HIV patients hold clues to Salmonella vaccine development

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A study published today in the journal *Science* offers a long-awaited explanation for the link between HIV infection and susceptibility to life-threatening nontyphoidal strains of *Salmonella*.

The research, funded by the Wellcome Trust and GlaxoSmithKline, goes on to identify targets that could be pursued for *Salmonella* vaccine development.

Nontyphoidal strains of *Salmonella* (NTS) usually cause vomiting and diarrhoea in developed countries and are mainly contracted by consuming infected foods, such as uncooked meat and eggs. NTS can also cause fatal bloodstream infections in people with compromised immunity, such as HIV-infected individuals, and children under two years of age or with malaria, anaemia or malnutrition.

This is a particular problem in Africa where *Salmonellae* are the most common bacteria to infect the blood. Such bloodstream infections can be treated with antibiotics, but drug resistance is on the increase and there is currently no vaccine available.

"The association between HIV infection and fatal cases of nontyphoidal *Salmonella* disease has been known since the onset of the AIDS pandemic 26 years ago, but this is the first time we've been able to offer a scientific explanation why", said Dr Cal MacLennan from the University of Birmingham, who led the research.

In a previous study of African children, the team of researchers working at the Malawi-Liverpool-Wellcome Trust Clinical Research Programme, at the College of Medicine, University of Malawi, and the University of Birmingham had shown that protective *Salmonella*-specific antibodies generated in the first two years of life are critical for controlling the infection.

In the new study, the researchers turned their attention to immunity in African adults. While blood samples from HIV-uninfected adults killed *Salmonella* without difficulty, those from many HIV-infected Africans could not kill *Salmonella*. Since HIV causes significant defects in the immune system, the team examined whether a lack of these antibodies might account for the absence of killing and explain why HIV infected adults are particularly susceptible to *Salmonella* infections.

Contrary to expectations, the team found that blood from HIV-infected adults harboured high levels of antibodies to *Salmonella*, molecules that normally help the immune system to fight infections. However, unlike the antibodies in healthy adults, these antibodies were unable to kill *Salmonella*. In fact, antibodies from these patients actually stopped the antibodies from healthy adults from killing *Salmonella*.

The team went on to show that this difference in ability to kill *Salmonella* is due to the part of the *Salmonella* that the antibodies bind to. The protective 'killing' antibodies bind to structures on the surface of the bacteria known as outer membrane proteins. When the 'killing' antibodies bind to outer membrane proteins, this then allows the immune system to destroy the *Salmonella* bacteria.

On the other hand, large numbers of antibodies in HIV-infected Africans bind to a structure that sticks out from the surface of the *Salmonella* known as LPS (lipopolysaccharide). These 'blocking' antibodies appear to divert the immune system away from the surface of the bacteria and

stop the 'killing' antibodies from doing their job.

When the researchers specifically removed the 'blocking' antibodies from HIV-infected blood samples, they found 'killing' antibodies present in the blood that could once again kill the bacteria. This shows that patients infected with HIV still have the protective 'killing' antibodies generated in the first two years of life that can control *Salmonella* infection, but the excess of 'blocking' antibodies stops the 'killing' antibodies from working.

"We normally think of HIV patients as being more susceptible to bacterial infections because of deficiencies in their immune systems, and often they have problems making antibodies when given vaccinations. In the present study, we found that it's actually an excess of antibodies that causes the problem" explained Dr MacLennan.

"The findings are important because LPS is currently being investigated as a potential target for a vaccine. Our observations that antibodies targeting LPS can actually impede the protective immune response to *Salmonella* would caution against this, suggesting that such a vaccine could do more harm than good."

A vaccine that protects both young children and HIV-infected adults from fatal cases of NTS is urgently needed in Africa. The findings from this study suggest that the outer membrane proteins could potentially serve as alternative vaccine targets and this is an area that the team is currently investigating.

More information: C.A. MacLennan et al. Dysregulated humoral immunity to nontyphoidal Salmonella in HIV-infected African adults. Science 2010, 328 (5977)

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