**Figure 1: Adoptive transfer of splenocytes into RAG1-/-**

**A.** Schematic of experimental timeline. The timeline observed for the mice from which the splenocytes were harvested is outlined in part one (donor mice). Splenocytes from the donors were injected into infected RAG1**-/-** mice as outlined in part 2 (recipient mice). **B.** Anti-toxin A IgG titers in wild-type donor mice. Mice infected for twenty-four days with *C. difficile* developed high titers of anti-toxin A IgG in their serum, while uninfected mice did not. The limit of detection is 1200. Infected vs. Uninfected p= 0.009277. **C.** Amount of serum IgG in the recipient Rag1-/- mice twenty-three days post injection of splenocytes. Note that two mice that were given splenocytes did not develop detectable IgG. The limit of detection is 1.56 ng/mL. Corrected p values are: Vehicle vs. Splenocytes (uninfected donor) p= 0.014, Vehicle vs. Splenocytes (infected donor) p= 0.011, Splenocytes (uninfected donor) vs. Splenocytes (infected donor) p= 0.814. **D.** Anti-toxin A IgG titers in recipient Rag1-/- mice twenty-three days post transfer of splenocytes. Only the mice that received splenocytes from infected donors had any detectable tiers. The limit of detection is 50. Corrected p values are: Vehicle vs. Splenocytes (infected donor) p= 0.008, Splenocytes (uninfected donor) vs. Splenocytes (infected donor) p= 0.008. For all data, statistical significance was calculated using a Wilcoxon test. When performing multiple comparisons, p values were corrected using Benjamini–Hochberg correction for multiple comparisons. The dark-grey hashed line represents the limit of detection for each assay while the dark-grey bars represent the median. All undetected results are plotted below the LOD line for visual clarity. For statistics when samples were below the LOD, a value equal to the LOD/√2 was used.

**Figure 2: Clearance of *C. difficile* colonization is associated with significantly different pre-transfer gut microbiota not treatment groups.**

**A.** Time course of intestinal colonization levels with *C. difficile* colored by treatment group. The thick lines represent the median colony forming units (CFU) of *C. difficile* per gram of feces at each time point for each treatment group. The colored hashed lines represent the median colonization within each cage. Colonization levels varied between cages within the same treatment group. The limit of detection was 100 CFU/g feces. **B.**  Colonization on day 26-post infection (day 23-post adoptive-transfer) colored by treatment group. Splenocyte transfer did not result in different levels of colonization with *C. difficile* between groups. LOD is same as in A. Corrected p values for all comparisons are p=0.835. For A and B: The dark-grey hashed line represents the limit of detection for each assay while the dark-grey bars represent the median. All undetected results are plotted below the LOD line for visual clarity. For statistics when samples were below the LOD, a value equal to the LOD/√2 was used. Statistical significance was calculated using a Wilcoxon test. When performing multiple comparisons, p values were corrected using Benjamini–Hochberg correction for multiple comparisons. **C**. Multidimensional scaling MDS plot of Bray-Curtis distances comparing communities in mice at day 1-post infection. Before adoptive transfer the cage that eventually cleared infection (black circles) had a significantly different community structure than the mice in the other cages (represented by the other shapes) ANOSIM R=0.7584, p=0.004.

**Figure 3: Effect of reconstitution of adaptive immunity on the microbiota.**

**A.** The Bray-Curtis dissimilarity distances between each mouse’s pre-antibiotic and day 21 post infection communities were computed. Values closer to 1 signify that the two communities are more dissimilar. Reconstitution of adaptive immunity does not alter the recovery of the community by this metric. Corrected p-values: Splenocytes (uninfected donor) vs. Splenocytes (infected donor) p= 0.082, Splenocytes (uninfected donor) vs. vehicle p= 0.149, Splenocytes (infected donor) vs. vehicle p= 0.714. **B.** The inverse Simpson diversity of the community is not different in mice given splenocytes or vehicle. Corrected p-values: Splenocytes (uninfected donor) vs. Splenocytes (infected donor) p= 0.9433, Splenocytes (uninfected donor) vs. vehicle p=0.7546 Splenocytes (infected donor) vs. vehicle p= 0.6623.Statistical significance was calculated using a Wilcoxon test. When performing multiple comparisons, p values were corrected using Benjamini–Hochberg correction for multiple comparisons. **C.** Strip chartshowing the showing the abundance per 10,000 sequences of the top ten OTUS with the highest LDA for distinguishing IgG negative mice from IgG positive mice. Each dot represents a single mouse. Bars represent the median.

**Figure 4: Microbiota is sufficient to explain clearance**.

**A.** Schematic of co-housing experiment. Open circles represent RAG1-/- mice while closed circles represent the wild-type mice. Mice were co-housed for thirty-three days starting before antibiotics up to infection. The colors of the boxes represent gender as well as grouping of mice. Group A denoted by the blue boxes are male RAG1-/- and WT mice that were cohoused before infection while group B, denoted by the purple boxes, represents the female RAG1-/- and WT mice that were cohoused. **B.** Multidimensional scaling MDS plot of Bray-Curtis dissimilarity between the fecal microbiota of the group A (blue) vs. group B (purple) mice before antibiotics or infection. The two groups of mice have a significantly different community structure, ANOSIM R=0.1756, p=0.041. **C.** Temporal *C. difficile* colonization by cage. Circles represent the median values for each cage while the error bars denote upper and lower quartiles. Open circles are the RAG1-/- mice while closed circles are the wild-type mice. The colors refer back to 4A and represent co-housing groups prior to infection. p=0.002 by Wilcoxon test. **D.** Same data as in figure 4C, showing colonization at 40 days post-infection for each cage. The black-hashed line represents the limit of detection, which was 100 CFU/g feces. All undetected results are plotted below the LOD line for visual clarity. For statistics when samples were below the LOD, a value equal to the LOD/√2 was used. Statistical significance was calculated using a Wilcoxon test.

**Figure 5: Intact community predicts outcome of *C. difficile* infection.**

**A.** Dot chart showing the top ten OTUs with highest mean decrease in accuracy from the Random Forest classifier. **B.** Strip chartshowing the abundance per 10,000 sequences of OTUs from 5A that distinguish between mice that went on to clear *C. difficile* versus the mice that remained colonized. Each dot represents a single mouse. Black bars represent the median.

**Supplemental figure 1: Colonization of *C. difficile* in wild type donor mice.**

Temporal colonization of *C. difficile* by cage, circles represent the median CFU/g feces for each cage while the error bars denote upper and lower quartiles. Grey represents the cage of mock-infected mice that were never colonized, while black points is colonization in the infected mice. The black-hashed line represents the limit of detection, which was 100 CFU/g feces. All undetected results are plotted below the LOD line for visual clarity.

**Supplemental figure 2: Colonization of *C. difficile* in wild type mice included in Random Forest analysis.**

Temporal colonization of *C. difficile* by cage, circles represents the median CFU/g feces for each cage while the error bars denote upper and lower quartiles. Colors represent the different cages of mice. The black-hashed line represents the limit of detection, which was 100 CFU/g feces. All undetected results are plotted below the LOD line for visual clarity.