Introduction
Salmonella typhi, an enteroinvasive gram negative bacterium, causes typhoid fever in humans. The bacteria enter the body through the oral route, penetrate the intestinal epithelium and disseminate throughout the reticuloendothelial system (Jones and Falkow, 1996). The invasion of intestinal epithelial cells is an essential step for the pathogenicity of S. typhi (and other pathogenic Salmonella species) and requires entry-promoting molecules that are largely encoded on a 35-40kb region located at centisome 63 of the Salmonella chromosome (Galan and Bliska, 1996). The majority of the loci encode components of the host cell contact-dependent type III secretion system, a novel protein secretion apparatus recently identified in Salmonella and many other pathogens that delivers effector proteins into the cytoplasm of eukaryotic cells (Galan and Zhou, 2000; Sansonetti, 2002). Studies aimed at understanding the role of these molecules in host-pathogen interaction have been carried out mostly with S. typhimurium in mice, which is considered to be a model for human typhoid. These studies have unraveled important functions for these molecules in bacterial invasion of intestinal epithelial cells, in intracellular survival and multiplication of Salmonella inside macrophages, and in delivering cytotoxic signals that bring about apoptosis of macrophages and dendritic cells (Schwan et al., 2000; Van der Velden et al., 2003). The invasion-promoting molecules induce membrane ruffling followed by macropinocytosis which directs internalization of bacteria into host cells, and also trigger activation of transcription factors that might stimulate secretion of cytokines and other inflammatory mediators (Gruenheid and Finlay, 2003). Many, if not all, of these effector molecules are functionally conserved amongst different Salmonella species suggesting that these pathogens might utilize similar mechanisms to interact with host cells. However, in spite of this high degree of similarity, many Salmonella serovars including S. typhi exhibit considerable host specificity, the reasons for which are not completely understood.

S. typhi causes systemic infection exclusively in humans although experimentally many features of the disease can be reproduced in chimpanzees (Parker, 1984). The host-pathogen interactions during infection with this bacterium are not well understood primarily due to non-availability of a suitable animal model. For many years S. typhimurium infection in mice has been used as a model to understand S. typhi pathogenesis. However, in spite of 90% homology which these two pathogens share at
the genome level (Young et al., 2002), the two differ considerably in a number of host-pathogen interactions including utilization of receptors for entering intestinal epithelial cells (Pier et al., 1998; Weinstein et al., 1998), replication abilities inside macrophages, cytotoxicity-inducing abilities etc. (Alpuche-Aranda et al., 1995; Schwan et al., 2000). More importantly, these two closely related pathogens cause different diseases in humans. S.typhi causes typhoid whereas S.typhimurium produces enteritis that is characterized by self limiting fever accompanied by diarrhea and sometimes dysentery. The latter symptoms are rarely observed during infection with S.typhi. These different manifestations may be produced by one or more as yet unidentified molecules not conserved between these two Salmonella species. These molecules may also determine the quality and magnitude of inflammatory and immune responses during infection with these two pathogens. A crucial distinction between S.typhi and S.typhimurium is the presence of outer capsule around S.typhi. The capsule commonly referred to as ‘Vi’ was first identified as the ‘virulence antigen’ of S.typhi (Felix and Pitt, 1934). It is a polymer of N-acetyl galacturonic acid with variable O-acetylation at C-3. Vi renders S.typhi resistant to phagocytosis and to the actions of complement (Looney and Steigbigel, 1986). The virulence of S.typhi correlates with the expression of this molecule as the majority of S.typhi isolates derived from blood of typhoid patients are encapsulated (Robbins and Robbins, 1984; Qadri et al., 1990; Jesudason et al., 1994). Studies carried out in human volunteers have shown that Vi positive strains of S.typhi are more virulent than Vi negative strains (Hornick et al., 1970a and 1970b). Immunization with Vi has been shown to confer protection against infection with S.typhi and currently it is one of the vaccines available for human use (Acharya et al., 1987; Klugman et al., 1987; Szu et al., 1991; Kossaczka et al., 1994; Szu et al., 1994). It is thus clear that Vi, by protecting S.typhi against many host defense mechanisms, plays an important role in the pathogenesis of typhoid. However, the interaction of this molecule with intestinal epithelial cells, the first cell type that S.typhi is believed to infect during typhoid fever has not been investigated.

The present study was undertaken to analyze the interaction of Vi with intestinal epithelial cells and mononuclear phagocytes, identify host molecule(s) that might be involved in binding to Vi and understand the significance of Vi-host cell interaction.