Role of αβ and γδ T Cells in the Host Response to Salmonella Infection as Demonstrated in T-Cell-Receptor-Deficient Mice of Defined Ity Genotypes

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Salmonella spp. are facultative intracellular bacteria which enter the body through the intestinal tract. We studied the roles of T cells expressing either the α and β chains or the γ and δ chains of the T-cell receptor (αβ T cells or γδ T cells, respectively) in the host defense against Salmonella using mice genetically deficient in either αβ T cells, γδ T cells, or both T-cell subsets. These mutant strains of mice were infected orally or intraperitoneally with Salmonella dublin, and the progression of the disease was monitored by determining bacterial numbers in the feces, gut wall, Peyer’s patches, mesenteric lymph nodes, spleen, and liver. Since susceptibility to Salmonella infection in mice is strongly affected by the alleles at the Ity locus, T-cell-mutant mice with either the Ity-sensitive or Ity-resistant phenotype were tested for resistance to S. dublin infection. We found that even though large numbers of intraepithelial and mucosal αβ and γδ T cells populate the normal intestine, they have no role in controlling the invasion of S. dublin into the intestine or the subsequent bacterial replication in the Peyer’s patches or gut wall. Furthermore, systemic infections were equally severe for the first 6 days in normal, αβ T-cell-deficient, and γδ T-cell-deficient mice, and αβ but not γδ T cells were required for clearance of S. dublin, regardless of the Ity phenotype. However, mice that lacked both T-cell subsets had higher bacterial counts in their livers 15 to 18 days after infection than did αβ T-cell-deficient mice, suggesting that γδ T cells can contribute to acquired immunity to S. dublin.

Nontyphoid Salmonella spp. including S. typhimurium, S. dublin, S. choleraesuis, and S. enteritidis cause a spectrum of diseases in humans ranging from self-limited gastrointestinal infections to systemic infections with high mortality (38). S. dublin, which is host adapted to bovines, can cause severe systemic disease in humans, and the incidence of S. dublin infections has increased more than 10-fold over the last 2 decades (10). Like S. typhimurium, S. dublin efficiently infects mice, which are commonly used as a model to study the pathogenesis of the infection and the host response to Salmonella (16).

Multiple bacterial and host factors determine the outcome of Salmonella infections. An important determinant of the innate host response to Salmonella is the Nramp1 gene, which is located at the Ity/Bcg/Lsh locus on mouse chromosome 1 (36). Nramp1 encodes a protein that belongs to a family of integral membrane proteins with 10 highly conserved transmembrane domains (42). Nramp1 genes which have a point mutation at nucleotide position 596 resulting in a glycine to aspartate substitution are susceptible not only to infection by nontyphoid Salmonella (e.g., they have the Ity phenotype) but also to Mycobacterium bovis (BCG) and Leishmania donovani (41). Macrophages from Ity mice cannot efficiently kill Salmonella or L. donovani (5, 25), and in vivo Salmonella grow more rapidly in the livers and spleens of susceptible mice (1). Ity mouse are >10^3-fold more susceptible than Ity- mice to intraperitoneal (i.p.) infection with S. dublin (6).

Salmonella enter the body through the small intestine and colon. Following penetration of the epithelial barrier, Salmonella are taken up by phagocytic cells in Peyer’s patches (PP) and the lamina propria. Bacteria then spread to the mesenteric lymph nodes (MLN) and from there to systemic sites, most importantly the spleen and liver (3). In experimental infections, i.p. administration can be used to mimic the systemic phase of the infection, bypassing the entry of the bacteria through epithelial cells in the gut. Oral Salmonella infection differs in some aspects from i.p. infection, since it results in a different kinetics of bacterial counts early after infection. Furthermore, the invading bacteria depend on a set of invasion-related genes after oral infection that are not required for systemic virulence (39).

During the early, innate host response against Salmonella, high levels of interferon-γ (IFN-γ) and tumor necrosis factor alpha (TNF-α) are produced (6), and in vivo neutralization of either IFN-γ or TNF-α with antibodies severely compromises the host’s ability to control the infection (28, 29, 34, 40). It is not clear whether T cells, especially those in the gut, i.e., intraepithelial lymphocytes (IELs) and lamina propria T cells, are important for production of these critical cytokines during the early phase of infection or if they influence the immune response to Salmonella through other mechanisms. IELs are particularly interesting in this regard, since they are potentially the first T cells to interact with Salmonella during gut invasion. IELs are in a position to play a role early in
infection because IELs have some properties of activated T cells, such as large size and expression of the T-cell activation marker CD69 (24), and because some IEL subsets produce keratinocyte growth factor (2), which may be important for wound healing and protection of epithelial surfaces. IELs in mice are composed of similar percentages of αβ and γδ T cells (37), so that either αβ or γδ IELs could affect invasion or growth of Salmonella.

The clearance of bacteria from tissues in the later stages of Salmonella infection is dependent on T cells, as athymic nude mice or T-cell-depleted mice survive the initial stages but fail to resolve the infection (17, 26, 27, 33, 35). Resolution of infection is potentially mediated by αβ, γδ, or both subsets of T cells. Several studies have addressed the relative role of αβ and γδ T cells in Salmonella infection. Humans infected with Salmonella typhi have an increased percentage of circulating γδ T cells (15). In mice, Emoto and colleagues observed an influx of γδ T cells into the peritoneal cavity after i.p. injection of S. choleraesuis (17, 26, 27, 33, 35). Resolution of infection in mice or T-cell-depleted mice survive the initial stages but fail to resolve the infection (17, 26, 27, 33, 35). Resolution of infection is dependent on T cells, as athymic nude mice or T-cell-depleted mice survive the initial stages but fail to resolve the infection (17, 26, 27, 33, 35).

MATERIALS AND METHODS

Mice. Mutant and control mice were purchased from Jackson Laboratories (Bar Harbor, Me.). TCRα−/− mice were typed by Southern blotting as previously described (32). TCRα−/− mice were typed by PCR as previously described (18). For αβ typing, tail DNA was amplified by PCR to yield a 210-bp fragment by using 10 pmol of a common primer and either Primer S containing the nucleotide associated with the αβ T-cell genotype or Primer R containing the nucleotide associated with the αβ T-cell genotype. Aliquots of the PCRs were run on a 1% agarose-ethidium bromide gel. DNA from BALB/c, BALB/c-D2, DBA/2, and C57Bl/6 mice (A) and DNA from TCRα knockout mice that we bred (B) are shown. TCRα−/− mice did not yield a product and could not be typed in this round of PCR analysis. TCRα−/−, 87, 89, and 92 mice are αβ+ and the rest are αβ−, since the presence of both bands indicates that mice are heterozygous at the γδ locus (TCRα−/−, 85, 90, 91, 93, 95, and 96), resulting in an αβ− phenotype.

Because of these seemingly contradictory results, we studied the role of αβ and γδ T cells in the resistance to S. dublin using mutant mice which were genetically deficient for αβ T cells, γδ T cells, or both T-cell subsets and which were segregated based on their γδ genotype. We found that αβ T cells, but not γδ T cells, are required for resolution of Salmonella infection in both αβ+ and αβ− mice. Neither αβ nor γδ T cells were important in limiting bacterial entry into the intestine or in slowing bacterial growth outside the intestine during the first 6 days after oral infection.

FIG. 1. Typing mice for Ity genotype by using PCR. DNA from tails was amplified by PCR by using a common downstream primer and either Primer S containing the nucleotide associated with Ity−/− genotype or Primer R containing the nucleotide associated with the Ity+ genotype. Aliquots of the PCRs were run on a 1% agrose-ethidium bromide gel. DNA from BALB/c, BALB/c-D2 Ity−/− congenics, DBA/2, and C57Bl/6 mice (A) and DNA from TCRα knockout mice that we bred (B) are shown. TCRα−/− 94 mice did not yield a product and could not be typed in this round of PCR analysis. TCRα−/−, 87, 89, and 92 mice are Ity+ and the rest are Ity−, so that either Ity+ or Ity− mice are composed of similar percentages of αβ and γδ T cells (37), so that either αβ or γδ IELs could affect invasion or growth of Salmonella.

Enteric agar (Becton Dickinson, Cockeysville, Md.) with kanamycin (20 μg/ml) was used for cultivation of S. dublin in a 200-μl volume for i.p. injection. Mice were fasted overnight before oral infection (16) and washed and resuspended in 0.1 M sodium bicarbonate for oral infection or 0.9% NaCl for i.p. injection. Mice were fasted overnight before oral infection (16) and inoculated with the indicated number of S. dublin in a 200-μl volume for feeding or a 100-μl volume for i.p. injection.

Salmonella colony counts. After the mice were sacrificed, various organs were removed. The distal portion of the small intestine was removed and flushed of contents. The three most distal PP of the small intestine were removed as previously described (16). A 3-cm-long piece of the remaining small intestine lacking PP was used in some experiments to determine bacterial numbers in the gut wall. Feces and pieces of liver were weighed before grinding. Each organ was ground in a homogenizer (Tri-R Instruments, Rockville Center, N.Y.) and then plated at various dilutions in saline on either tryptic soy broth (Difco) or Hektoen Enteric agar (Becton Dickinson, Cockeysville, Md.) with kanamycin (20 μg/ml). CFU were counted after incubation at 37°C overnight. Statistical analysis was performed with StatView 4.0 (Abacus Concepts, Berkeley, Calif.) by using unpaired Student’s t tests.

IFN-γ ELISA. Blood was collected from the tail vein of mice immediately prior to sacrificing. Levels of IFN-γ in the serum were determined by enzyme-linked immunosorbent assay (ELISA) as described previously (6).

RESULTS

Typing of mutant mice for Ity genotype. Alleles of the Nramp1 gene at the Ity locus are important for determining resistance and susceptibility to Salmonella infection in mice (41). Since the mice used for gene targeting were of mixed...
genetic background, i.e., 129 mice are Ity' and C57BL/6 (B6) mice are Ity, we developed a PCR-based assay to determine the Ity genotype of the mutant mice. Since Taq polymerase cannot extend a primer that does not anneal to the final nucleotide, two sense PCR primers were designed which have a 3' nucleotide complementary to either the wild-type or mutant base in the Nramp1 gene. A common antisense primer complementary to a region 210 bp downstream in the Nramp1 gene was used to generate PCR products. By using these two primer pairs the mutant and wild-type Nramp1 alleles could be accurately distinguished, as determined by appropriate amplification of the product associated with the Ity' but not the Ity allele in stock B6 mice and amplification of the Ity product but not the Ity' product in stock 129 mice. Since Nramp2 has significant sequence homology with Nramp1 in this region (1), it was important to establish the specificity of the primers under the conditions we used to amplify the DNA. Figure 1A shows that the appropriate primer amplified an Nramp1 gene from each of four strains of known Ity phenotypes. Since the BALB/c.D2 congenic mice have the same Nramp2 allele but different alleles of Nramp1, the fact that the two primers differentiate between these congenic strains supports the conclusion that the primers are specific for Nramp1. An example of PCR amplification of tail DNA from TCRα2/2 mice is shown in Fig. 1B.

Typing of the stock TCRα/−, TCRβ/−, and TCRγδ/− mice showed that they were all Ity'. In order to generate Ity' mutant mice, Ity' mice were back crossed to 129 mice, and the resultant F1 mice were bred to each other or to the parental mice.

αβ T cells but not γδ T cells are required to resolve S. dublin infection in Ity' mice. To examine the role of αβ T cells in controlling Salmonella infection, Ity' αβ T-cell-deficient mice and wild-type Ity' littermates were orally infected with S. dublin, and the severity of infection was monitored by determining bacterial numbers in the gut wall, PP, MLN, spleen, and liver (Fig. 2). Wild-type mice had begun to resolve the infection in the liver and spleen by day 15 p.i. and between day 15 and 30 in the MLN, whereas the bacterial counts in αβ T-cell-deficient mice continued to increase throughout the infection, and some T-cell-deficient mice died of the infection. The results of PP cultures are hard to interpret since those structures were very small in the αβ T-cell-deficient mice, making them hard to find and remove in their entirety. This result demonstrates that αβ T cells are necessary to resolve Salmonella infection. However, no difference was observed between mutant and control mice during the first 6 days of infection, indicating that αβ T cells are important only later in infection.

In contrast to the requirement for αβ T cells, comparison of Ity' γδ T-cell-deficient mice with Ity' wild-type littermates showed that γδ T cells are not necessary for resolving S. dublin infection. Throughout the 38-day experiment, no significant difference between γδ T-cell-deficient and wild-type mice was observed in the number of bacteria in any organ cultured (Fig. 3), including the intestinal wall, the contents of the terminal

**FIG. 2.** Oral infection of Ity' αβ T-cell-deficient mice and wild-type littermates. Mice were fed 5.6 × 10^7 CFU of S. dublin Lane pSD6 and sacrificed on the indicated days after infection, and CFU were determined. Circles represent counts from individual mice and lines represent the geometric means of the mice in the groups. (○), TCRα/− mice; •, wild-type littermates. Two mutant mice (○, top left graph) died during the experiment on day 12 and day 28, and Salmonella counts were not determined for these mice. No wild-type mice died during the experiment.
ileum, and the feces (data not shown). (This experiment was repeated once with the same result.)

Role of αβ and γδ T cells in Ity− mouse infected with S. dublin.

We then repeated the experiments using T-cell-deficient mice that were Ity−, including TCR\(^{\alpha 2^+\beta 2^+}\) TCR\(^{\delta 2^+\beta 2^+}\) mice. Since S. dublin kills Ity− mice 6 to 8 days after oral infection, we could only study earlier time points in this experiment. The infection was equally severe in all mice, regardless of their T-cell status, on days 2 and 4 after infection. We also found no significant difference in CFU in the livers, spleens, MLN, PP, intestinal walls of the ileum, and the feces (data not shown). By day 4 the geometric means of CFU were 5 \times 10^4 to 5 \times 10^5 in the spleen and 8 \times 10^3 to 2 \times 10^5 per g of liver in wild-type and all mutant mice.

Since Salmonella can be detected very rapidly in the distal ileum after feeding (within 15 to 20 min) and γδ T cells in the gut could potentially limit the initial invasion of Salmonella into the gut wall, we sacrificed another group of mice relatively early (4 to 9 h) after oral infection to find evidence for increased intestinal invasion in the γδ T-cell-deficient mice. However, no significant difference was found in the bacterial counts in the gut wall or PP between γδ T-cell-deficient mice and wild-type littermates regarding the Ity phenotype (Fig. 4). We also cultured the contents of the terminal ileum and the feces and found no differences in CFU per gram between the groups (data not shown). These results show that γδ IELs and other intestinal γδ T cells do not affect the invasion of S. dublin into the gut wall or PP after oral infection.

Even though there was no detectable difference in the ability of γδ T-cell-deficient mice and wild-type Ity+ mice to control Salmonella infection (Fig. 3), nor any difference for the first 4 days in Ity+ mice, it was possible that γδ T cells had a function in controlling Salmonella infection later in infection that was not apparent because αβ T cells compensated for their absence. To test this possibility, we compared Ity+ TCR\(^{\beta 2^+}\) mice with Ity+ TCR\(^{\beta 2^+\delta 2^+}\) mice. Since the doubly deficient mice were available only with the Ity− phenotype, we infected the mice with S. dublin LD842, an isogenic plasmid-cured strain that has a 50% lethal dose (LD\(_{50}\)) of 10^4 in Ity− mice after i.p. infection (11). The i.p. route was chosen for these experiments to reduce mouse-to-mouse variability, and this experiment focused on the later stages of infection, which are similar for oral and i.p. infection. No significant difference among TCR\(^{\beta 2^+\delta 2^+}\), TCR\(^{\beta 2^+}\), and wild-type mice in the bacterial counts in spleens or livers was detected on day 10 p.i. in two independent experiments (data not shown). Furthermore, as expected, in each of four independent experiments, mice lacking αβ T cells or all T cells had significantly more S. dublin in their spleens and livers than wild-type mice after 16 to 25 days of infection (Fig. 5). However, mice with no αβ or γδ T cells had, on average, about 10-fold more Salmonella in their spleens and livers than αβ T-cell-deficient mice (Fig. 5). Although the two groups overlapped, the difference between the groups was significant (\(P < 0.01\)). In addition, 2 of 24 TCR\(^{\beta 2^+\delta 2^+}\) mice died during the experiment, whereas none of the 22 TCR\(^{\beta 2^+\delta 2^+}\) mice died. Ity+ mice lacking...
γδ T cells cleared *S. dublin* LD842 infection as well as wild-type *Ityr* mice (data not shown), demonstrating that the effect of γδ T cells was revealed because of the absence of αβ T cells, not because *Ity* mice were used or because *S. dublin* LD842 was the infectious agent. These results suggest that γδ T cells play a role in the resolution of *Salmonella* infections, although this effect is small compared to the role of αβ T cells and is detectable only in the absence of αβ T cells.

**IFN-γ production in T-cell-deficient mice.** Since production of IFN-γ is critical for clearance of *Salmonella* (34), we tested the ability of TCRβ<sup>−/−</sup> and TCRβ<sup>−/−</sup> × TCRδ<sup>−/−</sup> mice to produce IFN-γ. αβ T-cell-deficient mice from the experiment shown in Fig. 2 produced levels of IFN-γ that were comparable to those in wild-type mice in response to *S. dublin* infection (Table 1). In both strains of mice, serum IFN-γ levels correlated with bacterial load, as was shown by Eckmann et al. (6). Furthermore, sera from both αβ T-cell-deficient and αβ and γδ T-cell-deficient mice contained high levels of IFN-γ following *S. dublin* LD842 infection (Table 1). These data show not only that IFN-γ is produced by cells other than T cells in response to infection, but also that IFN-γ production is not sufficient to induce clearance of *Salmonella* infection in the absence of αβ T cells.

**DISCUSSION**

In order to define the role of αβ and γδ T cells in the host defense against *Salmonella*, we used mice lacking αβ T cells, γδ T cells, and both αβ and γδ T cells. Several aspects of the immune response to *Salmonella* have been revealed in this study. First, the critical role of αβ T cells was demonstrated, since αβ T-cell-deficient mice were not able to resolve an oral infection with *S. dublin* regardless of their *Ity* phenotype. Second, γδ T cells do not contribute a unique function to the
immunity to *Salmonella* that cannot be compensated by αβ T cells. Thus, in mice with αβ T cells, we could not demonstrate a role for γδ T cells either in early infection when innate immunity predominates or later during the acquired immune response. However, our data suggest that γδ T cells can play a role in the later stages of *Salmonella* infection, although this effect can be detected only in the absence of αβ T cells. Taken together, this demonstrates that αβ T cells can fully compensate for the lack of γδ T cells, but the converse is true only to a very limited extent. Third, we show that neither αβ nor γδ T cells, in the intestine or in other sites, contribute to limiting bacterial entry into the intestine or bacterial growth during the early phase of *Salmonella* infection. This is further supported by the finding that *Ity* Rag2 γ−− mice, which lack all B and T cells, did not show increased severity of disease during the first 6 days of infection with *S. dublin* (data not shown). Similarly, a recent study from Guilloteau and colleagues, who infected SCID mice, which also lack all B and T cells, i.p. with *S. dublin* came to the same conclusion (14).

Two recent reports addressed the role of αβ and γδ T cells in *Salmonella* infection. One concludes that both αβ and γδ T cells are protective against *Salmonella*, while the other concludes that γδ T cells increase susceptibility to *Salmonella* infection. Emoto et al. found that γδ T-cell-deficient mice are more resistant to *S. choleraesuis* infection than wild-type mice (9). However, Emoto’s report contains no indication that their mice were categorized on the basis of *Ity* phenotype. Since the mice they used could have been heterozygous at the *Ity* locus, and since their groups contained small numbers of mice, variable distribution of the *Ity* phenotypes between the wild-type and γδ T-cell-deficient mice could account for their results. Other possible explanations for the difference between Emoto et al.’s results and ours, such as differences in response to *S. choleraesuis* and *S. dublin*, cannot be ruled out.

The other report, by Mixter and colleagues (30), showed that *Ity* mice depleted of either αβ or γδ T cells by the injection of anti-T-cell-receptor antibodies are more susceptible to oral infection with *S. enteritidis*, as measured by lower LD₅₀ values determined 14 days after infection. Since we assessed resistance by measuring bacterial counts in various organs and did not determine LD₅₀, Mixter et al.’s data could be reconciled with our findings if T-cell-deficient mice die with fewer numbers of *Salmonella* in the liver and spleen than wild-type mice. We tested this possibility and found that TCRβγ −−, TCRγδ −−, and wild-type mice with an *Ity* phenotype all die with approximately 3 x 10⁷ CFU per spleen (data not shown). Therefore, we do not favor the hypothesis that T-cell-deficient mice have a different cause of death than wild-type mice. We suspect that some of the differences in LD₅₀ in Mixter’s experiments were due to a secondary effect of antibody-mediated depletion of large numbers of cells, rather than being directly due to lack of αβ or γδ T cells, but there may also be differences between the host responses to *S. enteritidis* and *S. dublin*.

Studies similar to ours using *Listeria monocytogenes*, BCG, and *Mycobacterium tuberculosis* reveal some similarities but also some interesting differences among the immune responses to different facultative intracellular bacteria. Mombaerts and colleagues (31) showed that αβ T-cell-deficient and γδ T-cell-deficient mice can resolve *Listeria* infection but that mice without any T cells (Rag-1−− or TCRβγ −− × TCRδ −−) could not resolve infection. This shows that either αβ or γδ T cells are sufficient to clear *Listeria* infection, whereas our data show that αβ but not γδ T cells are sufficient to clear *Salmonella*. Another difference between the immune responses to *Listeria* and *Salmonella* is that the αβ T-cell response to *Listeria* primarily involves CD8⁺ cytotoxic T cells (22), whereas CD4⁺ helper T cells are more important for the host response to *Salmonella* (33).

The importance of αβ and γδ T cells was also studied in response to infection with BCG and *M. tuberculosis* (19, 23). In BCG infection, as in *Salmonella* infection, αβ T cells but not γδ T cells play a critical role in controlling infection. Studies with major histocompatibility class I- or class II-deficient mice show that CD4⁺ αβ T cells are more important than CD8⁺ αβ T cells in the clearance of BCG (21). Resistance to *M. tuberculosis*, a mycobacterium closely related to, but more virulent than BCG, is dependent upon both CD4⁺ and CD8⁺ αβ T cells (12, 13). γδ T-cell-deficient mice infected with *M. tuberculosis* have slightly higher CFU than wild-type mice, implying that γδ T cells are more important for clearance of *M. tuberculosis* than BCG. Together with the *Salmonella* and *Listeria* results, these findings suggest a correlation between the importance of γδ T cells and the relative importance of CD8⁺ versus CD4⁺ αβ T cells. One explanation for these data is that γδ T cells are able to functionally compensate for CD8⁺ αβ T cells but not CD4⁺ αβ T cells.

The mechanism of action of αβ and γδ T cells in host defense against *Salmonella* is poorly understood. Bacteria are eliminated in the late stages of infection mainly by activated macrophages, which are stimulated by a combination of bacterial signals, e.g., lipopolysaccharide, and T-cell-mediated signals. We show here that T-cell-deficient mice produce large amounts of IFN-γ after *Salmonella* infection, indicating that T cells are not an important source of this cytokine during *Salmonella* infection. Presumably, IFN-γ is produced by NK cells in *Salmonella*-infected mice, as has been proposed for early *Listeria* infection (20). However, despite the continued production of IFN-γ, mutant mice infected with *Salmonella* had a progressive infection and eventually died. Macrophages in T-cell-deficient mice may not be able to be activated by IFN-γ (or other T-cell cytokines), or T-cell surface ligands may be required to fully activate macrophages. Alternatively, the contribution of T cells to the immune response against *Salmonella* may also involve functions that are independent of macrophages.

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**Table 1. Serum IFN-γ levels in *S. dublin*-infected T-cell-subset-deficient mice***

<table>
<thead>
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<th><em>Ity</em> phenotype</th>
<th>Mice</th>
<th>Days post infection (p.i.)</th>
<th>CFU/spleen</th>
<th>CFU/g of liver</th>
<th>Serum IFN-γ (pg/ml)</th>
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<tr>
<td>R</td>
<td>TCRα⁺⁺⁺⁺</td>
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<td>15</td>
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<td>1.5 x 10⁴</td>
<td>&lt;300</td>
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<tr>
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<td>4.9 x 10⁴</td>
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<tr>
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<td>1.7 x 10⁴</td>
<td>&lt;250</td>
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* *Ity* mice were infected with *S. dublin* Lane as described in the legend to Fig. 2, and *Ity* mice were infected with *S. dublin* LD842 as described in the legend for Fig. 5. CFU are the geometric means of 4 to 5 mice. Serum IFN-γ levels from four mice in each group were determined by ELISA, and values are means ± standard errors. *R*, resistant; *S*, sensitive.
REFERENCES


