

Supplementary Information

Azithromycin alters the microbiome composition, function and resistome in women with *Chlamydia trachomatis* infections

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Supplementary Figures

Supplementary Figure S1. Alpha diversity measured by Shannon index and log richness of species for the paired vaginal, endocervical and rectal microbiomes for women without treatment, those who cleared their *C. trachomatis* infection post-treatment, and those who had persistent infection after treatment. *P* values are denoted within each box in the lower righthand corner.

Supplementary Figure S2. Beta diversity measured by Jaccard and Bray-Curtis metric for the paired vaginal, endocervical and rectal microbiomes for women without treatment, those who cleared their *C. trachomatis* infection post-treatment, and those who had persistent infection after treatment. *P* values are denoted within each box in the lower righthand corner.

Supplementary Figure S3. Chord diagram representation of the transition in sub-Community State Types (subCSTs) for the three cohort datasets for endocervical, vaginal and rectal sites. *Transition from a *Lactobacillus*-dominated microbiome (subCST I, II or V) to a microbiome dominated by *L. iners* or diverse anaerobic and facultative bacteria (subCST III or IV) or vice versa (‡).

Supplementary Figure S4. Taxonomic profiles of the vaginal microbiomes, paired with the endocervical and rectal microbiomes (not shown), based on relative abundance at the species at baseline and follow-up for the three study cohort datasets. The participant ID# is shown at the top of the respective box that contains baseline (left) and follow-up (right) bar graphs and the in sub-Community State Types (subCSTs) noted below the bar graphs. The samples exhibiting genito-rectal transmissions are shown in **Figure 6**.

Supplementary Figure S5. Taxonomic profiles of the endocervical microbiomes, paired with the vaginal and rectal microbiomes (not shown), based on relative abundance at the species at baseline and follow-up for the three study cohort datasets. The participant ID# is shown at the top of the respective box that contains baseline (left) and follow-up (right) bar graphs and the in sub-Community State Types (subCSTs) noted below the bar graphs. The samples exhibiting genito-rectal transmissions are shown in **Figure 6**.

Supplementary Figure S6. Taxonomic profiles of the rectal microbiomes, paired with the endocervical and vaginal microbiomes (data not shown), based on relative abundance at the species at baseline and follow-up for the three study cohort datasets. The participant ID# is shown at the top of the respective box that contains baseline (left) and follow-up (right) bar graphs and the in enterotype noted below the bar graphs. The samples exhibiting genito-rectal transmissions are shown in **Figure 6**.

Supplementary Figure S7: Function- and pathway-level community analysis of paired vaginal, endocervical and rectal microbiomes of women who did not have a *C. trachomatis* infection and did not receive treatment. A. The Function-level analysis shows the function that had significantly different relative abundances between baseline and follow-up microbiomes for the rectum. No functions were significantly different for the endocervical or vaginal sites. B. The microbial contribution for each function and the associated pathways are shown for baseline and follow up time points. C. The Pathway-level community analysis shows those pathways for each anatomic site that have a significant difference in relative abundance between the baseline and follow-up microbiomes ($P < 0.05$). Species represented in the graphs are color-coded as per the columns to the right.

Supplementary Figure S8. MAFFT alignment of *C. trachomatis* *rpIV* genes (encoding L22 protein) extracted from baseline and follow-up samples of the *Ct* persistence cohort and baseline samples of the *Ct* clearance group. *Ct* reference strain D/UW-3/CX was used as the sequence to identify the macrolide conferring resistance mutations in our clinical samples. Regions with nonsynonymous missense mutations are shown. Numbering above the nucleotide sequence indicates nucleotide position and numbering below the amino acid sequence indicates amino acid position. The macrolide binding site is noted in blue below the amino acid sequence. Presence of *rpIV* mutations in *Ct* is indicative of macrolide resistance as reported by Mestrovic et al., 2018 and Benamri et al., 2021.

Supplementary Figure S9. MAFFT alignment of *L. iners* *ermB* genes extracted from baseline and follow-up samples across all three cohorts, *L. iners* strain C0094A1 and C0210C1 harboring *ermB* and the ErmB protein homolog from *Enterococcus faecium* (available from CARD). Regions with nonsynonymous missense mutations are shown. Numbering above the nucleotide sequence indicates nucleotide position and numbering below the amino acid sequence indicates amino acid position. The *L. iners* *ermB* genes circulating in our microbiomes were found to be $\geq 99.1\%$ identical to the protein homolog model, and the strains C0094A1 and C0210C1 were 99.1% identical. Presence of *ermB* in *L. iners* is indicative of macrolide resistance as reported by the CARD model: <https://card.mcmaster.ca/ontology/36514>.

Supplementary Figure S10. MAFFT alignment of *G. vaginalis ermX* genes extracted from baseline and follow-up samples across all three cohorts, *G. vaginalis* strain JNFY11 harboring *ermX* and the *ErnX* protein homolog from plasmid pNG2 (available from CARD). Regions with nonsynonymous missense mutations are shown. Numbering above the nucleotide sequence indicates nucleotide position and numbering below the amino acid sequence indicates amino acid position. The *G. vaginalis ermX* genes circulating in our microbiomes were found to be $\geq 93.8\%$ identical to the protein homolog model and the strain JNFY11 was 99.3% identical. Presence of *ermX* in *G. vaginalis* is indicative of macrolide resistance as reported by the CARD model: <https://card.mcmaster.ca/ontology/36735>. Presence of more than one copy of *ermX* represented as 2 next to a given sample ID is indicative of the presence of a second copy of the *G. vaginalis ermX* gene within a microbiome.

Supplementary Tables

Supplementary Table S1. Metagenomic shotgun sequencing results and quality control statistics.

Supplementary Table S2. Metadata of samples used in this study, including data on age, ethnicity, *C. trachomatis*, BV, pH, *N. gonorrhoeae*, *M. genitalium* and HPV type.

Supplementary Table S3. Distribution of low risk (lr)HPV (black font) and high risk (hr)HPV (red & orange fonts) types in paired vaginal, endocervical and rectal microbiomes.

Supplementary Table S4. Comparison of subCommunity State Type (CST) and metagenomic (mg)CST in paired vaginal and endocervical microbiomes for the three cohort datasets at baseline.

Supplementary Table S5. Comparison of vaginal and endocervical subCST and mgCST classification systems and associations with BV and *C. trachomatis* (*Ct*).

Supplementary Table S6. subCST associations with BV and *C. trachomatis* infection in the vaginal and endocervical microbiomes.

Supplementary Table S7. Functions and pathways associated with the baseline time point for the *C. trachomatis* persistence cohort microbiomes.

Supplementary Table S8. Functions and pathways associated with the follow up time point for the *C. trachomatis* persistence cohort microbiomes.

Supplementary Table S9. Functions and pathways associated with the baseline time point for the *C. trachomatis* clearance cohort microbiomes.

Supplementary Table S10. Functions and pathways associated with the follow up time point for the *C. trachomatis* clearance cohort microbiomes.

Supplementary Table S11. Functions and pathways associated with the baseline time point for the *C. trachomatis* control cohort microbiomes.

Supplementary Table S12. Functions and pathways associated with the follow up time point for the *C. trachomatis* control cohort microbiomes.

Supplementary Table S13. Function-level community analysis of the microbiomes from the *Ct* clearance cohort.

Supplementary Table S14. Function-level community analysis of the microbiomes from the *Ct* persistence cohort.

Supplementary Table S15. Function-level community analysis of the microbiomes from the no treatment cohort.

Supplementary Table S16. Supplementary Table S16. *G. vaginalis ermX* and *L. iners ermB* genes that confer resistance to macrolide antibiotics, and *L. iners tet(W)* gene conferring tetracycline resistance and mutations in the *C. trachomatis rplV* gene that may confer macrolide resistance identified among endocervical, vaginal and rectal microbiomes for all cohorts at baseline (blue) and follow-up (red).

Supplementary Figure S1

Endocervix

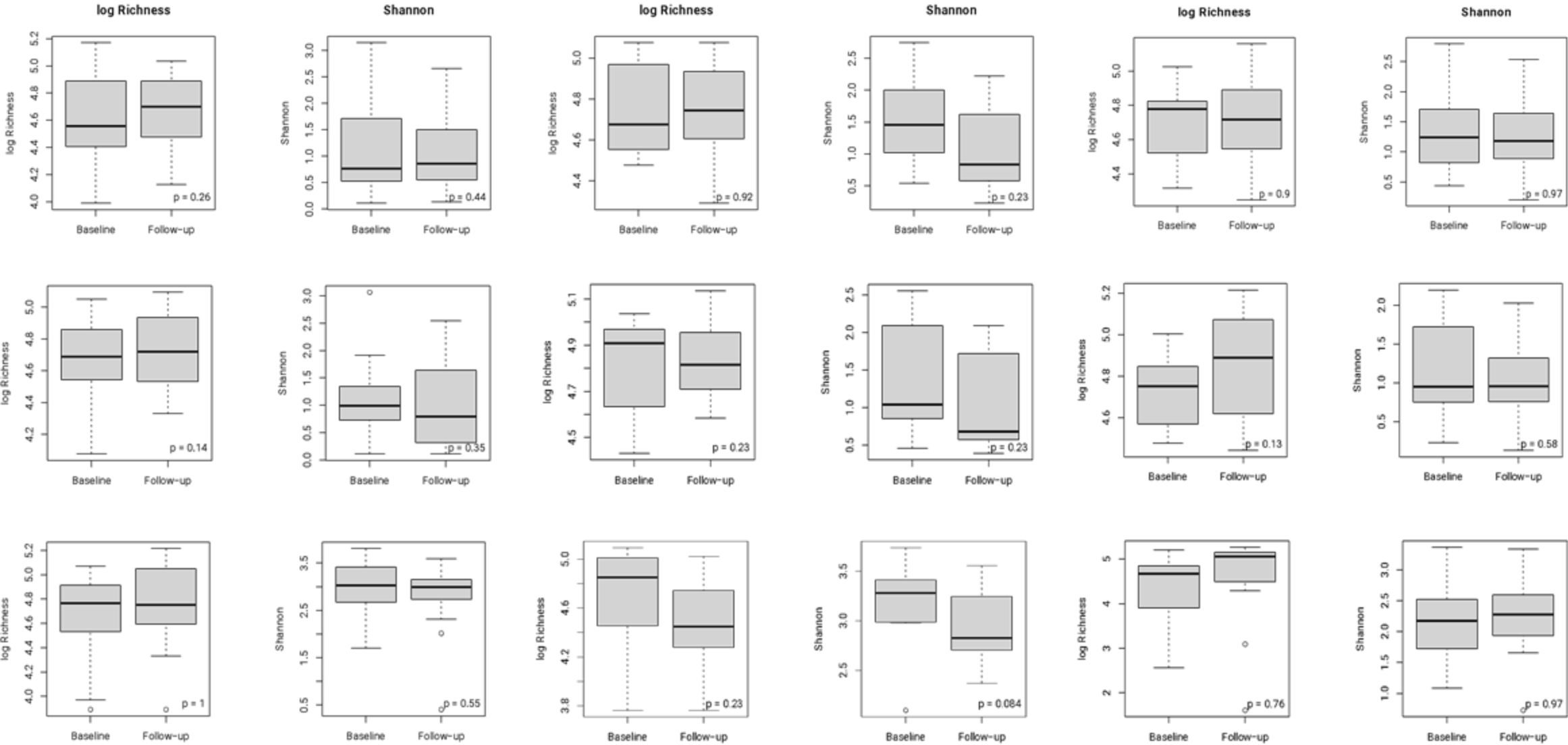
Vagina

Rectum

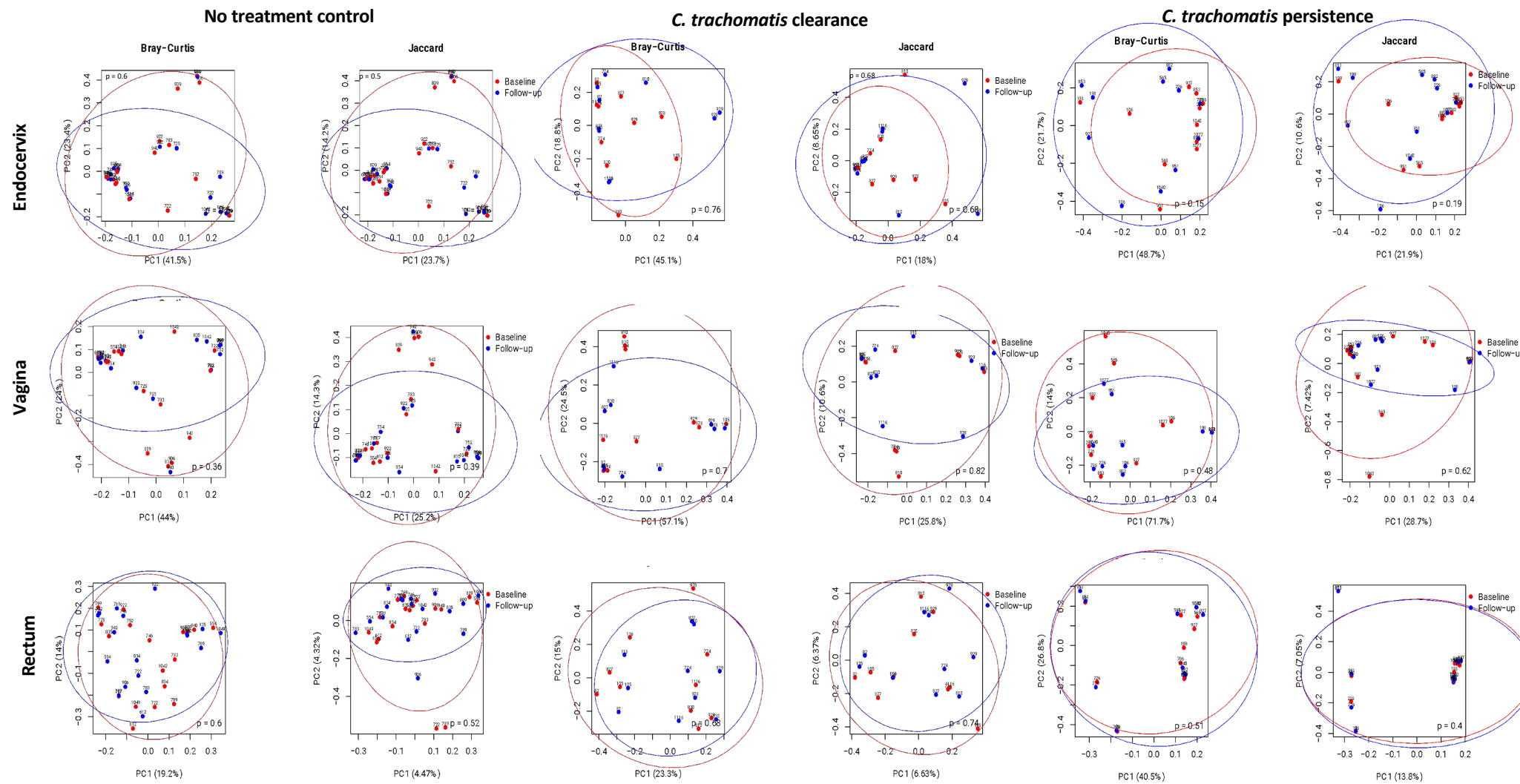
No treatment control

C. trachomatis clearance

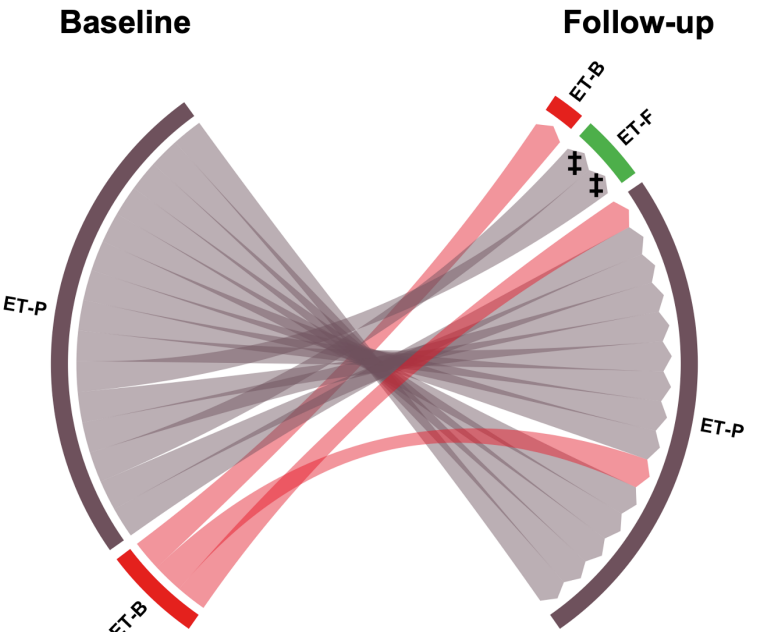
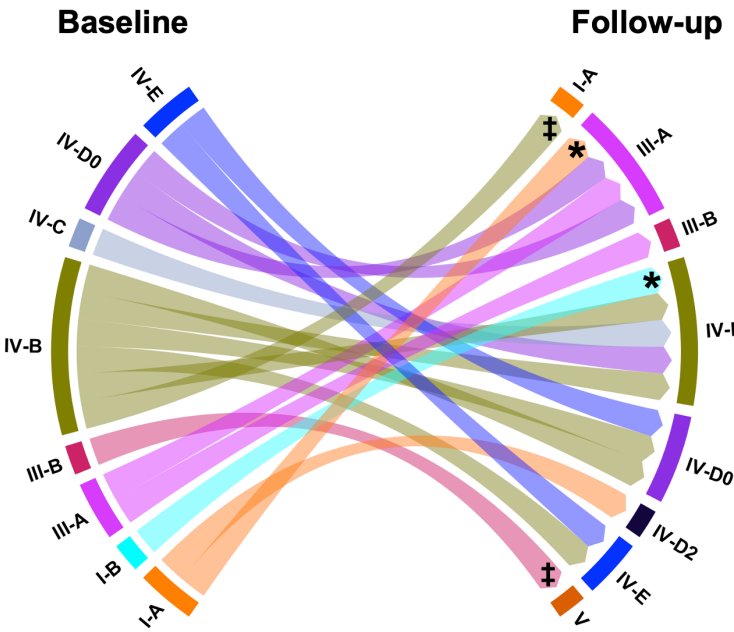
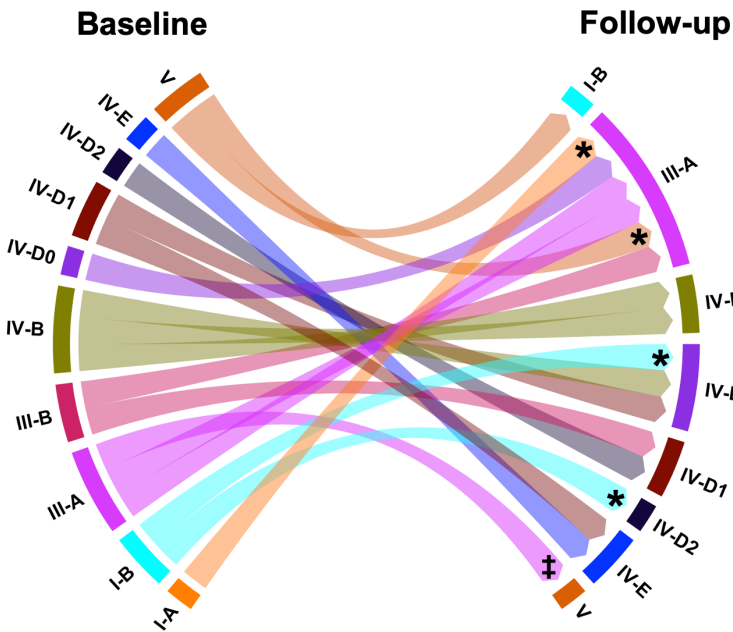
C. trachomatis persistence



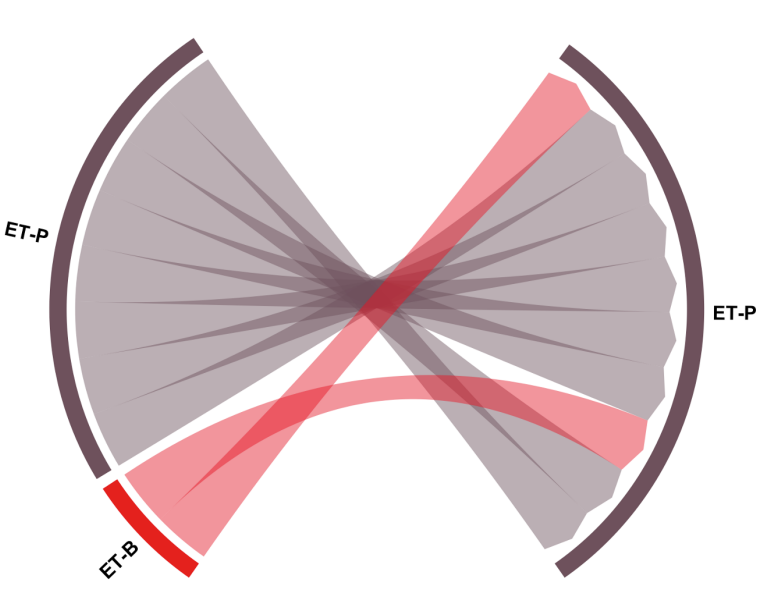
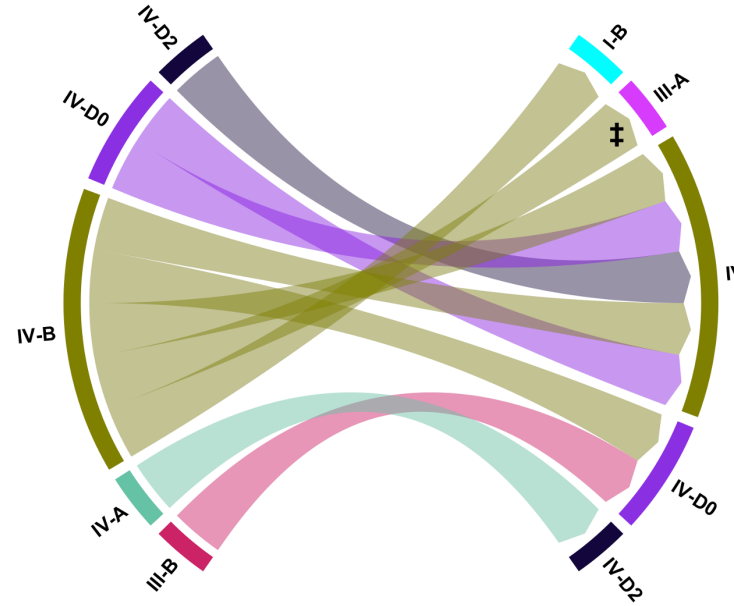
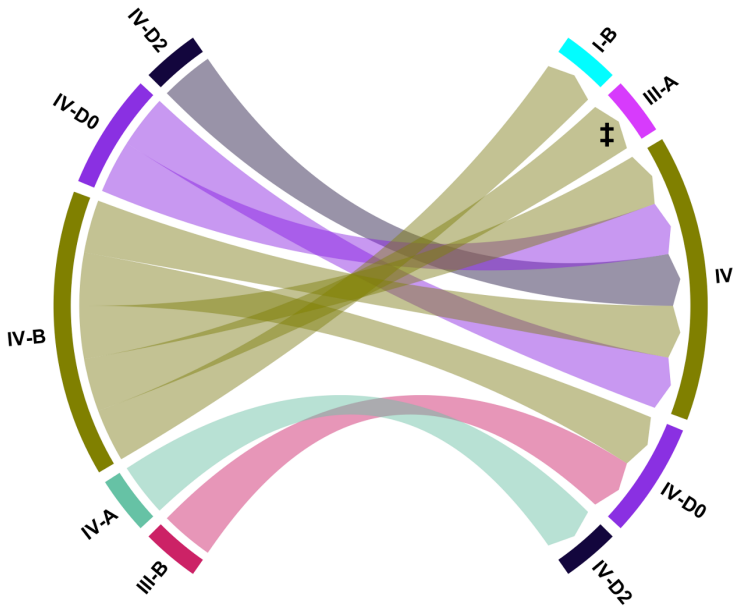
Supplementary Figure S2



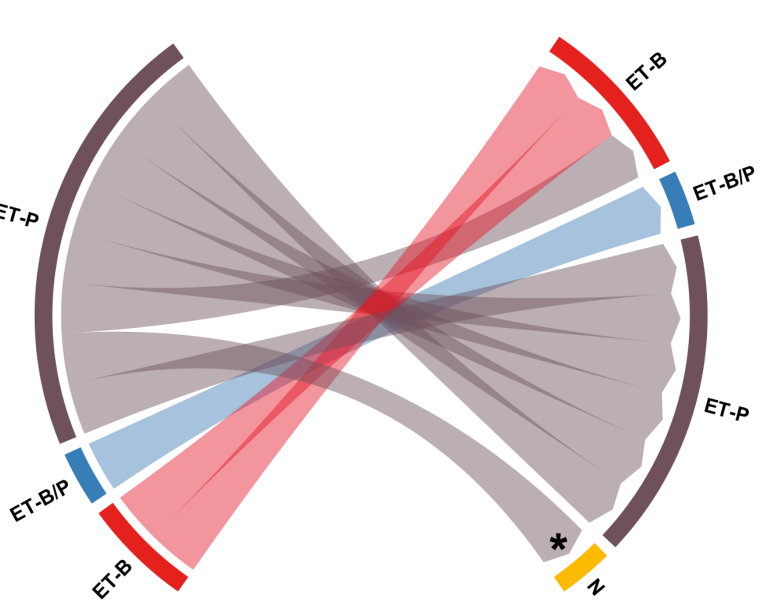
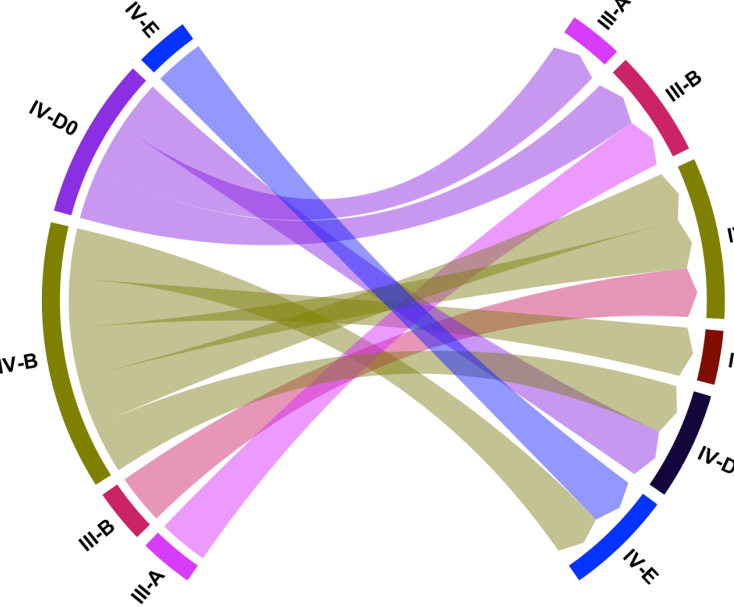
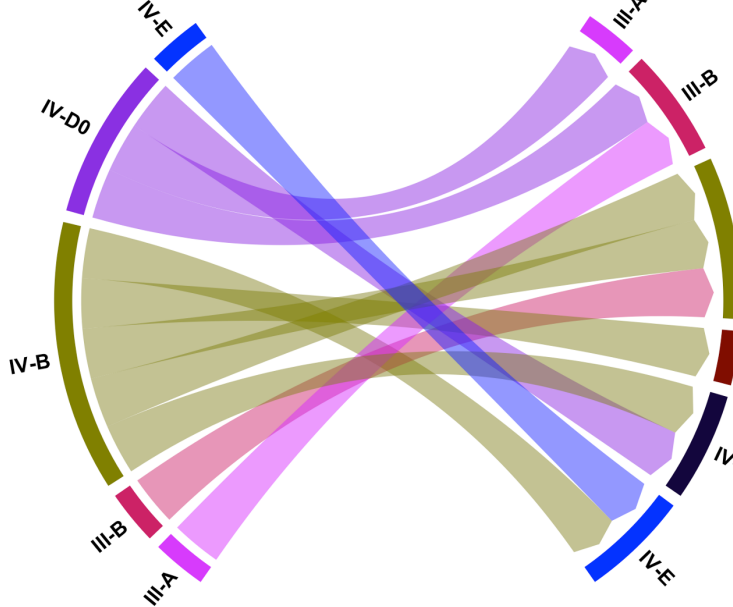
No treatment control



C. trachomatis clearance



C. trachomatis persistence

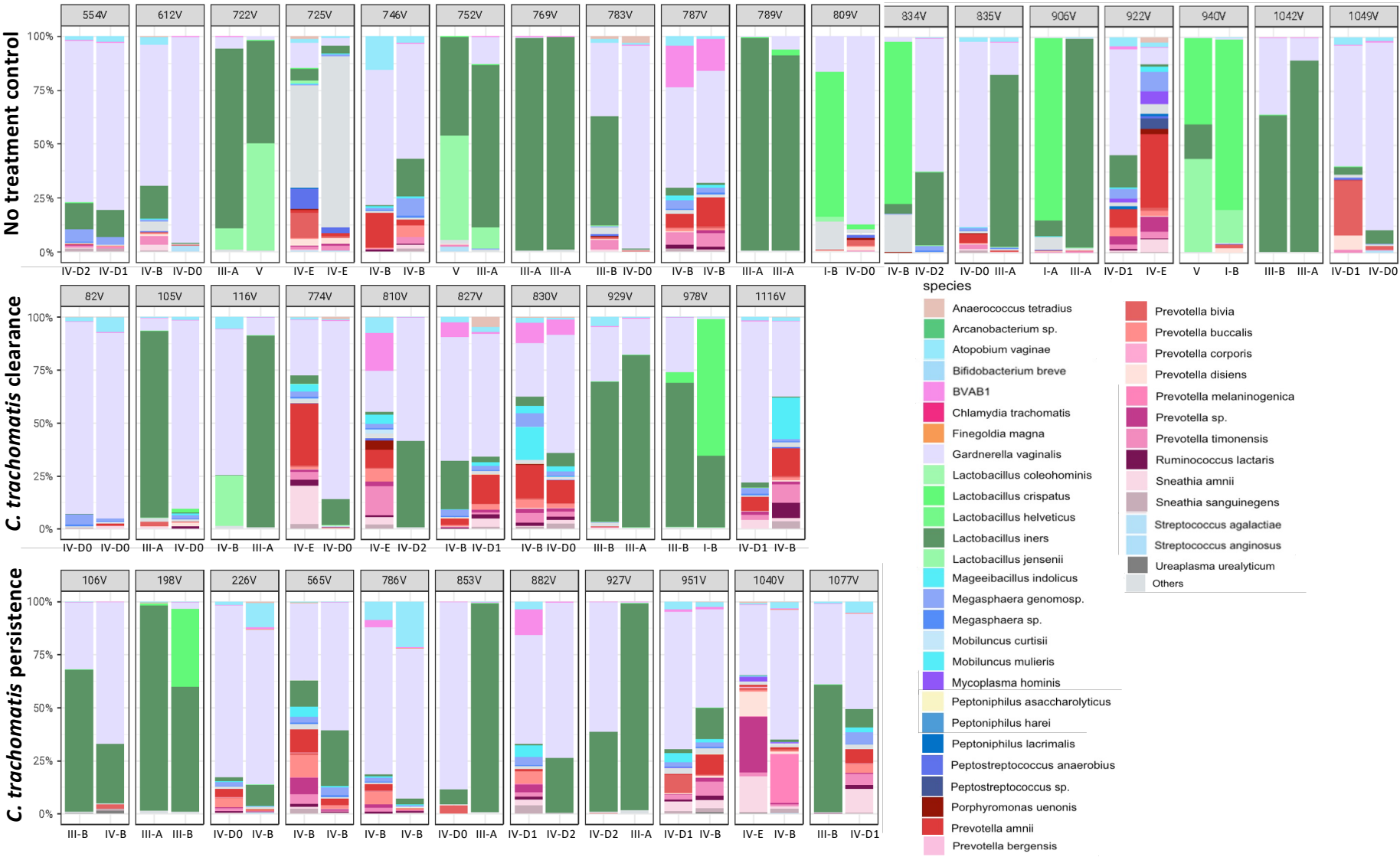


Vagina

Endocervix

Rectum

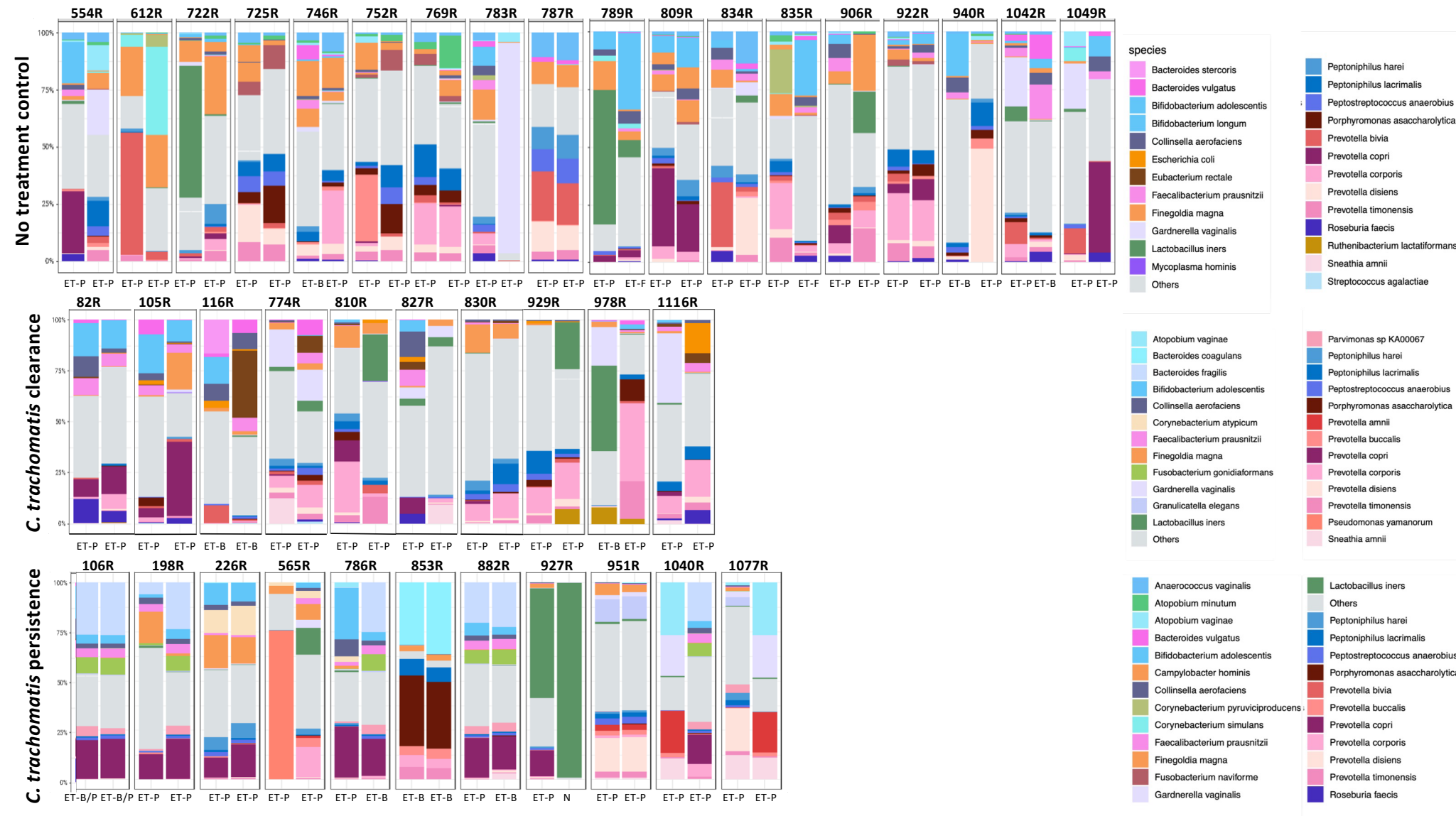
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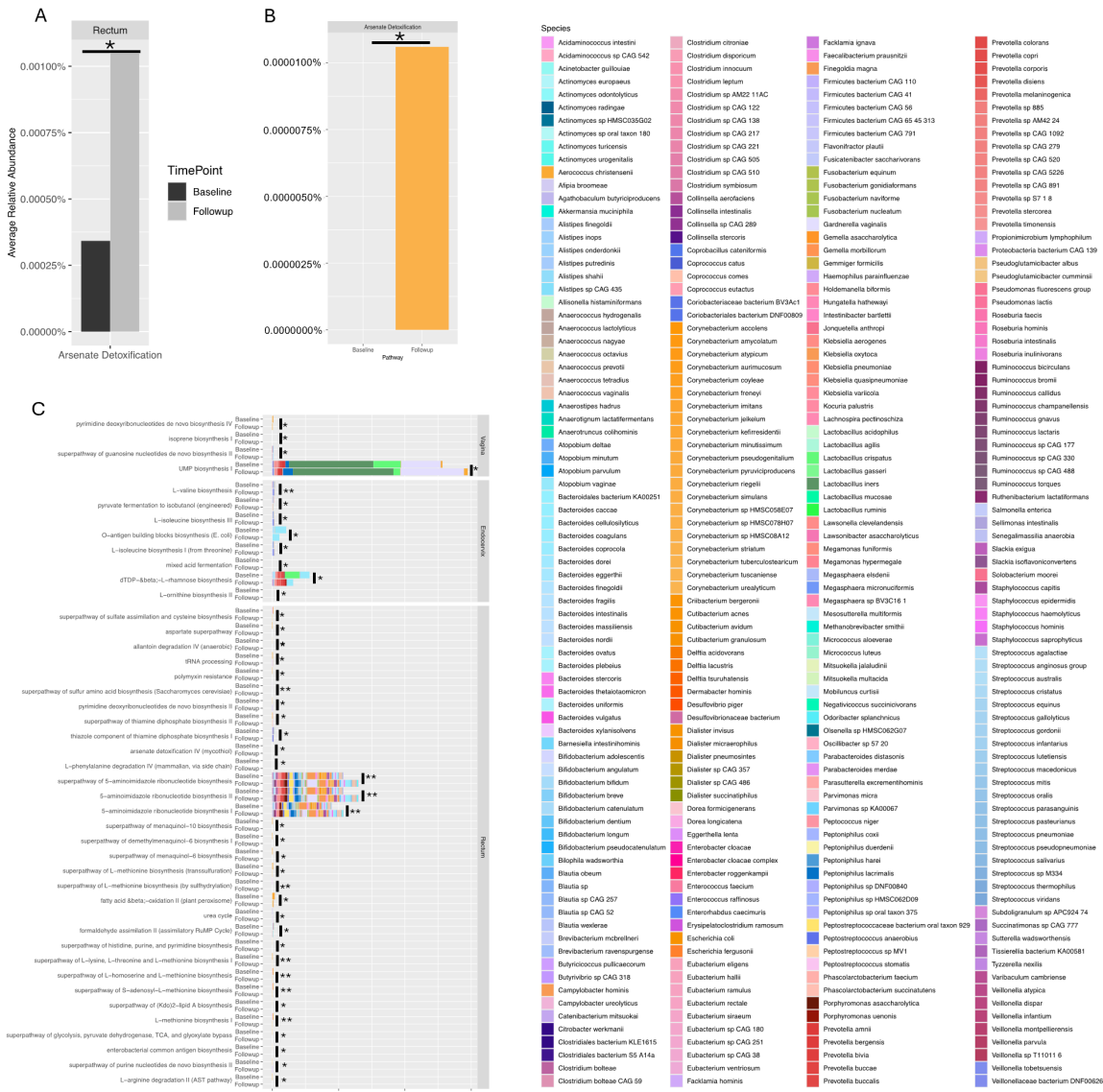
Supplementary Figure S5

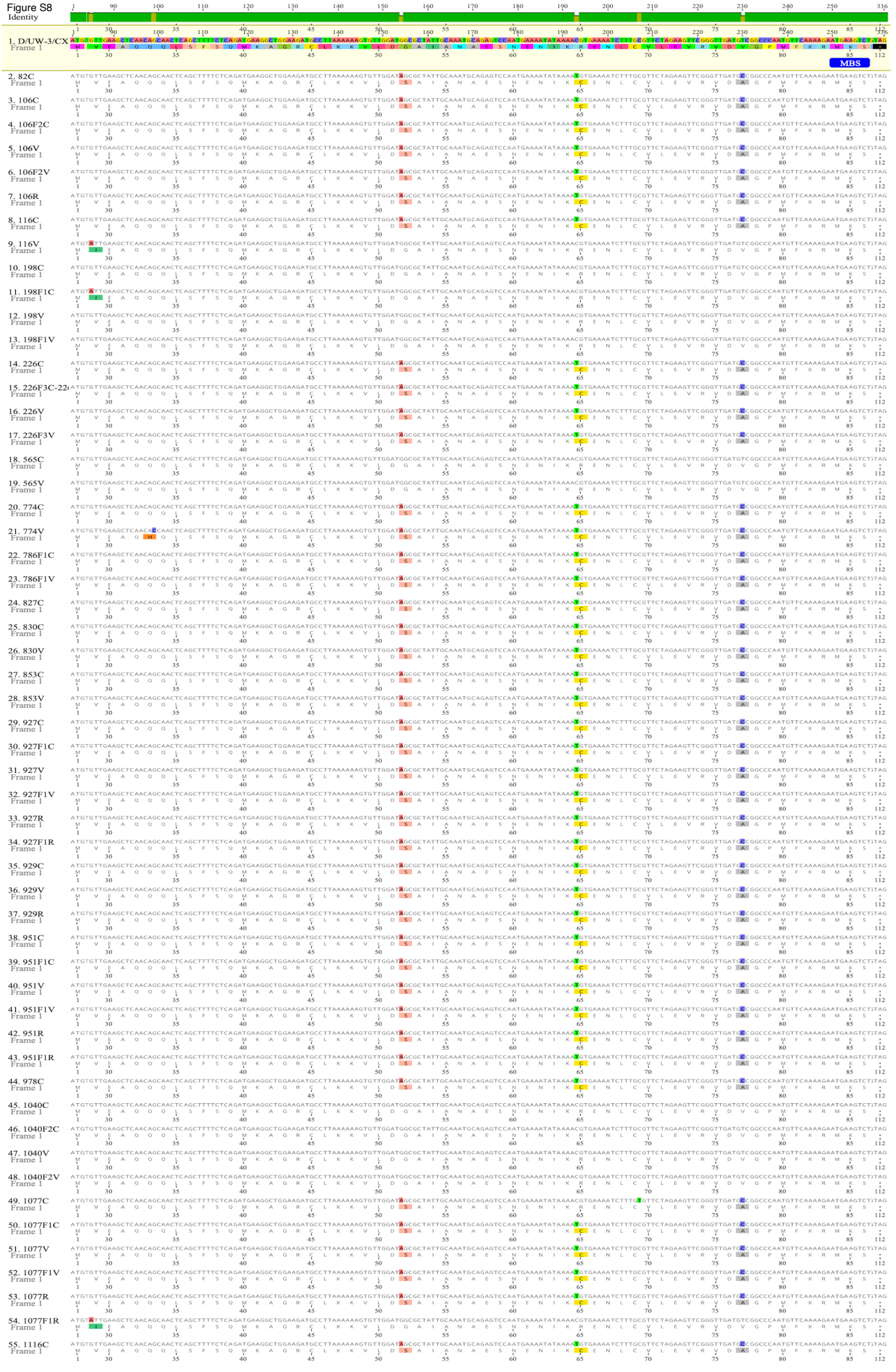


Supplementary Figure S6

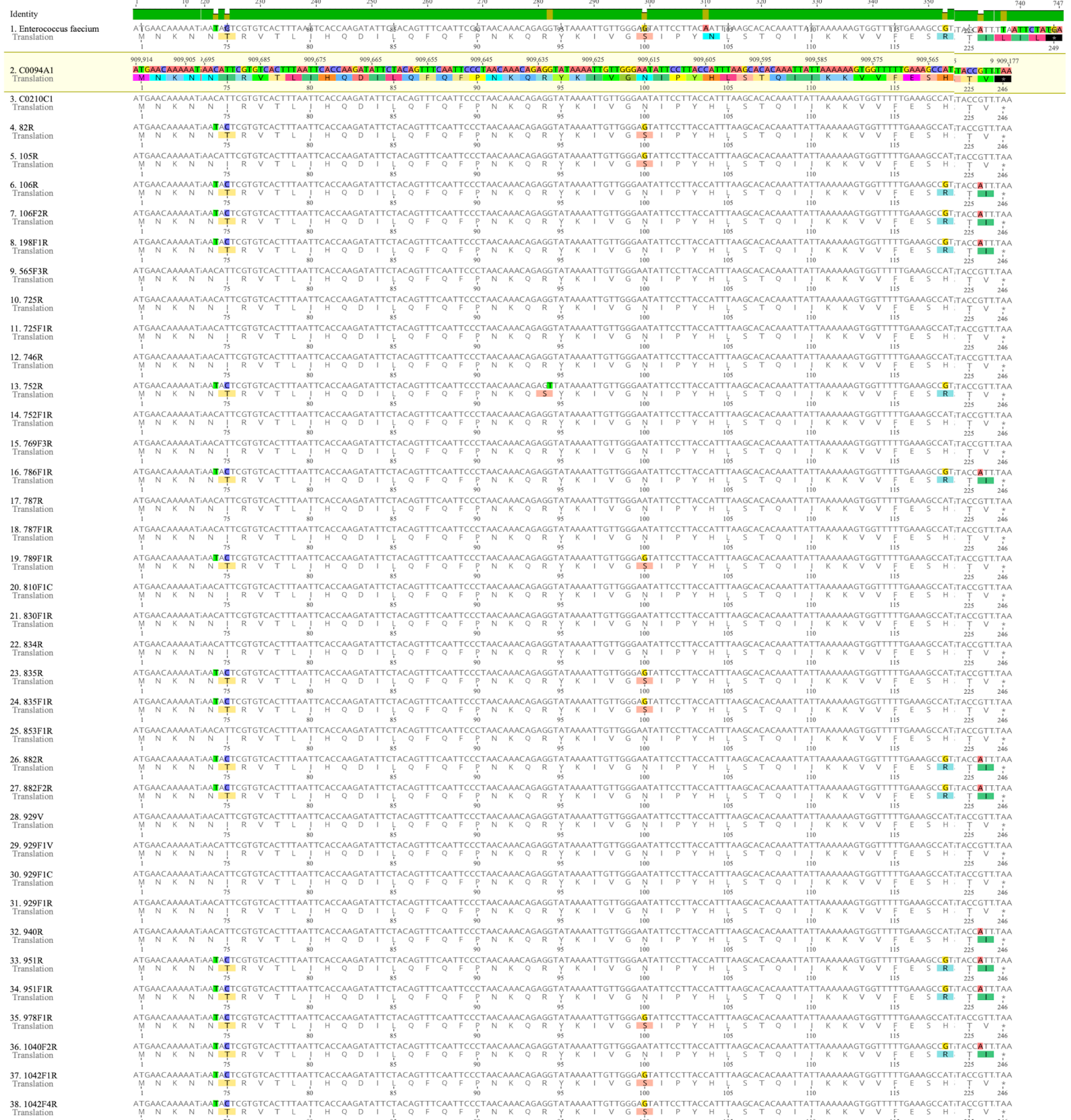


Supplementary Figure S7





Supplementary Figure 8



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