Fig. S1. Fraction of the population constituted by rifampicin-resistant bacteria on Day 8 of selection from the constant-low lineages is shown. For the alternate-low lines, the numbers of days of selection are indicated in parentheses. Mean ± SD from three independent measurements are plotted. N.D. indicates that no rifampicin-resistant bacteria were detected.

Fig. S2. Colony diameters of wild type (Wt) or Day 6 populations from control lineages (Ctrl 1-10). Individual colony diameters are plotted as a scatter and median and interquartile range is indicated. No statistically significant differences were observed between the medians of wild type and control lineages.

Fig. S3. Small-colony phenotype is stable to passaging. Replicate populations were established from 2 isolated colonies of wild type or A8-S SCV each. Each population was passaged in rifampicin-free medium and periodically plated for estimation of colony diameters. Colony diameters at difference number of generations of passaging are shown as scatter plots and median and interquartile colony diameter are indicated.

Fig. S4. Illustrative growth curves of wild type (Wt) and A4-S/A5-S/A8-S small colony isolates in the absence (a) or presence (b) of low rifampicin (3 µg/mL). Though no difference in growth rate was detectable, all three SCVs grew to higher densities than wild type.

Fig. S5. Illustrative dose-response curves showing growth (carrying capacity) of wild type *E. coli* (grey) and 5 rifampicin-resistant isolates (black) from alternate-low lineage 1 (a) and constant-low lineage 1 (b) in the presence of varying concentrations of rifampicin. Mean ± SD from three measurements are shown. All isolates from the same lineage had indistinguishable dose-response characteristics.

Fig. S6. Pie-charts showing the distribution of lineages that evolved high-level resistant (IC50 > 50x Wt), low level resistant (IC50 5-50x Wt) or no resistance (IC50 < 3x Wt) in the alternate low (A-low), alternate-high (A-high), constant-low (C-low) and constant-high (C-high) selection schemes.

Fig. S7. Growth of wild type (Wt) *E. coli* or *rpoB:His526Q* allele-harbouring strains from constant-low or alternate-low selection schemes (H526Q-C and H526Q-A respectively) in the presence of varying concentrations of rifampicin. Mean ± SD from three measurements are shown.