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Accessibility of O Antigens Shared between *Salmonella* Serovars Determines Antibody-Mediated Cross-Protection

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Abstract

Pathogenic *Salmonella* serovars produce clinical manifestations ranging from systemic infection typhoid to invasive nontyphoidal *Salmonella* disease in humans. These serovars share a high degree of homology at the genome and the proteome level. However, whether infection or immunization with one serovar provides protection against other serovars has not been well studied. We show in this study that immunization of mice with live typhoidal serovar, *Salmonella* Typhi, generates cross-reactive immune responses, which provide far greater resistance against challenge with nontyphoidal serovar *Salmonella* Enteritidis than with another nontyphoidal serovar, *Salmonella* Typhimurium. Splenic T cells from these immunized mice produced similar levels of IL-2 and IFN-γ upon ex vivo stimulation with Ags prepared from *S* Enteritidis and *S* Typhimurium. In contrast, Abs against *S* Typhi interacted with live intact *S* Enteritidis but did not bind intact *S* Typhimurium. These pathogen-reactive Abs were largely directed against oligosaccharide (O)-antigenic determinant of LPS that *S* Typhi shares with *S* Enteritidis. Abs against the O determinant, which *S* Typhi shares with *S* Typhimurium, were present in the sera of immunized mice but did not bind live intact *Salmonella* because of surface inaccessibility of this determinant. Similar accessibility-regulated interaction was seen with Abs generated against *S* Typhimurium and *S* Enteritidis. Our results suggest that the ability of protective Abs elicited with one *Salmonella* serovar to engage with and

consequently provide protection against another *Salmonella* serovar is determined by the accessibility of shared O Ags. These findings have significant and broader implications for immunity and vaccine development against pathogenic *Salmonellae*.