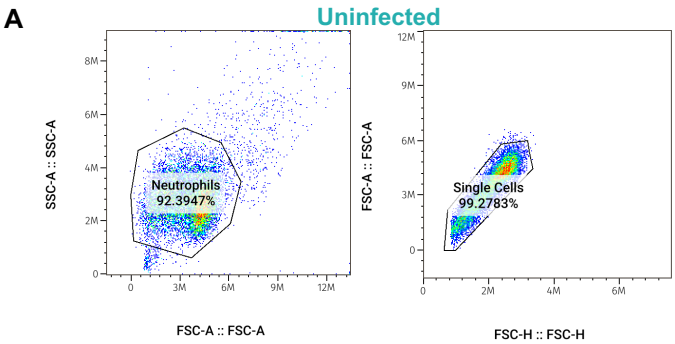
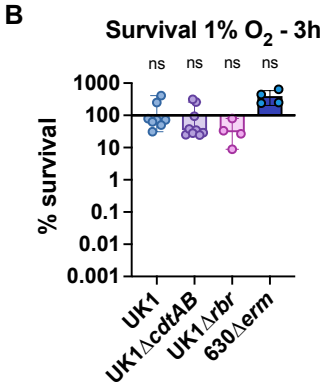
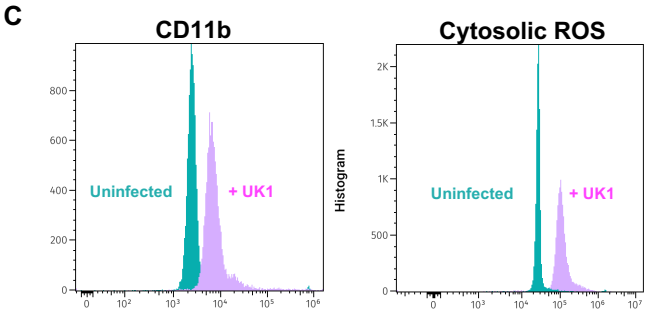
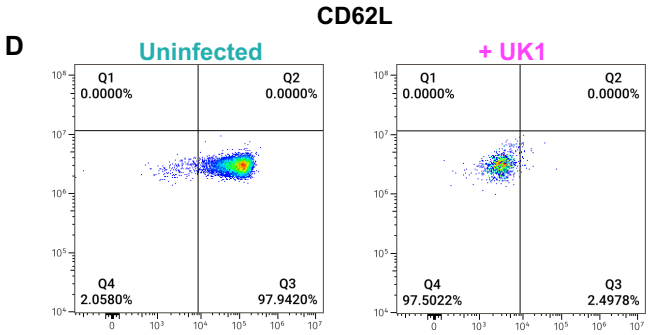
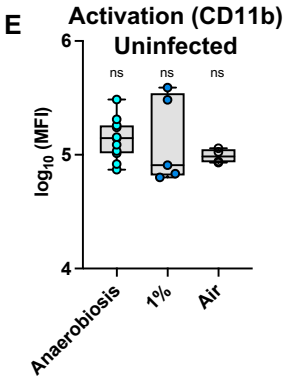
Supp Fig. 1

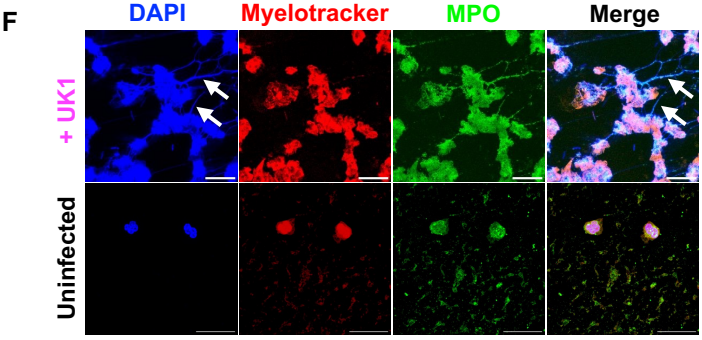






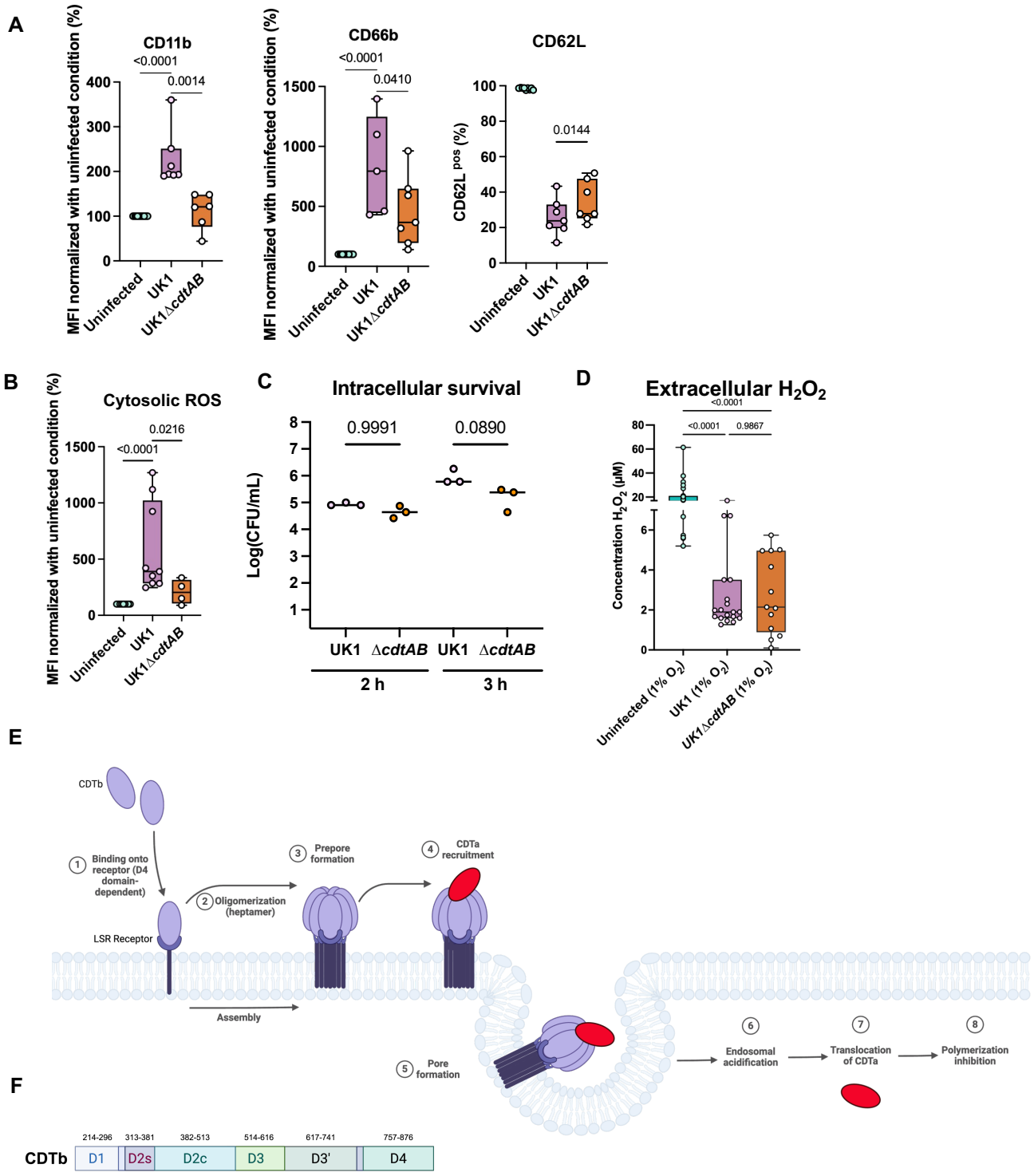






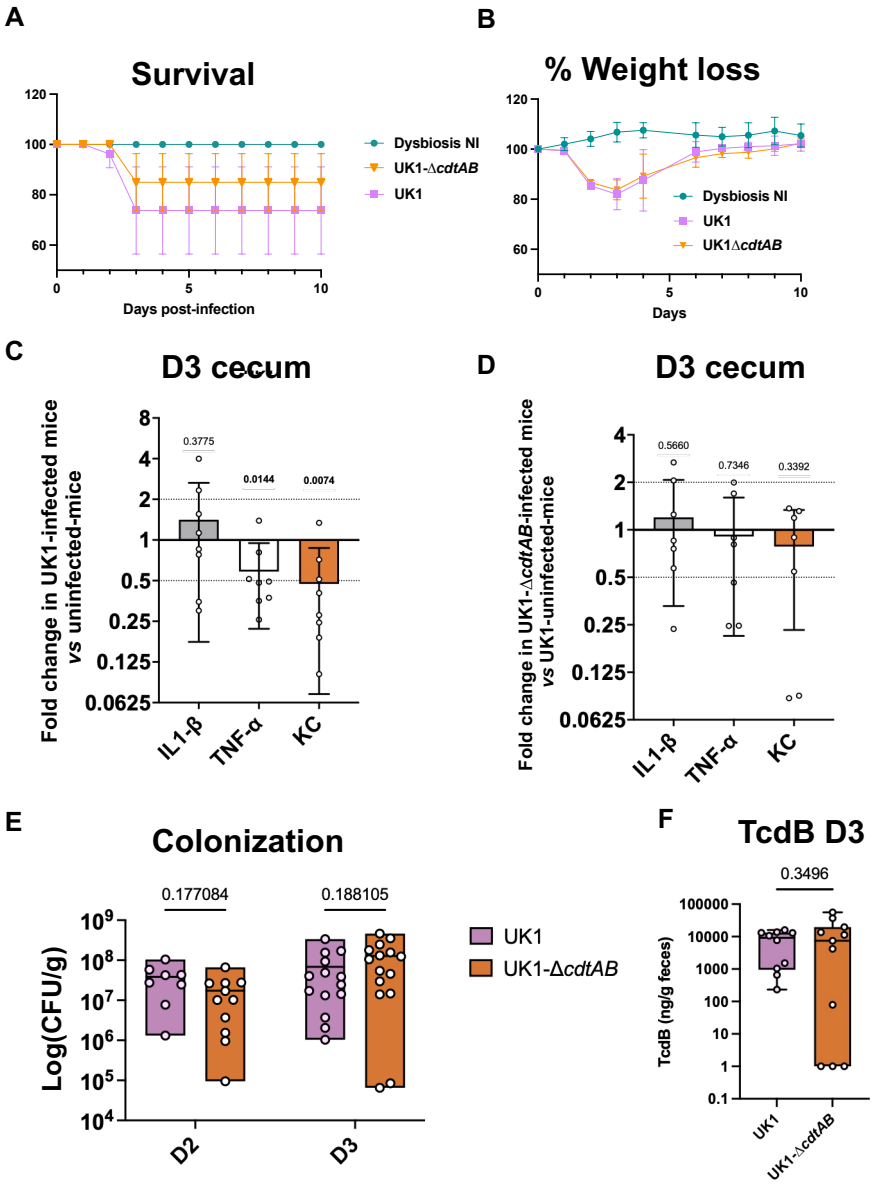
A. Gating strategy to assess markers of activation detected on human neutrophils with flow cytometry assay. The neutrophil population was gated according to size and granularity. Dupes were excluded from the gate. **B.** Survival (%) of UK1, UK1 Δ*cdtAB*, UK1 Δ*rbr* mutants and 630Δ*erm* after 3 h in RPMI medium incubated at 1% O_2. CFUs were determined before or after exposure. Ordinary one-way ANOVA was performed followed by Dunett's multiple comparison test with the UK1 strain. **C.** Representative histograms of CD11b and CellRoxGreen cytosolic probe targeting cytosolic ROS of uninfected neutrophils (blue) or neutrophils infected with UK1 strain (pink) after 1 h at 1% O_2. **D.** Representative CD62L shedding among gated neutrophil uninfected population and neutrophil infected with UK1 strain after 1 h at 1% O_2. **E.** MFI of CD11b at the surface of uninfected neutrophils measured by flow cytometry expressed in $\log_{10}$(MFI). Neutrophils were incubated 1 h in anaerobiosis, 1% O_2 or air. **F.** Immuno-fluorescence images acquired by confocal microscope of uninfected neutrophils or UK1-infected neutrophils during 1h under 1% O_2 incubation. NETs were observed with DAPI (Blue), MPO (Green) and Myelotracker®-Cy3 (Red) and marked by white arrows.

Supp Fig. 2



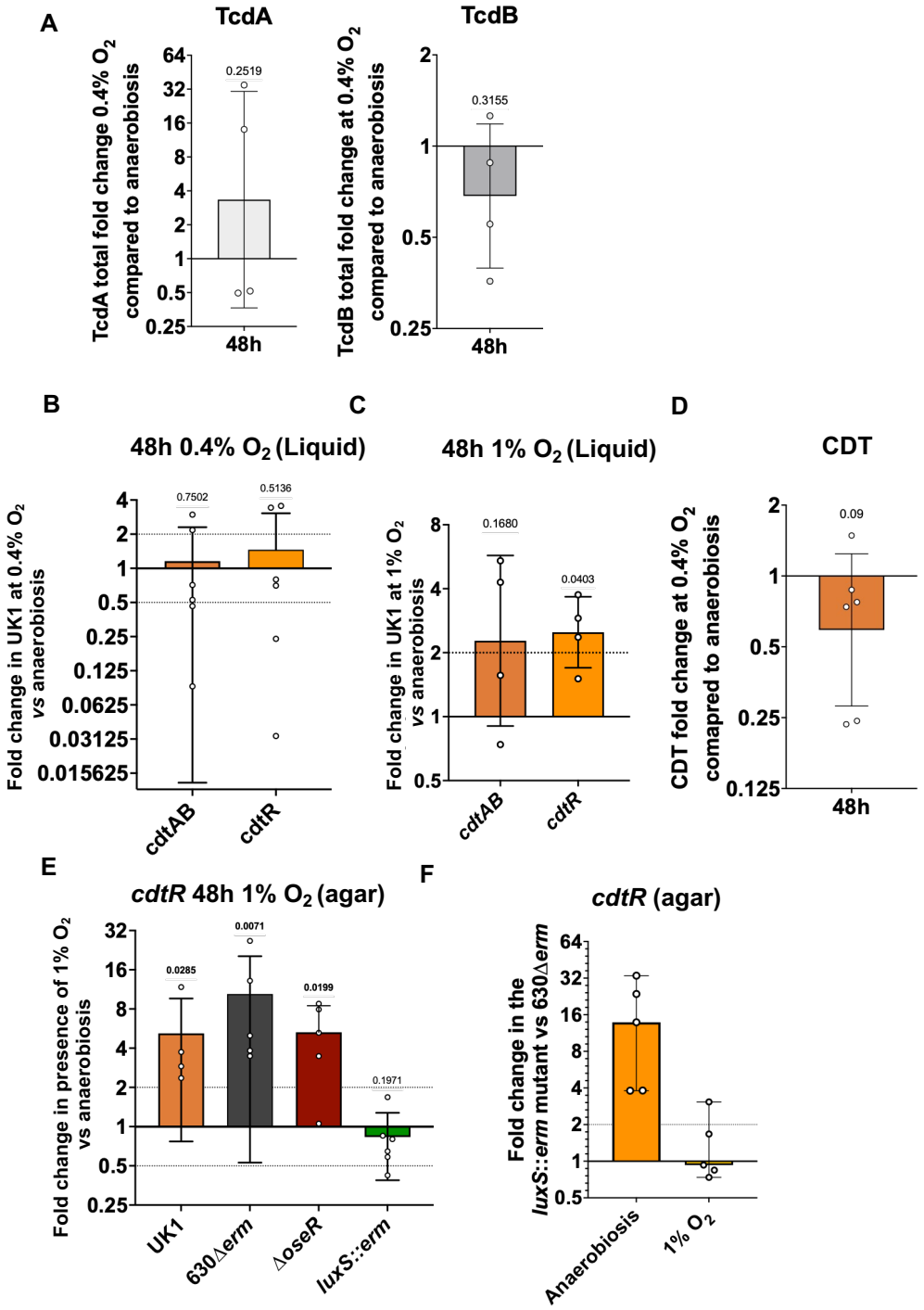
A. MFI of CD11b and CD66b at the surface of uninfected or infected neutrophils after flow cytometry assay. MFI of infected CD11b or CD66b stained neutrophils normalized by MFI of uninfected conditions expressed in %. CD62L shedding is represented in % of positive neutrophil population for CD62L fluorescent intensity in the defined gate. Neutrophils were infected by UK1 or UK1 Δ*cdtAB* strain for 1 h at 1% O_2. One-way ANOVA with multiple comparisons (mean ± S.D., n >3, *p*-values are indicated). **B.** MFI of CellRox probe targeting cytosolic ROS at the surface of uninfected or infected neutrophils after flow cytometry assay. expressed in %. **C.** Log(CFU/mL) of intracellular UK1 or UK1 Δ*cdtAB* after 2 h or 3 h of contact with neutrophils in presence of 10 µg.µL^{-1} of vancomycin added after 30 min of incubation without antibiotic. Ordinary one-way ANOVA (mean ± S.D., n =3, *p*-values are indicated). **D.** Concentration of H_2O_2 in µM (measured at OD_{560nm}) in the supernatant of neutrophils uninfected or infected by the UK1 strain or the Δ*cdtAB* mutant for 1 h at 1% O_2. Results are from at least 3 independent extractions of neutrophils and 3 independent bacterial culture for each neutrophil extraction. One-way ANOVA with multiple comparisons (mean ± S.D., n >3, *p*-value are indicated). **E.** Schematic representation of CDT binding and pore-forming mechanism in epithelial cells. **F.** Schematic representation of domains of CDTb.

Supp Fig. 3



Percentage of survival (**A**) or weight loss (**B**) relative to the initial weight measured on D0 of C57BL/6 mice infected with UK1 or UK1Δ*cdtAB* according to days post-infection (Average of 2 different experiments, n=20 and n=14; for dysbiosis n=3 and n=10). **C.** Differential expression (RT-qPCR) of IL1-β, TNF-α and KC in cecum of mice infected by UK1 D3 post-infection in fold change normalized by collected cecum at D0 before infection (Mean ± S.D., n=9 at D2 and n=5 at D0). **D.** Differential expression (RT-qPCR) in fold change of IL1-β, TNF-α and KC from cecum of infected mice by UK1 Δ*cdtAB* in comparison with mice infected by UK1 at D3 post-infection. Expression was normalized by expression from collected cecum at D0 before infection (Mean ± S.D., n=7 at D2 and n=5 at D0). **D.** Log_{10}(CFU/g) of UK1 or UK1Δ*cdtAB* strains counted in feces of infected mice D2 or D3 post-infection. **E.** ELISA TcdB toxin quantification in $ng.g^{-1}$ of feces from infected mice by UK1 (n=10) or UK1 Δ*cdtAB* (n=11) D3 post infection. Two-tailed unpaired t-test was performed, and *p*-values are indicated.

Supp Fig. 4



A. Quantification by ELISA of the TcdA and TcdB toxins in supernatant of UK1 strain incubated 48 h at 0.4 % O_2 compared to anaerobiosis (Mean ± S.D., n=4). Mann-Whitney statistical test was performed. *p*-value is indicated. **B-C** Differential expression by RT-qPCR analysis in fold change of the *cdtAB* and *cdtR* genes of UK1 incubated at 0.4 % O_2 (**B**) or at 1 % O_2 (**C**) during 48 h in liquid TY medium compared to anaerobiosis (Mean ± S.D., n=4). One sample *t*-tests were used with a comparison of the fold change to 1 for qRT-PCR analysis. **D.** Quantification by ELISA of CDT in supernatant of UK1 strain incubated 48 h at 0.4 % O_2 in liquid TY compared to anaerobiosis (Mean ± S.D., n=4). Mann-Whitney statistical test was performed. *p*-value is indicated. **E-F.** Differential expression by RT-qPCR analysis in fold change of the *cdtR* gene of 630Δ*erm,* 630Δ*erm*Δ*oseR* and 630 *luxS::erm* incubated at 1 % O_2 during 48 h on agar TY in comparison with anaerobiosis (Mean ± S.D., n=4) (**E**) and (**F**) *cdtR* gene of 630 *luxS::erm* incubated in anaerobiosis or 1% O_2 during 48 h on agar TY in comparison with 630Δ*erm* strain (Mean ± S.D., n=5). *p*-value is indicated.