Supplementary Methods:

Epidemiological modelling of phage dynamics

We develop an epidemiological model to understand the joint dynamics of both virulent and temperate phages in a bacterial host population with a functional CRISPR-Cas system. Initially, a fully susceptible bacterial population is inoculated with 10^4 virions. Like in our batch culture experiments, we model the sequential transfer of the community after transferring 1% of the population every day into a new environment with fresh medium. We contrast two different scenarios that differ only in the initial composition of the phage inoculum.

Scenario 1: Competition between *related* phages with virulent and temperate life cycles

Following the experiment carried out in our study (Fig. 2a,b) we assume that the phage inoculum is composed of two variants of a single phage species: a temperate strain (the density of this strain is noted $V_A(t)$), and a virulent strain (the density of this strain is noted $V_V(t)$). Both strains can infect susceptible bacteria (the density of susceptible bacteria is noted $S(t)$). Upon infection, three different outcomes are possible:

(i) Because the two viruses are related, they share the same genome (apart from the gene controlling lysis/lysogeny) and the bacteria can evolve CRISPR resistance against both virus types (the density of resistant bacteria is noted $R(t)$) with a probability of acquisition A.

(ii) The phage infection leads to the lysis of the infected cell and produces a burst of B new virions. The infection by the virulent phage always results in the lysis of the bacteria but the infection by the temperate phage only leads to lysis with a probability $1-\phi$.

(iii) With probability ϕ, the infection with the temperate phage results in the integration of the virus in the bacterial genome which yields a lysogenic bacterium (the density of lysogenic bacteria is noted $L(t)$).

When lysogens reproduce, they transmit the temperate phage vertically. Note that superinfection inhibition prevents both the temperate and the virulent phages from re-infecting lysogenic bacteria (because both phages are assumed to be related). The prophage in the lysogenic bacterium can reactivate and lyse host cells. Imperfect targeting of the prophage by CRISPR immunity is assumed to yield large induction rates α_{CR} of the prophage. Lysogenic bacteria can lose the CRISPR locus with a rate μ (the density of lysogenic bacteria with an inactive CRISPR is noted $L_{KO}(t)$). Prophages in these lysogenic bacteria are no longer targeted by CRISPR and have a lower induction rate $\alpha_{KO} < \alpha_{CR}$.

The above life cycle yields the following set of differential equations (see Supplementary Table 1 for the definition of the parameters of this model):

$$\dot{S}(t) = r\big(1 - T(t)\big)S(t) - abS(t)V(t) - mS(t) \quad (1)$$

$$\dot{R}(t) = abA(1-\theta)S(t)V(t) + r\big(1 - T(t)\big)R(t) - mR(t)$$

$$\dot{L}(t) = ab\big(1 - A(1-\theta)\big)\phi S(t)V_A(t) + \rho(1-\mu)\big(1 - T(t)\big)L(t) - (\alpha_{CR}(1-\theta) + \alpha_{KO}\theta + m)L(t)$$

$$\dot{L}_{KO}(t) = \rho\big(1 - T(t)\big)\big(\mu L(t) + L_{KO}(t)\big) - (\alpha_{KO} + m)L_{KO}(t)$$

$$\dot{V}_A(t) = ab\big(1 - A(1-\theta)\big)(1-\phi)S(t)V_A(t)B + (\alpha_{CR}(1-\theta) + \alpha_{KO}\theta)L(t)B + \alpha_{KO}L_{KO}(t)B - (aT(t) + m_V)V_A(t)$$

$$\dot{V}_V(t) = ab\big(1 - A(1-\theta)\big)S(t)V_V(t)B - (aT(t) + m_V)V_V(t)$$

with: $T(t) = S(t) + R(t) + L(t) + L_{KO}(t)$ and $V(t) = V_A(t) + V_V(t)$.

Note that the parameter θ refers to the ability for the phage to produce an anti-CRISPR protein (Acr) that prevents both the evolution of CRISPR resistance and immunity against the prophage in lysogenic cells. We plot the dynamics of bacteria and phages across transfers with a wildtype phage (Extended Data Fig. 6a-d) and an Acr-phage (Extended Data Fig. 6e-h). These dynamics are very consistent with the experimental results (compare with Fig. 2a,b). In particular, we recover the short-term increase in the frequency of the virulent phage during the initial epidemic. In addition, we do recover the increase in frequency of bacteria with an inactive CRISPR when the phage does not encode an Acr, but not when the phage encodes an Acr.

Scenario 2: Competition between unrelated phages with virulent and temperate life cycles

In this second scenario we assume that the virulent and the temperate viruses are unrelated. This has two main consequences. First, CRISPR immunity can be specific to each strain (after the acquisition of a spacer targeting one strain or the other). We thus have to consider three different types of resistant bacteria (see Table S1 for the definition of the parameters of this model):

(1) bacteria resistant to the temperate virus only (the density of these bacteria is noted $R_A(t)$);

(2) bacteria resistant to the virulent virus only (the density of these bacteria is noted $R_V(t)$);

(3) bacteria resistant to both temperate and virulent viruses after the acquisition to two spacers, one against each virus type (the density of these bacteria is noted $R_{AV}(t)$),

Second, a lysogenic bacterium can be superinfected by the virulent phage.

This yields a modified set of differential equations:

$$\dot{S}(t) = r\big(1 - T(t)\big)S(t) - abS(t)V(t) - mS(t) \quad (2)$$

$$\dot{R}_A(t) = abA(1-\theta)S(t)V_A(t) + r\big(1 - T(t)\big)R_A(t) - (abV_V(t) + m)R_A(t)$$

$$\dot{R}_V(t) = abA(1-\theta)S(t)V_V(t) + r\big(1 - T(t)\big)R_V(t) - (abV_A(t) + m)R_V(t)$$

$$\dot{R}_{AV}(t) = abA(1-\theta)\big(R_V(t)V_A(t) + R_A(t)V_V(t)\big) + r\big(1 - T(t)\big)R_{AV}(t) - mR_{AV}(t)$$

$$\dot{L}(t) = ab\big(1 - A(1-\theta)\big)\phi S(t)V_A(t) + \rho(1-\mu)\big(1 - T(t)\big)L(t) - (\alpha_{CR}(1-\theta) + \alpha_{KO}\theta + m)L(t) - abL(t)V_V(t)$$

$$\dot{L}_V(t) = abA(1-\theta)L(t)V_V(t) + \rho(1-\mu)\big(1 - T(t)\big)L_V(t) + ab\big(1 - A(1-\theta)\big)\phi R_V(t)V_A(t) - (\alpha_{CR}(1-\theta) + \alpha_{KO}\theta + m)L_V(t)$$

$$\dot{L}_{KO}(t) = \rho\big(1 - T(t)\big)\Big(\mu\big(L(t) + L_V(t)\big) + L_{KO}(t)\Big) - abL_{KO}(t)V_V(t) - (\alpha_{KO} + m)L_{KO}(t)$$

$$\dot{V}_A(t) = ab\big(1 - A(1-\theta)\big)(1-\phi)(S(t) + R_V)V_A(t)B + \big((\alpha_{CR}(1-\theta) + \alpha_{KO}\theta)L(t) + \alpha_{KO}L_{KO}(t)\big)B - (aT(t) + m_V)V_A(t)$$

$$\dot{V}_V(t) = ab\Big(\big(1 - A(1-\theta)\big)\big(S(t) + R_A + L(t)\big) + L_{KO}(t)\Big)V_V(t)B - (aT(t) + m_V)V_V(t)$$

with: $T(t) = S(t) + \underbrace{R_A(t) + R_V(t) + R_{AV}(t)}_{R_T(t)} + \underbrace{L(t) + L_V(t) + L_{KO}(t)}_{L_T(t)}$.

This scenario yields more complex dynamics because it can maintain transient polymorphism in both bacteria and phage populations through negative frequency dependence (Extended Data Fig. 9h, j, l, n). The presence of a virulent phage in the population maintains the fitness benefit associated with carrying an active CRISPR-Cas system (note how the selection for CRISPR is associated with the high frequency of the virulent phage). Yet, after the spread of resistant bacteria, the virulent phage is outcompeted by the temperate phage and, among the lysogens, there is selection for the loss of the CRISPR-Cas system.

To match the biology of our experimental system we also modeled a situation where CRISPR-Cas cannot acquire immunity against the virulent phage. Yet, we allow the evolution of costly surface mutations that block the infection by the virulent phage. This yields the following set of differential equations (where the subscript V refers to surface mutation blocking the virulent phage):

$$\dot{S}(t) = r(1-\mu_R)\big(1 - T(t)\big)S(t) - abS(t)V(t) - mS(t) \quad (3)$$

$$\dot{R}_A(t) = abA(1-\theta)S(t)V_A(t) + r(1-\mu_R)\big(1 - T(t)\big)R_A(t) - (abV_V(t) + m)R_A(t)$$

$$\dot{R}_V(t) = r\mu_R\big(1 - T(t)\big)S(t) + r(1-c)\big(1 - T(t)\big)R_V(t) - (abV_A(t) + m)R_V(t)$$

$$\dot{R}_{AV}(t) = abA(1-\theta)R_V(t)V_A(t) + r\mu_R\big(1 - T(t)\big)R_A(t) + r(1-c)\big(1 - T(t)\big)R_{AV}(t) - mR_{AV}(t)$$

$$\dot{L}(t) = ab\big(1 - A(1-\theta)\big)\phi S(t)V_A(t) + \rho(1-\mu)(1-\mu_R)\big(1 - T(t)\big)L(t) - (\alpha_{CR}(1-\theta) + \alpha_{KO}\theta + m)L(t) - abL(t)V_V(t)$$

$$\dot{L}_V(t) = \rho(1-\mu)\mu_R\big(1 - T(t)\big)L(t) + \rho(1-\mu)(1-c)\big(1 - T(t)\big)L_V(t) + ab\big(1 - A(1-\theta)\big)\phi R_V(t)V_A(t) - (\alpha_{CR}(1-\theta) + \alpha_{KO}\theta + m)L_V(t)$$

$$\dot{L}_{KO}(t) = \rho(1-\mu_R)\big(1-T(t)\big)\big(\mu L(t) + L_{KO}(t)\big) - abL_{KO}(t)V_V(t) - (\alpha_{KO} + m)L_{KO}(t)$$

$$\dot{L}_{KO,V}(t) = \rho\big(1-T(t)\big)\Big(\mu_R L_{KO}(t) + \mu(1-c)L_V(t) + (1-c)L_{KO,V}(t)\Big) - (\alpha_{KO} + m)L_{KO,V}(t)$$

$$\dot{V}_A(t) = ab\big(1-A(1-\theta)\big)(1-\phi)(S(t)+R_V)V_A(t)B + \Big((\alpha_{CR}(1-\theta) + \alpha_{KO}\theta)\big(L(t)+L_V(t)\big) + \alpha_{KO}\Big(L_{KO}(t)+L_{KO,V}(t)\Big)\Big)B - (aT(t)+m_V)V_A(t)$$

$$\dot{V}_V(t) = ab\Big(\big(1-A(1-\theta)\big)\big(S(t)+R_A+L(t)\big) + L_{KO}(t)\Big)V_V(t)B - (aT(t) + m_V)V_V(t)$$

We observe very similar dynamics as in the previous scenario: the spread of multi-resistant hosts, the fixation of the temperate phage and the loss of CRISPR. However, when the cost of resistance against the virulent phage is high, the virulent phage can be maintained in the population because a polymorphism is maintained between susceptible and resistant bacteria by negative frequency dependent selection (Extended Data Fig. 9i, k, m, o). Note however, that the presence of the virulent phage does not maintain CRISPR because in this scenario, bacteria do not rely on CRISPR immunity to resist infection by the virulent phage.

Overall conclusion of modelling*:* Our model tracks both the evolution of phages (life cycle, evolution of *acr*) and bacteria (evolution of CRISPR immunity or surface mutations). The good fit between the output of the model (Extended Data Fig. 6 and 9h-o) and our experimental results (Fig. 2 and Extended Data Fig. 9a-g, respectively) supports the hypothesis that the cost of virulence is driving the evolution of phage life cycle (lytic versus lysogenic life cycle) and the cost of auto-immunity in lysogenic bacteria is driving the evolutionary loss of CRISPR-Cas in bacteria. Besides, the model allows to explore other scenarios such as the competition between unrelated viruses. Most scenarios lead to the evolutionary loss of CRISPR-Cas in lysogens. Indeed, in our model, once resistance against virulent phage is present (i.e. CRISPR-based or surface mutant), there is no need to invest in immunity because it carries high fitness costs in lysogenic bacteria.

Note that our experiments (and our model) describe the evolution of a closed system. More complex scenarios, for example where a bacterial population is constantly exposed to new unrelated virulent phages (e.g. immigrating from other locations), remain to be explored.

Supplementary Table 1: Parameters of the model with default values

Parameter	Definition	Default value
r	Growth rate of uninfected cells	$0.7\ h^{-1}$
ρ	Growth rate of infected cells	$0.7\ h^{-1}$
K	Carrying capacity	$10^9\ cells$
B	Burst size	$50\ virion.cell^{-1}$
a	Adsorption constant	$5\ \times 10^{-10}\ h^{-1}.cell^{-1}$
b	Probability of fusion after adsorption	10^{-1}
ϕ	Probability of genome integration	0.5
A	Probability of acquisition of a new spacer targeting the phage	10^{-4}
θ	Efficacy of CRISPR inhibition by Acr	0 (wildtype phage) 1 (Acr-phage)
α_{CR}	Induction rate of the prophage when the CRISPR immunity targets the prophage	$5\ 10^{-2}\ h^{-1}$
α_{KO}	Induction rate of the prophage when the CRISPR immunity does not target the prophage	$10^{-3}\ h^{-1}$
m	Mortality rate of bacteria	$0\ h^{-1}$
m_V	Mortality rate of virions	$0\ h^{-1}$
μ	Mutation towards CRISPR KO	10^{-4}
μ_R	Mutation towards *sm* resistance against the lytic virus (see equation (3))	10^{-4}
c	Fitness cost associated with sm resistance against the lytic virus (see equation (3))	0.5

Bioinformatic analysis of widespread priming off temperate phages

The maladaption hypothesis predicts that bacteria that continue to benefit from prophages, yet contain mismatched spacers against the prophage, would be under pressure to reduce or lose CRISPR-Cas function. Specifically, bacteria with spacers having near matches within the prophage would be maladapted (e.g. PA14 CRISPR2 spacer 1/DMS3) as self-targeting or self-priming could occur. If this were widespread, we predict that (i) spacers matching prophages would be common within the pan-spacer repertoire for a genus (ii) genomes with self-targeting or self-priming spacers would either have *acr(s),* or that the CRISPR-Cas system would be non-functional.

(i) Spacers matching temperate phages are common

To test if it is common for bacteria to possess pre-existing spacers that may promote priming off temperate phages, we tested a set of all spacers from 171,361 bacterial genomes against a database of prophage sequences[21]. Genomes from RefSeq 93 (n=136,507) were supplemented with Genbank genomes absent from RefSeq (giving a total of 171,361). CRISPR arrays were identified using CRISPRDetect[34]; 1,239,937 spacers were collected (spacers of atypical size were removed as potential artefacts) and identified by the genomic contig, position and species. A set of prophage sequences from the PHAST[21] database were de-replicated and split into 133 genera from 6570 complete genomes (total n=19,996). For each bacterial genus in which prophages were found, we searched for prophage targets using a non-redundant set of spacers (generated by CD-HIT-dup, default parameters) from species within the same genus (using BLASTN; blastn-short, e-value cut-off=0.001, DB-size=10000, word-size=7, gap-open penalty=10, gap-extension=-2, mismatch=-1, match reward=1). A total of 85,931 hits with 0-5 mismatches were identified within all genera (e.g. from any *Streptococcus* spacer against any *Streptococcus* prophage there were 10,850 hits).

Compared with a negative control, where the non-redundant prophage database was hexanucleotide shuffled 10 times to reveal the number of random hits (276 +/- 30), there was a significant increase in within-genus prophage hits from spacers with either 0 mismatches or 1-5 mismatches (Extended Data Fig. 7a). Next, the distributions of mismatch frequencies were computed per genus for those with over 500 within genus spacer-phage matches (0-5 mismatches). All genera had significantly more matches compared with a shuffled dataset (Extended Data Fig. 7b). The distributions of number of mismatches differed between genera. For example, *Pseudomonas* spp. and *Mycobacterium* spp. had many exact matches but other genera displayed more evenly distributed mismatch frequencies (Extended Data Fig. 7c). In conclusion, it is common for many bacterial genera to contain pre-existing spacers that are likely to either provide interference or priming off invading temperate phage genomes. These data support maladaptation hypothesis of CRISPR-Cas against temperate phages.

(ii) Self-targeted and self-primed genomes are enriched for Acr(s).

Our experimental data indicated that the maladaptive effects of CRISPR-Cas against temperate phages can be countered through Acr proteins or be tolerated due to CRISPR-Cas inactivation or

loss. First, we sought to further test this finding by searching sequenced bacterial genomes for self-targeting or self-priming and whether this correlated with the presence of *acr* genes. Strains of *P. aeruginosa* provide a good test set since there are many sequenced isolates, several *acr* genes have been identified, and prophages are common. In addition, the main CRISPR-Cas types are I-E and I-F, where priming has been demonstrated experimentally.

To test if self-targeting leads to increased Acr presence, CRISPR arrays were identified using CRISPRDetect in 98 of 168 *P. aeruginosa* genomes. CRISPRCasFinder[35] was used to assign whether *cas* gene sets were complete and only those strains analysed further. These strains were characterized as either containing no self-targets or self-matches using the self-targeting spacer searcher (STSS)[36], with the BLASTN parameters modified to permit up to 5 mismatches (0-5). Next, *acr* genes were identified by building hmm using proteins with >40% identity to the set of known *acr* genes from STSS. We observed a statistically significant enrichment for increased frequencies of *acr* genes in the presence of self-targeting spacers, in support of our experimental data (Extended Data Fig. 8a). An even stronger association between *acr* genes and self-matches was observed when the analysis considered self-targets within prophages (identified using PHASTER[37]) (Extended Data Fig. 8b).

Note that further analysis of this dataset did not reveal increased frequencies of *cas* gene deletions from genomes with priming spacers against prophages (data not shown). This is likely explained by (i) the limited number of *P. aeruginosa* genomes that that match our search criteria, (ii) genetic linkage that causes deletions to typically encompass both *cas* genes and CRISPR arrays (Extended Data Fig. 4c-e), and (iii) presence of unidentified *acr* genes in prophage genomes that are not detected by our search algorithm due to sequence divergence from currently described *acr* genes.

References :

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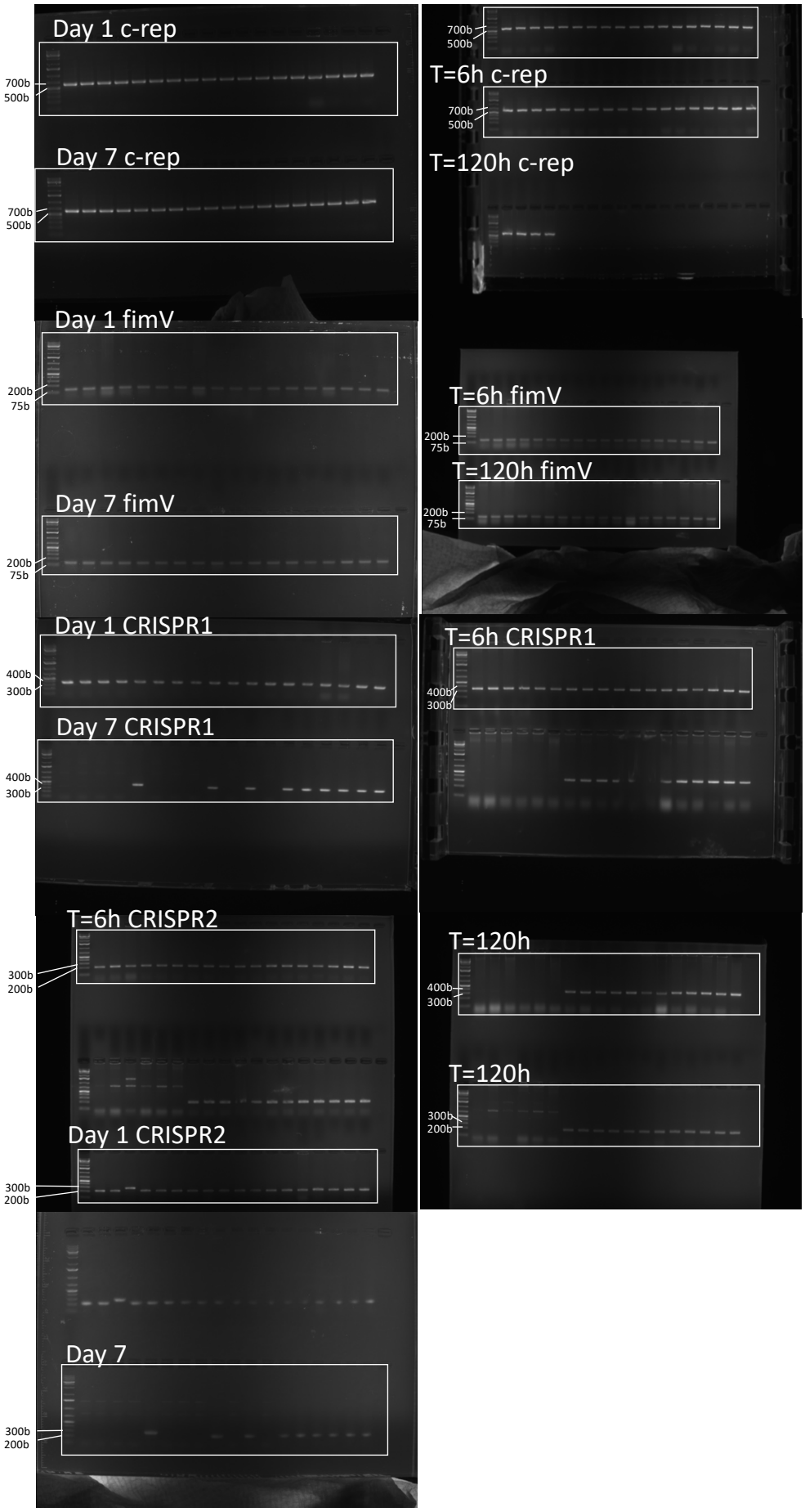

Supplementary Figure 1 : Source data images for PCR amplification results presented in Figure 4a-d. Cropped areas are indicated by white boxes.