**Inventory of Supporting Information**

**Extended Data Figure 1.** Efficacy of the phage cocktail-V1 against mouse infections and its host coverage across a range of clinical isolates. **(A)** Experimental scheme for the animal experiment. Grey numbers represent number of mice, black numbers represent hours post-infection. The illustration was created using BioRender. **(B)** The reduction of bacterial load in vital tissues of control mice compared to the treatment group. Each data point represents an individual mouse (*n* = 6). Box plots show median (centre line), interquartile range (box edges: 25th-75th percentiles), whiskers extending to the most extreme values within 1.5× interquartile range, and outliers as individual points beyond whiskers. Total represents data from all samples (*n* = 24) combined. Statistical analysis was performed using the Mann-Whitney U test (two-sided) with exact *p*-values to compare medians of bacterial count between groups. **(C)** The propagation of three different phages in various tissues of treated mice. The data (*n* = 6) are shown in box plots as above. Statistical analysis was performed using the Mann-Whitney U test as above. **(D)** Host range map of cocktail-V1 (øEnA02, øEnC07, and øEnC15) and its individual components tested against 120 *Enterobacter cloacae* complex (ECC) isolates from The Alfred Hospital. Each column represents an ECC isolate classified based on their Sequence Type (ST) and is color-coded accordingly. Red boxes indicate complete phage lysis of the respective ECC isolate, yellow boxes represent partial lysis, and light blue boxes indicate no observed lysis.

**Extended Data Figure 2.** Growth kinetic assay (left) and the corresponding phage score plot (right). The data presented in the ﬁgure reﬂects the performance of the adapted phage in days (D1-D10). D0 represents unadapted (ancestor phage) and Pos Cont and the host names indicate conditions where bacterial growth was observed without the phage treatment. (A) øEnC07 and host AH17D011 (pilot study) and corresponding phage score (*n* = 3); error bars represent standard error of mean. (B) øEnA02 and host AH19K022 and corresponding phage score (*n* = 1). (C) øEnC15 and host CPO390 and corresponding phage score (*n* = 1).

**Extended Data Figure 3.** Phage scores comparing ancestral (An) and evolved phages (Ev) against *Enterobacter cloacae* complex isolates (*n* = 36). Each dot represents the mean phage score from four technical replicates; error bars represent standard error of mean. Higher scores indicate greater phage susceptibility. The legend shows the specific phage-host adaptation pairs tested: ancestral phages An\_EnC07, An\_EnC15, and An\_EnA02, and their corresponding evolved derivatives Ev\_EnC07:AH17D011, Ev\_EnC15:CPO390, and Ev\_EnA02:AH19K020.

**Extended Data Figure 4.** Single nucleotide polymorphisms (SNPs) observed within various genotypes of evolved (adapted) phages. The genome map of øEnC07 is displayed as a reference genome to indicate complete genome, with distinct phage-specific gene regions indicated (DNA replication, head-tail baseplate-neck-collar, and tail fiber regions). Red arrows mark positions of SNPs) identified in evolved phage derivatives øEnA02, øEnC07, and øEnC15 following host adaptation. Each SNP is labelled with the amino acid substitution and genomic position. The brown-shaded regions highlight tail fiber genes where the majority of adaptive mutations occurred. Scale bar represents 2.5kb.

**Extended Data Figure 5.** Host range analysis of individual phages and phage cocktails against *Enterobacter cloacae* complex isolates. (A) Host range map of five newly isolated phages tested against 36 *Enterobacter cloacae* complex (ECC) isolates. Each row represents an ECC isolate, classified based on Sequence Type (ST), and is colour-coded accordingly. Singletons are STs that only occurred once. (B) Host range map of eight different phage combinations tested against a larger panel of 156 ECC isolates. Each row represents a phage cocktail (A-I). The bar chart quantifies the number of hosts lysed by selected phage combinations. The ev\_ prefix denotes evolved/host-adapted phage variants. Combinations are ordered by their lytic activities. [Phage cocktail compositions: A = øEnA02 + øEnC07 + øEnC15, B = ev\_øEnA02 + ev\_øEnC07 + ev\_øEnC15, C = øEnA02 + øEnC07 + øEnC15 + øTaquito, D = øEnA02 + øEnC07 + øEnC15 + øNando, E = ev\_øEnA02 + ev\_øEnC07 + ev\_øEnC15 + øTaquito, F = ev\_øEnA02 + ev\_øEnC07 + ev\_øEnC15 + øNando, G = ev\_øEnA02 + ev\_øEnC07 + ev\_øEnC15 + øTaquito + øNando, I = øEnA02 + øEnC07 + øEnC15 + øTaquito + øNando].

**Extended Data Figure 6.** Growth kinetics of phage-resistant mutants. (A) Serial passage evolution of each bacterial isolate (APO57, CPO093, CPO165, CPO448, EA) over five days, showing growth dynamics across six biological replicates (R1-R6). (B) Growth curves of phage-resistant mutants when challenged with individual phage components and *Entelli-02* full cocktail. Each panel shows independent resistant mutants (R1, R2, R3). Positive control denotes bacteria only growth. (C) Comparative growth kinetics of phage-resistant mutants (R1, R2, R3) relative to their corresponding wild-type (WT) parental strains (solid black lines) for five bacterial isolates. Growth is measured as optical density at 600nm (OD600) over 24 hours.

**Extended Data Figure 7.** Growth curves showing the interaction between *Entelli-02* phage cocktail and seven different antibiotics across wild type isolates and phage-resistant mutants. Each panel represents a different isolate-treatment combination, with four treatment categories: antibiotics alone (yellow), bacteria only control (grey), *Entelli-02* -antibiotic combination (teal), and *Entelli-02* (orange). Bacterial strains tested include wild-type isolates (APO57, CPO093, CPO165, CPO448, EA) and their corresponding phage-resistant mutants (two clones, R1 and R2) derived from each component *Entelli-02* phages. Growth is measured as optical density at 600nm (OD600) over 24 hours.

**Extended Data Figure 8. Growth inhibition and *in-vivo* efficacy of phages against two ECC isolates (A-F).** (A) Growth kinetics (OD600) of ECC isolate APO57 over 24 hours following treatment with cocktail-V1 and its phage components. Positive control represents bacterial growth without phage treatment. (B) Growth kinetics (OD600) of APO57 treated with *Entelli-02* and its phage components. (C) *In-vivo* phage titres of different phages recovered from tissues of mice infected with APO57 and treated with *Entelli-02*. Data points represent individual mice (*n* = 6/group × 4 organs or tissue). Box plots show median (centre line), interquartile range (box edges: 25th-75th percentiles), whiskers extending to the most extreme values within 1.5× interquartile range, and outliers as individual points beyond whiskers. Statistical analysis was performed using the Mann-Whitney U test (two-sided) with exact *p*-values to compare medians of phage count between groups. (D) Growth kinetics (OD600) of ECC isolate ALF22D176 challenged with cocktail-V1 and its phage components. (E) Growth kinetics (OD600) of ECC isolate ALF22D176 challenged with *Entelli-02* and its phage components. (F) *In-vivo* phage titres recovered from tissues of mice infected with ALF22D176. Box plots show phage titres in four organs/tissues, with medians, interquartile ranges, and outliers indicated as above. Data points represent individual mice (*n* = 6/group × 4 organs or tissue). Statistical analysis was performed as above. Dotted lines in panels C and F represent detection limits.

**Extended Data Table 1**. Volume and phage titre recovery during phage production

**Extended Data Table 2.** Genome and prophage analysis of *Entelli-02*

**Supplementary Data/Figures**

**Supplementary Figure 1.** Comparative genome analysis and phylogenetic relationships of phages in the phage cocktail. (A) Whole-genome BLAST comparison of the five phages included in the cocktail, visualized using Clinker (https://github.com/gamcil/clinker).Genome sizes (in base pairs) are indicated. (B) Maximum likelihood phylogenetic tree of phages belonging to the *Karamvirus* and *Pseudotevenvirus* genera within the *Straboviridae* family, based on whole-genome alignment. Branch support values are shown as bootstrap percentages. Cocktail phages are highlighted in red.

**Supplementary Figure 2.** Average nucleotide identity of cocktail phages with their close match of the genus *Karamvirus* and *Pseudotevenvirus* genera within *Straboviridae*.

**Supplementary Figure 3.** (A) Host range map of the phages against wild-type (*n* = 36) and phage-resistant mutants (n = 3). The rows show the bacterial isolates, and the columns show the isolated phages. Red means that the phage completely lysed the host and light blue means no lysis of the host. (B) Colonisation of ECC isolate APO57 in different mouse organs 12 hours post intraperitoneal infection. Mice were injected with 8.1 × 10⁵ CFU of APO57 per mouse (dotted line). Bacterial loads were measured in various organs 12 hours post-infection. Mouse 3 cleared the infection, while low-level colonization was observed in mice 1 and 2. (C) Colonisation of ECC isolate APO57 in mouse organs 12 hours post intraperitoneal infection.Mice were injected intraperitoneally with 4.67 × 10⁶ CFU of ECC per mouse (dotted line). At 24 hours post-infection (hpi), all mice showed clinical signs and consistent bacterial colonization across vital organs. Dots represent data form each mouse (*n* = 3). (D) Representative photograph of spot plate assay on ECC isolates and classification of complete and partial lysis due to phage infection.

**Supplementary Data 1.** List of isolates collection

**Supplementary Data** **2.** Comprehensive list of single nucleotide polymorphisms and nucleotide variants detected in phage-resistant mutants.

**Supplementary Table 1.** Plasmids and primers used in the complementation experiments