Two-pronged immune response offers hope for effective Salmonella vaccine

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Research from Malawi, Birmingham and Liverpool has renewed hope that an effective vaccine could be developed against nontyphoidal strains of *Salmonella*. The work, funded by the Wellcome Trust and GlaxoSmithKline, suggests that the body's immune system could be primed to tackle even the most resilient of strains.

In developed countries, nontyphoidal Salmonella (NTS) strains are mainly food-borne and usually cause gastroenteritis. In rare cases, they can lead to bacteraemia (bacterial infections of the blood). However, in the developing world, bacteraemia is far more common and serious: fatality rates can be as high as almost one in four among children under two years old and HIV-infected adults.

In previous research led by Dr Calman MacLennan, scientists based at the Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW) in Blantyre, Malawi , showed that disease-causing strains of NTS were able to survive outside cells in the blood of children. This survival mechanism enables the bacteria to replicate unchecked, possibly leading to high levels of mortality associated with bacteraemia.

Dr MacLennan and colleagues also identified protective *Salmonella*-specific antibodies that develop in African children within the first two years of life, the period in which the majority of NTS-related cases of bacteraemia occur. These particular antibodies recognise the bacteria in the blood and then kill the bacteria without the help of immune cells. It is possible that these antibodies develop in response to a

relatively mild infection by NTS or similar bacteria. Young children who have yet to encounter these bacteria lack the antibodies and are at greatest risk from infection.

However, the *Salmonella* bacteria can evade the antibodies by hiding away within phagocytes, another group of cells involved in the body's immune reaction. Phagocytes ordinarily 'eat' invasive bacteria before destroying them, but the *Salmonella* bacteria have adapted to avoid being destroyed once inside the phagocytes.

In addition, some strains have become resistant to the killing effect of antibodies even when they are outside these cells. If the bacteria are not completely cleared from the body, then it is possible for infection to reoccur if a patient's immune system is compromised, for example through HIV infection.

"Nontyphoidal *Salmonella* is a very serious problem in Africa and we urgently need a vaccine," says Dr MacLennan. "Our previous work gave some hope that a vaccine could be developed that produces antibodies to protect against fatal *Salmonella* infections. But unless we can develop a vaccine that completely clears the body of bacteria, including resistant strains, such a vaccine could quickly become redundant."

Today, the researchers from the University of Malawi College of Medicine, Liverpool School of Tropical Medicine and the University of Birmingham, publish a study in the *Proceedings of the National Academy of Sciences*, which demonstrates a second way that the immune system uses antibodies to kill the bacteria. The results are encouraging for the prospects of developing a vaccine, suggesting that a vaccine against NTS could be more effective than previously thought.

The research, carried out by Miss Esther Gondwe, a Malawian PhD student at MLW in Dr MacLennan's group, found that the bacteria could

be tagged by the antibodies before being 'eaten' by the phagocytes. This made it more likely that the phagocytes would consume them, but would also flag them as unwanted guests, enabling the phagocytes to recognise and destroy them.

This two-pronged approach enables the immune system to kill *Salmonella* bacteria both within and outside of the blood cells, enabling the body to rid itself of the bacteria including strains that are resistant to killing outside of cells. It further highlights the role that antibodies play in protecting people from *Salmonella* infection.

"Antibodies clearly play a very important role in protecting people from *Salmonella* infection," says Dr MacLennan. "This makes even stronger the case for developing a vaccine which can stimulate antibody production. Such a vaccine could potentially save the lives of thousands of African children who would otherwise die."

Dr MacLennan and colleagues will now look for the most effective antibodies for attacking the bacteria in the blood and for activating phagocytes to kill. Finding the best antibodies will be key to developing a much-needed vaccine.

More information: Gondwe EN et al. Importance of antibody and complement for oxidative burst and killing of invasive nontyphoidal Salmonella by blood cells in Africans. Published online in advance in *PNAS*; 25 January 2010.

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