expensive and covers only 7 of the 91 known pneumococcal strains.)

Pneumococcus causes serious infections in children and the elderly, including pneumonia and meningitis (inflammation of the brain). Since 2000, U.S. infants have been routinely immunized against pneumococcus, but most developing countries (where nearly one million children die from pneumococcal infections annually) cannot afford the existing vaccine.

Richard Malley, MD, of Children's Division of Infectious Diseases, and Marc Lipsitch, D. Phil., of HSPH have been studying how natural immunity against pneumococcus develops, and have shown that in addition to antibodies, T-cells can provide broad protection against this pathogen. In this new study, Malley and Lipsitch identify the specific protective T-cells – so-called TH17 cells – and show that they protect against infection by releasing IL-17, a protein that enables human blood cells to kill pneumococcus in the nose more efficiently. This is significant, since colonizing a person's nose is the first necessary step of infection.

Researchers had known that children, as they get older, carry pneumococcus in the nose for shorter periods of time and have less risk of disease, but it hadn't been known how this resistance develops. Malley, Lipsitch and their colleagues now show that adults and older children, but not newborn babies, have TH17 cells that target pneumococci, suggesting that exposure to pneumococcus normally leads to production of these cells. In mice, they show directly that exposure to pneumococcus triggers the development of these T cells and shortens the duration of nasal carriage of the pathogen.

The investigators also describe an efficient way of measuring TH17 cells, which could help determine whether a new vaccine is rallying an effective response. "We are now evaluating vaccine candidates and changing them so they not only induce antibodies, but also induce this specific type of immunity," says Malley. "A vaccine that induces both protective antibodies and T-cell immunity to pneumococcus may be a very effective way to protect against this potentially devastating disease."

Malley's own lab is developing an inexpensive whole-cell pneumococcal vaccine that elicits a robust TH17 response in mice. With support from the Program for Appropriate Technology in Health (PATH), a nonprofit group funded in part by the Bill and Melinda Gates Foundation, the vaccine is being manufactured for future human testing by Instituto Butantan, a manufacturer in Brazil. Malley's laboratory is testing various forms of the vaccine in animals, including nasal and oral versions. The advantage of a whole-cell vaccine is that it can broadly protect against all pneumococcal strains and would be very inexpensive to produce and administer.

Malley believes the ability to induce protective T-cell responses may have relevance for other infections of childhood, such as Staphylococcus aureus and Haemophilus influenzae. Such responses are also being evaluated in pathogens against which antibodies are ineffective, such as

herpes simplex, malaria and tuberculosis.

Source: Children's Hospital Boston