Electronic appendix to Bacteriophage-Mediated Competition in *Bordetella* Bacteria

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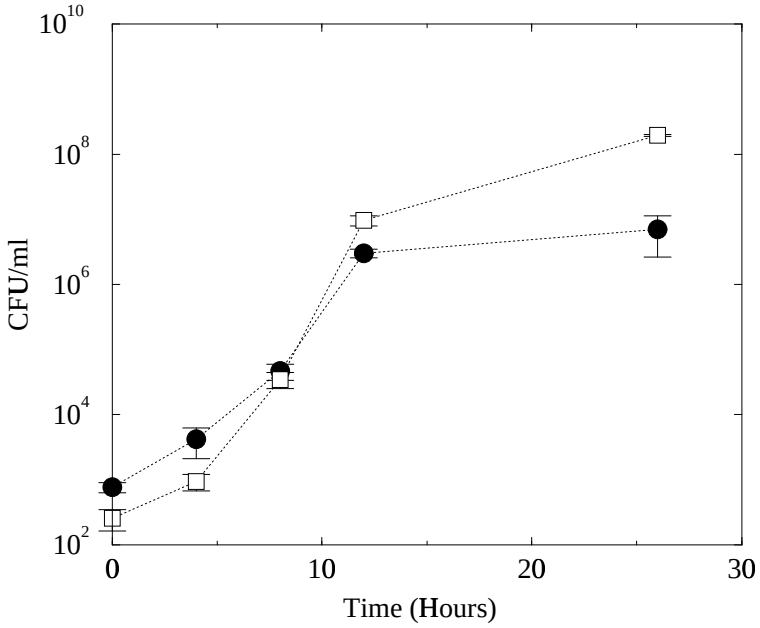

Figure 1: *In vitro* evidence of the spontaneous release of phage. The strain carrying the lysogenic phage (Bb::Φ, open squares) outnumbers the susceptible strain (BbGm, filled circles) without exogenously added phage. The error bars denote the standard deviation of the number of the colony forming units (CFU) of each bacterial strain.

1 Spontaneous Phage Induction

The spontaneous induction of the phage from lysogens is inevitable, yet can take place at different time points, which could be more than 24 hours after co-culturing two strains. (Note that the bacteria grow in the log growth phase for the first 24 hours.) Thus in Figure 3, 4 and 5 in the main text we added exogenous lysogenic phage to induce phage-mediated competition at earlier time, while bacteria grow in the log growth phase. Here we present in vitro evidence of phage-mediated competition in the absence of exogenous phage as shown on appendix Fig. 1. The strain (Bb::Φ) carrying the phage and the susceptible strain (BbGm) are co-cultured without exogenously added phage. The initial ratio of the strain Bb::Φ to the strain BbGm is reversed around 8-12 hours, which is mediated by the lysogenic phage spontaneously

released from Bb::Φ. Based on this result, we use the spontaneous lysis rate $\delta = 5.4 \times 10^{-4}$ in the numerical simulations.

2 Theoretical Model of a Generalized Phage-Mediated Competition

Our primary model of phage-mediated competition depicted in Figure 1 in the main text is limited to the case where one host is perfectly phage-resistant and the other is phage-susceptible. However in general cases both invading and resident hosts can be susceptible to phage infection but with differential susceptibilities. Here we model the invasion of a host A endogenously and exogenously carrying the phage to another host B. The hosts are characterized by the differential susceptibilities κ_A and κ_B against the phage, and the phage pathologies P_A and P_B. We rescale and non-dimensionalize the variables, $i_j = I_j/S_B(0)$, $s_j = S_j/S_B(0)$, $l_j = L_j/S_B(0)$, $\phi = \Phi/S_B(0)$, $n_{max} = N_{max}/S_B(0)$, $\tau = at$, $\alpha = \delta/a$, $\beta = \lambda/a$ and $\gamma_j = \kappa_j S_B(0)/a$, where $j = A, B$. Then we obtain

$$\begin{aligned}
\frac{ds_j}{d\tau} &= (1 - n/n_{max} - \gamma_j\phi)s_j \qquad (1)\\
\frac{di_j}{d\tau} &= (1 - P_j)\gamma_j\phi s_j + (1 - n/n_{max} - \alpha)i_j\\
\frac{dl_j}{d\tau} &= P_j\gamma_j\phi s_j - \beta l_j\\
\frac{d\phi}{d\tau} &= \chi(\alpha\sum_j i_j + \beta\sum l_j) - \sum_j \gamma_j\phi s_j
\end{aligned}$$

where $n = \sum_j (i_j + s_j + l_j)$ and j =A,B. The initial conditions for appendix Eq. (1) are $i_B(0) = l_A(0) = l_B(0) = 0$, $s_B(0) = 1$, $s_A(0) > 0$, $i_A(0) > 0$ and $\phi(0) \geq 0$. The above general model and appendix Eq. (1) are reduced to the primary model depicted in Figure 1 and Equation (1) in the main text when $P_A = 0$, $\gamma_A = 0$ and $S_A(0) = 0$.

2.1 Derivation of the Invasion Criterion

CASE I: If $\phi(0) = 0$ and $\alpha = 0$, then the 7-dimensional ODE system reduces to

$$\begin{aligned} \frac{ds_j}{d\tau} &= (1 - (\sum_j s_j + i_A)/n_{max})s_j, \\ \frac{di_A}{d\tau} &= (1 - (\sum_j s_j + i_A)/n_{max})i_A. \end{aligned}$$

where $j = A, B$ and $i_B(\tau) = l_A(\tau) = l_B(\tau) = 0$ for $\tau > 0$. All populations s_j and i_A will grow with the same growth rate and the initial ratio $i_A(0) : s_A(0) : s_B(0)$ remains unchanged to be $i_A(\tau) : s_A(\tau) : s_B(\tau)$ for all $\tau > 0$. In other words, there will be no pathogen-mediated competition.

CASE II: When $\phi(0) > 0$, we can derive the invasion criteria in Equations (2) and (3) in the main text in the limit $\gamma_j \to \infty$ and $\beta \to \infty$.

CASE II-A: $\tau = 0$ **Limit.**

An appropriate timescale near $\tau = 0$ is $\sigma = \tau/\epsilon$ where $\epsilon = 1/\beta$. The effect of the transformation $\sigma = \tau/\epsilon$ is to magnify the neighborhood of $\tau = 0$, i.e., for a fixed $0 < \tau \ll 1$, we have $\sigma \gg 1$ as $\epsilon \to 0$. With the transformations $\sigma = \tau/\epsilon$, $s_j(\tau;\epsilon) = \hat{s}_j(\sigma;\epsilon)$, $i_j(\tau;\epsilon) = \hat{i}_j(\sigma;\epsilon)$, $l_j(\tau;\epsilon) = \hat{l}_j(\sigma;\epsilon)$, $\phi_j(\tau;\epsilon) = \hat{\phi}_j(\sigma;\epsilon)$, $\xi_j = \gamma_j/\beta$, appendix Eq. (1) become

$$\begin{aligned} \frac{d\hat{s}_j}{d\sigma} &= \epsilon(1 - n/n_{max})\hat{s}_j - \xi_j\hat{\phi}\hat{s}_j \qquad (2) \\ \frac{d\hat{i}_j}{d\sigma} &= (1 - P_j)\hat{\phi}\hat{s}_j\xi_j + \epsilon(1 - n/n_{max} - \alpha)\hat{i}_j \\ \frac{d\hat{l}_j}{d\sigma} &= P_j\hat{\phi}\hat{s}_j\xi_j - \hat{l}_j \\ \frac{d\hat{\phi}}{d\sigma} &= \chi\sum_j \hat{l}_j - \sum_j \xi_j\hat{\phi}\hat{s}_j + \epsilon\chi\alpha\sum_j \hat{i}_j \end{aligned}$$

In a regular perturbation theory (Murray 1980) the solutions are expanded in order of ϵ, $\hat{s}_j(\sigma;\epsilon) = \sum_{n=0}\epsilon^n\hat{s}_{j,n}(\sigma)$, $\hat{i}_j(\sigma;\epsilon) = \sum_{n=0}\epsilon^n\hat{i}_{j,n}(\sigma)$, $\hat{l}_j(\sigma;\epsilon) = \sum_{n=0}\epsilon^n\hat{l}_{j,n}(\sigma)$, $\hat{\phi}(\sigma;\epsilon) = \sum_{n=0}\epsilon^n\hat{\phi}_n(\sigma)$. We now set $\epsilon = 0$ to get

$O(1)$ system,

$$\frac{d\hat{s}_{j,0}}{d\sigma} = -\xi_j \hat{\phi}_0 \hat{s}_{j,0} \quad (3)$$

$$\frac{d\hat{i}_{j,0}}{d\sigma} = (1-P_j)\xi_j \hat{\phi}_0 \hat{s}_{j,0} \quad (4)$$

$$\frac{d\hat{l}_{j,0}}{d\sigma} = P_j \xi_j \hat{\phi}_0 \hat{s}_{j,0} - \hat{l}_{j,0} \quad (5)$$

$$\frac{d\hat{\phi}_0}{d\sigma} = \chi \sum_j \hat{l}_{j,0} - \sum_j \xi_j \hat{\phi}_0 \hat{s}_{j,0} \quad (6)$$

with the initial conditions $\hat{i}_{B,0}(0)=\hat{l}_{A,0}(0)=\hat{l}_{B,0}(0) = 0$, $\hat{s}_{B,0}(0) = 1$, $\hat{s}_{A,0}(0) \geq 0$, $\hat{i}_{A,0}(0) > 0$ and $\hat{\phi}_0(0) > 0$.

By integrating appendix Eq. (3) and (4), we obtain

$$\hat{s}_{j,0}(\sigma) = \hat{s}_{j,0}(0) Exp(-\int_0^\sigma \xi_j \hat{\phi}_0(x)dx), \quad (7)$$

$$\hat{i}_{j,0}(\sigma) = \hat{i}_{j,0}(0) + (1-P_j)\hat{s}_{j,0}(0)\int_0^\sigma F_j(y)dy \quad (8)$$

where $F_j(y) = \xi_j \hat{\phi}_0(y) Exp(-\int_0^y \xi_j \hat{\phi}_0(x)dx)$. Appendix Eq. (5) and (6) can be rewritten

$$\frac{d\hat{l}_{j,0}}{d\sigma} = P_j \hat{s}_{j,0}(0) F_j(\sigma) - \hat{l}_{j,0}(\sigma) \quad (9)$$

$$\frac{d\hat{\phi}_0}{d\sigma} = \chi \sum_j \hat{l}_{j,0}(\sigma) - \sum_j \hat{s}_{j,0}(0) F_j(\sigma) \quad (10)$$

Lemma 1. *$\hat{\phi}_0(\sigma)$ is strictly positive for $\sigma \geq 0$ if $\hat{\phi}_0(0) > 0$ and $\chi P_j > 1$.*

Proof. Let $Z(\sigma) = \hat{\phi}_0(\sigma) + \chi \sum_j \hat{l}_{j,0}(\sigma)$. $Z(0) > 0$ because $\hat{\phi}_0(0) > 0$. Because $\hat{i}_{j,0}(\sigma)$, $\hat{s}_{j,0}(\sigma)$, $\hat{l}_{j,0}(\sigma)$ and $\hat{\phi}_0(\sigma)$ are non-negative for $\sigma \geq 0$, $\frac{dZ}{d\sigma} = \sum_j (\chi P_j - 1) s_j(0) F_j(\sigma) \geq 0$ if $\chi P_j > 1$. Therefore $Z(\sigma)$ is strictly positive and non-decreasing for all $\sigma \geq 0$. Suppose now that there exists $\sigma_o > 0$ such that $\hat{\phi}_0(\sigma) = 0$ for $\sigma > \sigma_o$. Then both $F_j(\sigma)$ and $\hat{l}_{j,0}(\sigma)$ will become zero for $\sigma > \sigma_o$, resulting in $Z(\sigma) = 0$ for $\sigma > \sigma_o$. This contradicts that $Z(\sigma)$ is strictly positive for all $\sigma \geq 0$. Therefore $\hat{\phi}_0(\sigma) > 0$ for all $\sigma \geq 0$. □

Lemma 2. *$F_j(y)$ is strictly positive for $y > 0$ and $F_j(y)$ asymptotically approaches zero as $y \to \infty$.*

Proof. Strict positiveness of $F_j(y)$ for $y > 0$ follows from lemma 1. For the second part, we divide the integration in the exponent into two parts,

$$\int_0^y dx\xi_j\hat{\phi}_0(x) = \int_0^{y-w} dx\xi_j\hat{\phi}_0(x) + \int_{y-w}^y dx\xi_j\hat{\phi}_0(x)$$

where $y \gg 1$ and $w \in (0, y)$ must be such that $\hat{\phi}_0(x)$ is either non-decreasing or non-increasing in the interval $x \in [y-w, y]$. Then there exists $\lambda \in [0, 1]$ such that $\int_{y-w}^y dx\xi_j\hat{\phi}_0(x) = [\lambda\xi_j\hat{\phi}_0(y) + (1-\lambda)\xi_j\hat{\phi}_0(y-w)]w$. By defining $\hat{\phi}_{min} \equiv min_{x\geq 0}\hat{\phi}_0(x)$, $\int_0^{y-w} dx\xi_j\hat{\phi}_0(x) \geq (y-w)\xi_j\hat{\phi}_{min}$ and $\int_{y-w}^y dx\xi_j\hat{\phi}_0(x) \geq [\lambda\xi_j\hat{\phi}_0(y) + (1-\lambda)\xi_j\hat{\phi}_{min}]w$. Then we can obtain

$$\begin{aligned} F_j(y) &= \xi_j\hat{\phi}_0(y)Exp(-\int_0^y dx\xi_j\hat{\phi}_0(x)) \\ &\leq \xi_j\hat{\phi}_0(y)e^{-\lambda w\xi_j\hat{\phi}_0(y)}e^{-(y-\lambda w)\xi_j\hat{\phi}_{min}} \\ &\leq \frac{1}{\lambda w}e^{-(y-\lambda w)\xi_j\hat{\phi}_{min}-1} \end{aligned}$$

where in the third line we used $xe^{-x} \leq e^{-1}$for all $x > 0$. As $y \to \infty$, $F_j(y) \to 0$. □

Lemma 3. *Let $G_j(\sigma) = \int_0^\sigma F_j(y)dy$. $G_j(\sigma)$ asymptotically approaches 1 as $\sigma \to \infty$.*

Proof.

$$\begin{aligned} G_j(\sigma) &= \int_0^\sigma dy\xi_j\hat{\phi}_0(y)Exp(-\int_0^y dx\xi_j\hat{\phi}_0(x)) \\ &= \int_0^\sigma dyH_j'(y)e^{-H_j(y)} \\ &= 1 - e^{-H_j(\sigma)} \end{aligned}$$

where $H_j(y) = \int_0^y dx\xi_j\hat{\phi}(x)$ and $H_j(0) = 0$. Using $H_j(\sigma) \geq \sigma\xi_j\hat{\phi}_{min}$, $e^{-H_j(\sigma)} \leq e^{-\sigma\xi_j\hat{\phi}_{min}}$ for $\sigma > 0$. As $\sigma \to \infty$, $e^{-H_j(\sigma)} \to 0$ and $G_j(\sigma) \to 1$. □

Using the above lemmas, we know that both $\hat{s}_{j,0}(\sigma)$ and $\hat{l}_{j,0}(\sigma)$ approaches zero as $\sigma \to \infty$ while keeping $0 < \tau \ll 1$. In the limit of $\sigma \to \infty$ we obtain, using appendix Eq. (8) and initial conditions, $\hat{s}_{B,0}(0) = 1$, $\hat{i}_{B,0}(0) = \hat{l}_{A,0}(0) = \hat{l}_{B,0} = 0$, and

$$\begin{aligned} r_{AB}(\sigma) &= \frac{\hat{i}_{A,0}(\sigma) + \hat{s}_{A,0}(\sigma) + \hat{l}_{A,0}(\sigma)}{\hat{i}_{B,0}(\sigma) + \hat{s}_{B,0}(\sigma) + \hat{l}_{B,0}(\sigma)} \\ &= \frac{(1-P_A)\hat{s}_{A,0}(0) + \hat{i}_{A,0}(0)}{(1-P_B)} \end{aligned} \tag{12}$$

where $r_{AB}(0) = \hat{i}_{A,0}(0) + \hat{s}_{A,0}(0)$. When $\hat{s}_{A,0}(0) \gg \hat{i}_{A,0}(0)$, Equation (3) in the main text is recovered, in the limit of $\gamma_j \to \infty$, $\beta \to \infty$ and $\sigma \to \infty$ while keeping $0 < \tau \ll 1$,

$$r_{AB}(\sigma) = r_{AB}(0)(1-P_A)/(1-P_B) \tag{13}$$

Moreover when $P_A = 0$, $\gamma_A = 0$ and $\hat{s}_{A,0}(0) = 0$, Equation (2) in the main text is recovered, in the limit of $\gamma_B \to \infty$, $\beta \to \infty$ and $\sigma \to \infty$ while keeping $0 < \tau \ll 1$,

$$r_{AB}(\sigma) = r_{AB}(0)/(1-P_B) \tag{14}$$

In case II-B we will prove that these ratios in appendix Eqs. (13) and (14) remain unchanged in the limit of $\tau = \infty$.

CASE II-B: $\tau = \infty$ limit.

To study the long time limit, we go back to appendix Eq. (1). Using the quasi-steady state approximation of the third equation in appendix Eq. (1) $\frac{1}{\beta}\frac{dl_j}{d\tau} = 0 = P_j \phi s_j \gamma_j/\beta - l_j$, in the limit $\gamma_j \to \infty$ and $\beta \to \infty$, and $\chi P_j > 1$, we obtain $\frac{d\phi}{d\tau} = \chi\alpha \sum_j i_j + \phi \sum_j (\chi P_j - 1)\gamma_j s_j \geq 0$ for $\tau \gg 1$ (Equality holds when $\alpha = 0$ and $s_j(\tau) = 0$). Because $\phi(\tau)$ is strictly positive and non-decreasing for $\tau \gg 1$ and $\phi\gamma_j \gg 1$, $\frac{ds_j}{d\tau} = (1 - n/n_{max} - \phi\gamma_j)s_j < 0$ for $\tau \gg 1$. Therefore using $l_j(\tau) = P_j\phi\gamma_j s_j(\tau)/\beta$, $s_j(\tau) = l_j(\tau) = 0$ for $\tau \gg 1$. In the limit of $\beta \to \infty$, $\gamma_j \to \infty$ and $\tau \gg 1$, appendix Eq. (1) reduce to the effective three dimensional ODE

$$\frac{di_j}{d\tau} = (1 - \frac{\sum_j i_j}{n_{max}} - \alpha)i_j$$

$$\frac{d\phi}{d\tau} = \chi\alpha \sum_j i_j$$

Note that the first equation for $i_j(\tau)$ is independent of $\phi(\tau)$. Now if $\alpha \geq 1$, $\frac{di_j}{d\tau} < 0$ for $\tau \gg 1$ and $i_j(\infty) = 0$, which means that both A and B populations go extinct. Otherwise if $0 \leq \alpha < 1$, both $i_A(\tau)$ and $i_B(\tau)$ will grow with the same growth rate. Thus the ratio $r_{AB}(\sigma)$, determined in the limit of $\sigma \to \infty$ while keeping $0 < \tau \ll 1$, remains unchanged in the limit $\tau \gg 1$.

Case III. If $\phi(0) = 0$ and $\alpha > 0$, this is equivalent to case II. Suppose that $\phi(\tau) > 0$ when $\tau > \tau_{min}$ where τ_{min} is the earliest time when the first phage are spontaneously induced. By defining a new time frame $\tau' = \tau - \tau_{min}$ and rescaling all the concentrations by $S_B(\tau_{min})$, case III becomes equivalent to case II.

3 Numerical Investigation of the Invasion Criteria

The invasion criteria in Equations (2) and (3) in the main text are exact in the limit of large infection-induced lysis rate β and contact rate γ with restrictions on $\chi P_j > 1$ and on the spontaneous lysis rate $0 \leq \alpha < 1$. In order to investigate their validity for small β and γ, we perform numerical simulations. First, the linear relationship in Equation (2) in the main text between the phage pathology P and $r_{AB}(0)/r_{AB}(\infty)$ is validated by extensive numerical calculations with 2000 parameter sets where all parameters are selected uniformly from the biologically relevant intervals (see appendix Fig. 2 for detailed information). Note that $\chi P > 1$ is used for numerical calculations. When γ and β are relatively large, i.e., $0.1 < \gamma, \beta < 10$, all data points fall into the linear line $r_{AB}(0)/r_{AB}(\infty) = 1 - P$ as illustrated in appendix Fig. 2. When $0 < \gamma, \beta < 0.1$, the deviation from the linear relationship increases for small phage pathology P. Thus we conclude that the linear relationship in Equation (2) in the main text, $r_{AB}(0)/r_{AB}(\infty) = 1 - P$, is robust to parameter variations and valid for small γ and β.

Next, we also validate the generalized invasion criterion from Equation (3) in the main text numerically with diverse sets of parameters. Appendix Fig. 3 shows that the linear relationship in Equation (4) between $r_{AB}(0)/r_{AB}(\infty)$ and $(1 - P_A)/(1 - P_B)$ is robust against parameter variations. Note that we impose restrictions on $\chi P_j > 1$ and $s_A(0) \gg i_A(0)$ in the numerical calculations. However the linear relationship in Equation (3) in the main text becomes inaccurate when the pathogen is more virulent on the invading

population A than on the resident population B, i.e., when P_A is large and P_B is small.

4 Two phage-mediated competition between two bacterial strains

In this section we investigate the steady state outcome of a general two-phage-mediated competition between two bacterial strains. We show that the invasion criterion obtained for the single lysogenic phage-mediated competition remains unchanged when competition is mediated by two phage strains. We also demonstrate that all the detailed kinetic interactions of a two-phage-mediated competition can be condensed into a single parameter, the effective phage pathology.

We consider a model system where bacterial strains A and B are sensitive to infection by either of two homologous phage strains 1 and 2. Bacteria carrying one phage are immune against infection by another. A small fraction of the population of bacterial strain A carry the phage strain 1 and another small fraction of that population bear the phage strain 2, and thus the bacterial strain A is the source of two phage. A phage strain $m \in \{1, 2\}$, denoted by $\Phi^{(m)}$, has contact rate $\kappa_j^{(m)}$, infection-induced lysis rate $\lambda_j^{(m)}$, spontaneous lysis rate $\delta_j^{(m)}$, and pathology $P_j^{(m)}$, when acting on bacterial strain $j \in \{A, B\}$. We define, rescale and non-dimensionalize the variables as in section 2; susceptible bacterial density $s_j = S_j/S_B(0)$, lysogenic bacterial density $i_j^{(m)} = I_j^{(m)}/S_B(0)$, latent bacterial density $l_j^{(m)} = L_j^{(m)}/S_B(0)$, phage density $\phi^{(m)} = \Phi^{(m)}/S_B(0)$. Other parameters are the maximum carrying capacity $n_{max} = N_{max}/S_B(0)$, the non-dimensionalized time $\tau = at$, the spontaneous lysis rate $\alpha_j^{(m)} = \delta_j^{(m)}/a$, the infection-induced lysis rate

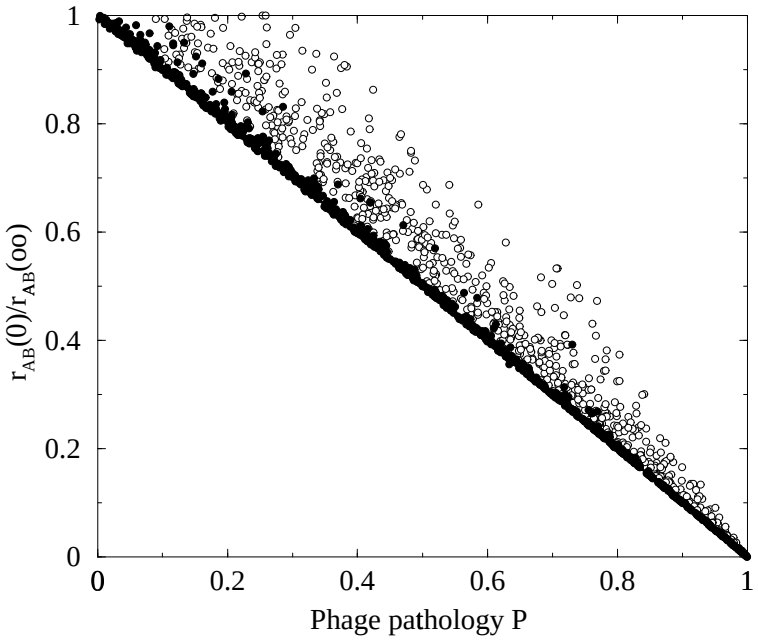

Figure 2: Numerical verification of the invasion criterion in Equation (2) in the main text. A thick solid line is the prediction from Equation (2) in the main text. $r_{AB}(0)/r_{AB}(\infty)$ was numerically evaluated by solving appendix Eq. (1) with 2000 sets of parameters chosen uniformly in the intervals $0 < P < 1$ for phage pathology, $1/P < \chi < 100$ for burst size, $0 < \alpha < 0.5$ for normalized spontaneous induction rate, $0 < I_A(0), \phi(0) < 10 S_B(0)$ for the initial concentrations of infected bacteria A and phage with respect to the initial concentration of susceptible bacteria B. Filled circles represent the data from 1000 sets of parameters with relatively large γ and β ($0.1 < \gamma, \beta < 10$). Open circles are from another 1000 sets of parameters with small γ and β ($0 < \gamma, \beta < 0.1$).

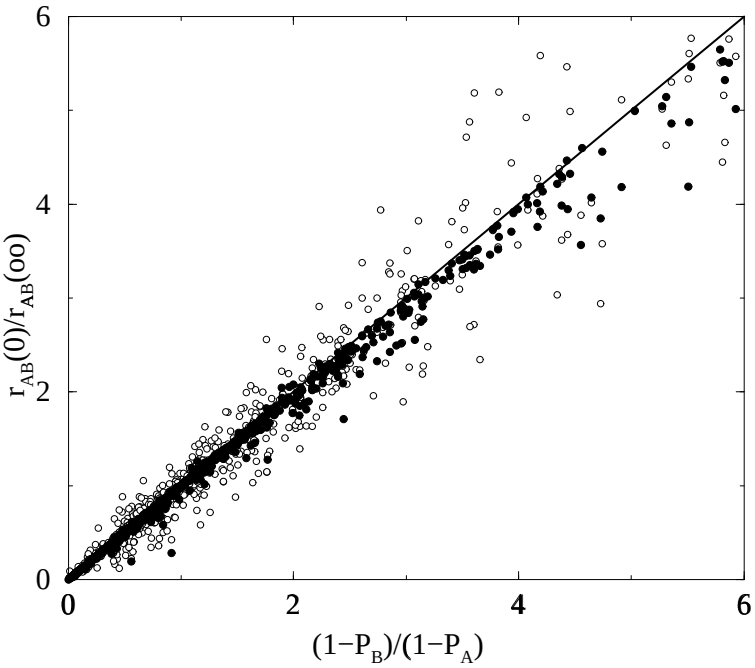

Figure 3: Numerical verification of the generalized invasion criterion in Equation (3) in the main text. $r_{AB}(0)/r_{AB}(\infty)$ was numerically evaluated by solving appendix Eq. (1) with 2000 sets of parameters chosen uniformly in the intervals $0 < P_A, P_B < 1$ for phage pathologies on the host A and B, $1/min\{P_A, P_B\} < \chi < 100$ for burst size, $0 < \alpha < 0.5$ for normalized spontaneous induction rate, $10^{-1}S_B(0) < S_A(0) < 10S_B(0)$ and $0 < I_A(0), \phi(0) < 10^{-2}S_B(0)$ for the initial concentrations of susceptible and infected bacteria A and phage. Filled circles represent the data from 1000 sets of parameters with relatively large γ_j and β ($0.1 < \gamma_j, \beta < 10$). Open circles are from another 1000 sets of parameters with small γ_j and β ($0 < \gamma_j, \beta < 0.1$).

$\beta_j^{(m)} = \lambda_j^{(m)}/a$ and the contact rate $\gamma_j^{(m)} = \kappa_j^{(m)} S_B(0)/a$. We obtain

$$\begin{aligned}
\frac{ds_j}{d\tau} &= (1 - n/n_{max} - \sum_m \gamma_j^{(m)} \phi^{(m)}) s_j \qquad (15)\\
\frac{di_j^{(m)}}{d\tau} &= (1 - P_j^{(m)}) \gamma_j^{(m)} \phi^{(m)} s_j + (1 - n/n_{max} - \alpha_j^{(m)}) i_j^{(m)} \\
\frac{dl_j^{(m)}}{d\tau} &= P_j^{(m)} \gamma_j^{(m)} \phi^{(m)} s_j - \beta_j^{(m)} l_j^{(m)} \\
\frac{d\phi^{(m)}}{d\tau} &= \sum_j \{\chi_j^{(m)} (\alpha_j^{(m)} i_j^{(m)} + \beta_j^{(m)} l_j^{(m)}) - \gamma_j^{(m)} \phi^{(m)} s_j\}
\end{aligned}$$

where $n = \sum_j (s_j + \sum_m (i_j^{(m)} + l_j^{(m)}))$, $j \in \{A, B\}$ and $m \in \{1, 2\}$. The initial conditions for appendix Eq. (15) are $i_B^{(m)}(0) = l_A^{(m)}(0) = l_B^{(m)}(0) = 0$, $s_B(0) = 1$, $s_A(0) > 0$, $i_A^{(m)}(0) > 0$ and $\phi^{(m)}(0) \geq 0$.

When $\phi^{(m)}(0) = \alpha_A^{(m)} = 0$, there will be no phage-mediated competition. Thus in this section we consider $\sum_m \phi^{(m)}(0) > 0$. We will derive the invasion criterion in the limit of a fast infection process (i.e., $\gamma_j^{(m)} \to \infty$ and $\beta_j^{(m)} \to \infty$). An appropriate time-scale near $\tau = 0$ is $\sigma = \tau/\epsilon$ where $\epsilon = 1/\beta$, $\beta = max_{j,m}\{\beta_j^{(m)}\}$, $\xi_j^{(m)} = \gamma_j^{(m)}/\beta$, and $\eta_j^{(m)} = \beta_j^{(m)}/\beta$. Just as in section 2, we use a regular perturbation theory [1] and the solutions are expanded in order of ϵ, $\hat{s}_j(\sigma;\epsilon) = \sum_{n=0} \epsilon^n \hat{s}_{j,n}(\sigma)$, $\hat{i}_j^{(m)}(\sigma;\epsilon) = \sum_{n=0} \epsilon^n \hat{i}_{j,n}^{(m)}(\sigma)$, $\hat{l}_j^{(m)}(\sigma;\epsilon) = \sum_{n=0} \epsilon^n \hat{l}_{j,n}^{(m)}(\sigma)$, $\hat{\phi}^{(m)}(\sigma;\epsilon) = \sum_{n=0} \epsilon^n \hat{\phi}_n^{(m)}(\sigma)$. We now set $\epsilon = 0$ to get the $O(1)$ system,

$$\begin{aligned}
\frac{d\hat{s}_{j,0}}{d\sigma} &= -(\xi_j^{(1)} \hat{\phi}_0^{(1)} + \xi_j^{(2)} \hat{\phi}_0^{(2)}) \hat{s}_{j,0} \qquad (16)\\
\frac{d\hat{i}_{j,0}^{(m)}}{d\sigma} &= (1 - P_j^{(m)}) \xi_j^{(m)} \hat{\phi}_0^{(m)} \hat{s}_{j,0} \qquad (17)\\
\frac{d\hat{l}_{j,0}^{(m)}}{d\sigma} &= P_j^{(m)} \xi_j^{(m)} \hat{\phi}_0^{(m)} \hat{s}_{j,0} - \eta_j^{(m)} \hat{l}_{j,0}^{(m)} \qquad (18)\\
\frac{d\hat{\phi}_0^{(m)}}{d\sigma} &= \sum_j \{\chi_j^{(m)} \eta_j^{(m)} \hat{l}_{j,0}^{(m)} - \xi_j^{(m)} \hat{\phi}_0^{(m)} \hat{s}_{j,0}\} \qquad (19)
\end{aligned}$$

with the initial conditions $\hat{i}_{B,0}^{(m)}(0) = \hat{l}_{A,0}^{(m)}(0) = \hat{l}_{B,0}^{(m)}(0) = 0$, $\hat{s}_{B,0}(0) = 1$, $\hat{s}_{A,0}(0) > 0$, $\hat{i}_{A,0}^{(m)}(0) > 0$ and $\sum_m \hat{\phi}_0^{(m)}(0) > 0$.

By integrating appendix Eq. (16) and (17), we obtain

$$\begin{aligned}
\hat{s}_{j,0}(\sigma) &= \hat{s}_{j,0}(0)Exp[-\int_0^\sigma dx(\xi_j^{(1)}\hat{\phi}_0^{(1)}(x)+\xi_j^{(2)}\hat{\phi}_0^{(2)}(x))], && (20)\\
\hat{i}_{j,0}(\sigma) &= \sum_m \hat{i}_{j,0}^{(m)}(\sigma) && (21)\\
&= \sum_m \hat{i}_{j,0}^{(m)}(0)+\hat{s}_{j,0}(0)\int_0^\sigma dy(\xi_j^{(1)}\hat{\phi}_0^{(1)}(y)+\xi_j^{(2)}\hat{\phi}_0^{(2)}(y))e^{-\int_0^\sigma dx(\xi_j^{(1)}\hat{\phi}_0^{(1)}(x)+\xi_j^{(2)}\hat{\phi}_0^{(2)}(x))}\\
&- \hat{s}_{j,0}(0)\int_0^\sigma dy(P_j^{(1)}\xi_j^{(1)}\hat{\phi}_0^{(1)}(y)+P_j^{(2)}\xi_j^{(2)}\hat{\phi}_0^{(2)}(y))e^{-\int_0^\sigma dx(\xi_j^{(1)}\hat{\phi}_0^{(1)}(x)+\xi_j^{(2)}\hat{\phi}_0^{(2)}(x))}\\
&= \hat{i}_{j,0}(0)+(1-e^{-H(\sigma)}-P_{eff}^j)\hat{s}_{j,0}(0)
\end{aligned}$$

where $H(\sigma)=-\int_0^\sigma dx(\xi_j^{(1)}\hat{\phi}_0^{(1)}(x)+\xi_j^{(2)}\hat{\phi}_0^{(2)}(x))$. We define the effective phage pathology on the bacterial strain j as

$$P_{eff}^j \equiv \int_0^\sigma dy(P_j^{(1)}\xi_j^{(1)}\hat{\phi}_0^{(1)}(y)+P_j^{(2)}\xi_j^{(2)}\hat{\phi}_0^{(2)}(y))e^{-\int_0^\sigma dx(\xi_j^{(1)}\hat{\phi}_0^{(1)}(x)+\xi_j^{(2)}\hat{\phi}_0^{(2)}(x))}. \quad (22)$$

As shown in lemma 3 in section 2.1, if either $\xi_j^{(1)}\hat{\phi}_0^{(1)}(x)$ or $\xi_j^{(2)}\hat{\phi}_0^{(2)}(x)$ is zero for $x \geq 0$, P_{eff}^j becomes either $P_j^{(2)}$ or $P_j^{(1)}$ in the limit of $\sigma \to \infty$. This means that when either phage strain 1 cannot infect the bacterial strain j or if phage strain 1 is absent, the effective phage pathology on the bacterial strain j is solely determined by the pathology of phage strain 2. Otherwise, the effective phage pathology on the bacterial strain j depends on the values of the kinetic parameters, namely the contact rate $\xi_j^{(m)}$, the initial concentration $\Phi^{(m)}(0)$ and the replication rate of phage strain m (i.e., the phage burst size $\chi_j^{(m)}$ and the infection-induced lysis rate $\eta_j^{(m)}$).

Using Eq. (18)–(20) and lemma 1–3 in section 2.1 of the electronic appendix, we know that $\hat{s}_{j,0}(\sigma) \to 0$, $\hat{i}_{j,0}^{(m)}(\sigma) \to 0$, and $e^{-H(\sigma)} \to 0$ as $\sigma \to \infty$. In the limit of $\sigma \to \infty$, we obtain the ratio of the concentration of the two strains, using initial conditions $\hat{s}_{B,0}(0)=1$ and $\hat{i}_{B,0}(0)=0$,

$$r_{AB}(\sigma) = \frac{\hat{i}_{A,0}(0)+(1-P_{eff}^A)\hat{s}_{A,0}(0)}{(1-P_{eff}^B)} \quad (23)$$

where $r_{AB}(0)=\hat{i}_{A,0}(0)+\hat{s}_{A,0}(0)$. When $\hat{s}_{A,0}(0) \gg \hat{i}_{A,0}(0)$,

$$r_{AB}(\sigma) = r_{AB}(0)(1-P_{eff}^A)/(1-P_{eff}^B) \quad (24)$$

Eq. (24) has the same form as Eq. (3) in the main text for the single-phage-mediated competition between two bacterial strains. The phage pathology parameters P_A and P_B in Eq. (3) are replaced with the effective phage pathologies P^A_{eff} and P^B_{eff} in Eq. (24) for two-phage-mediated competition between two bacterial strains A and B. Thus the two-phage-induced total damage on the bacterial strain j can be condensed into a single parameter, represented as the effective phage pathology P^j_{eff}.

Next, we show that the effective phage pathology P^j_{eff} is bounded between the two individual phage pathology values. This indicates that the two phage-induced damage on a bacterial strain j cannot be greater than the maximum damage induced by one of the two phage and cannot be smaller than the minimum harm induced by one of the two phage. We also demonstrate that $P^j_{eff} \to P^{(2)}_j$ if $\xi^{(2)}_j \hat{\phi}^{(2)}_0(y) \gg \xi^{(1)}_j \hat{\phi}^{(1)}_0(y)$ for $y \geq 0$ and $P^j_{eff} = P^{(2)}_j$ if $\xi^{(1)}_j \hat{\phi}^{(1)}_0(y) = 0$ for $y \geq 0$. This implies the following: (a) if phage strain 2 has greater contact rate on bacterial strain j and the higher replication rate than phage strain 1 does, the effective phage pathology P^j_{eff} is mainly determined by the pathology value of phage strain 2. (b) If phage strain 1 is absent or if the bacterial strain j is immune against infection by phage strain 1, the effective phage pathology P^j_{eff} is only determined by the pathology value of phage strain 2.

Lemma 4. *Suppose* $0 \leq P^{(1)}_j < P^{(2)}_j \leq 1$ *for a given bacterial strain* j. *Then* P^j_{eff} *is bounded by* $P^{(1)}_j$ *and* $P^{(2)}_j$, *i.e.,* $P^{(1)}_j \leq P^j_{eff} \leq P^{(2)}_j$. $P_{eff} \to P^{(2)}_j$ *if* $\xi^{(2)}_j \hat{\phi}^{(2)}_0(y) \gg \xi^{(1)}_j \hat{\phi}^{(1)}_0(y)$ *for* $y \geq 0$, *and* $P_{eff} \to P^{(1)}_j$ *if* $\xi^{(1)}_j \hat{\phi}^{(1)}_0(y) \gg \xi^{(2)}_j \hat{\phi}^{(2)}_0(y)$ *for* $y \geq 0$.

Proof. Using $0 \leq P^{(1)}_j < P^{(2)}_j \leq 1$, we obtain a simple inequality,

$$\xi^{(1)}_j \hat{\phi}^{(1)}_0(y) + \frac{P^{(2)}_j}{P^{(1)}_j} \xi^{(2)}_j \hat{\phi}^{(2)}_0(y) \geq \xi^{(1)}_j \hat{\phi}^{(1)}(y) + \xi^{(2)}_j \hat{\phi}^{(2)}_0(y) \tag{25}$$

where the equality holds if $\xi^{(2)}_j \hat{\phi}^{(2)}_0(y) = 0$ or $\xi^{(1)}_j \hat{\phi}^{(1)}_0(y) \gg \xi^{(2)}_j \hat{\phi}^{(2)}_0(y)$ for $y \geq 0$. In similar manner,

$$\frac{P^{(1)}_j}{P^{(2)}_j} \xi^{(1)}_j \hat{\phi}^{(1)}_0(y) + \xi^{(2)}_j \hat{\phi}^{(2)}_0(y) \leq \xi^{(1)}_j \hat{\phi}^{(1)}_0(y) + \xi^{(2)}_j \hat{\phi}^{(2)}_0(y) \tag{26}$$

where the equality holds if $\xi_j^{(1)}\hat{\phi}_0^{(1)}(y) = 0$ or $\xi_j^{(2)}\hat{\phi}_0^{(2)}(y) \gg \xi_j^{(1)}\hat{\phi}_0^{(1)}(y)$ for $y \geq 0$. By using the first inequality, we obtain

$$\begin{aligned} P_{eff}^j &\equiv P_j^{(1)} \int_0^\sigma dy(\xi_j^{(1)}\hat{\phi}_0^{(1)}(y) + \frac{P_j^{(2)}}{P_j^{(1)}}\xi_j^{(2)}\hat{\phi}_0^{(2)}(y))e^{-H(y)} \qquad (27) \\ &\geq P_j^{(1)} \int_0^\sigma dy H'(y)e^{-H(y)} \\ &= P_j^{(1)}(1 - e^{-H(\sigma)}) \end{aligned}$$

where $H(y) = -\int_0^\sigma (\xi_j^{(1)}\hat{\phi}_0^{(1)}(x) + \xi_j^{(2)}\hat{\phi}_0^{(2)}(x))dx$. By using the second inequality, we obtain

$$\begin{aligned} P_{eff}^j &\equiv P_j^{(2)} \int_0^\sigma dy(\frac{P_j^{(1)}}{P_j^{(2)}}\xi_j^{(1)}\hat{\phi}_0^{(1)}(y) + \xi_j^{(2)}\hat{\phi}_0^{(2)}(y))e^{-H(y)} \qquad (28) \\ &\leq P_j^{(2)} \int_0^\sigma dy H'(y)e^{-H(y)} \\ &= P_j^{(2)}(1 - e^{-H(\sigma)}) \end{aligned}$$

Using lemma 3 in section 2.1 of the electronic appendix, we reduce $P_j^{(1)}(1 - e^{-H(\sigma)}) \leq P_{eff} \leq P_j^{(2)}(1 - e^{-H(\sigma)})$ to $P_j^{(1)} \leq P_{eff} \leq P_j^{(2)}$ in the limit of $\sigma \to \infty$. We also use the condition for the equality in appendix Eq. (25) to obtain that $P_{eff} \to P_j^{(2)}$ if $\xi_j^{(2)}\hat{\phi}_0^{(2)}(y) \gg \xi_j^{(1)}\hat{\phi}_0^{(1)}(y)$ for $y \geq 0$. Similarly, we use the condition for the equality in appendix Eq. (26) to obtain that $P_{eff} \to P_j^{(1)}$ if $\xi_j^{(1)}\hat{\phi}_0^{(1)}(y) \gg \xi_j^{(2)}\hat{\phi}_0^{(2)}(y)$ for $y \geq 0$. □

Analysis similar to case II-B in section 2.1 indicates that the steady state ratio of the concentration of two strains remains the same as Eq. (24) in the limit of $\tau \to \infty$ (which is not shown here).

SPECIAL EXAMPLE OF TWO-PHAGE-MEDIATED COMPETITION: $s_A(0) = 0$, $i_A(0) = \Phi^{(2)} > 0$ and $\Phi^{(1)} = 0$. We consider competition between resistant (Bb::$\Phi^{(1)}$) and sensitive (BbGm) bacterial strains mediated by exogenously added lytic phage ($\Phi^{(2)} \equiv \Phi\Delta$cI, see Table 1 in the main text) and by lysogenic phage spontaneously released from lysogens (Bb::$\Phi^{(1)}$). We use Eq. (15) to describe the dynamics of this specific system. The bacterial strain A corresponds to Bb::$\Phi^{(1)}$ (lysogens) and the

strain $B \equiv$BbGm (the strain with the Gm marker). The phage pathology of the lysogenic phage ($\Phi^{(1)}$) is set to $P_B^{(1)} = 0.98$, that of the lytic phage ($\Phi^{(2)}$) is $P_B^{(2)} = 1$. Because the lytic phage are derived from the lysogenic phage, they are homologous and strain A (Bb::$\Phi^{(1)}$) and lysogenic bacteria of strain B (BbGm::$\Phi^{(1)}$) are immune to infection by either of the two phage, $\Phi^{(1)}$ and $\Phi^{(2)}$. We also assume that the contact rate κ, the infection induced lysis rate λ, the spontaneous lysis rate δ and the phage burst size χ are the same for both the lytic and the lysogenic phage. For numerical simulations of mixed phage-mediated competition, we used the same parameter values used for the numerial simulations in Figure 3(a) in the main text.

Appendix Fig. 4(a) shows that the steady state outcome of the bacterial competition strongly depends on the initial concentration of the lytic phage ($\Phi^{(2)}$). No exogenous lysogenic phage were added to the system, yet they are spontaneously induced from the lysis of lysogens (Bb::$\Phi^{(1)}$). The sensitive bacteria are exposed to both the lysogenic and the lytic phage, and disappear rapidly from the system, a fraction of them transforming into resistant lysogenic phage-carrying bacteria. If both the contact rate κ and the spontaneous lysis rate δ (or the initial concentration of lysogenic phage $\Phi^{(1)}(0)$) are non-zero, the effective phage pathology P_{eff}^B is smaller than one and the bacteria of strain B never go extinct, and survive as lysogenic phage-carriers. (Note that in our mixed phage-mediated competition experiment depicted in Figure 5(b) in the main text, $\kappa = 1.08 \times 10^{-5}$ ml/hour/CFU, $\delta = 0.00054$/hour/bacterium and $\Phi^{(1)}(0) = 0$.) However as the initial concentration of lytic phage increases, the effective phage pathology P_{eff}^B approaches one, thus an order of magnitude increase in the initial concentration of the lytic phage $\Phi^{(2)}(0)$ leads to a dramatic decrease in the steady state concentration of the bacterial strain B.

It is also shown in appendix Fig. 4(b) that the effective phage pathology on the sensitive BbGm depends on the infection-induced lysis rate, one of the kinetic parameters of the system. The effective phage pathology in Eq. (22) depends implicitly on the infection-induced lysis rate λ; a higher infection-induced lysis rate is related to a higher replication rate of the lytic phage. Correspondingly, as the infection-induced lysis rate increases, the effective phage pathology P_{eff}^B approaches the phage pathology of the lytic phage ($P_B^{(2)} = 1$), leading to a decrease in the steady state concentration of the bacterial strain B. Thus the stationary outcome of the two-phage-mediated competition is determined by the effective phage pathology, which depends

on the values of the kinetic parameters.

References

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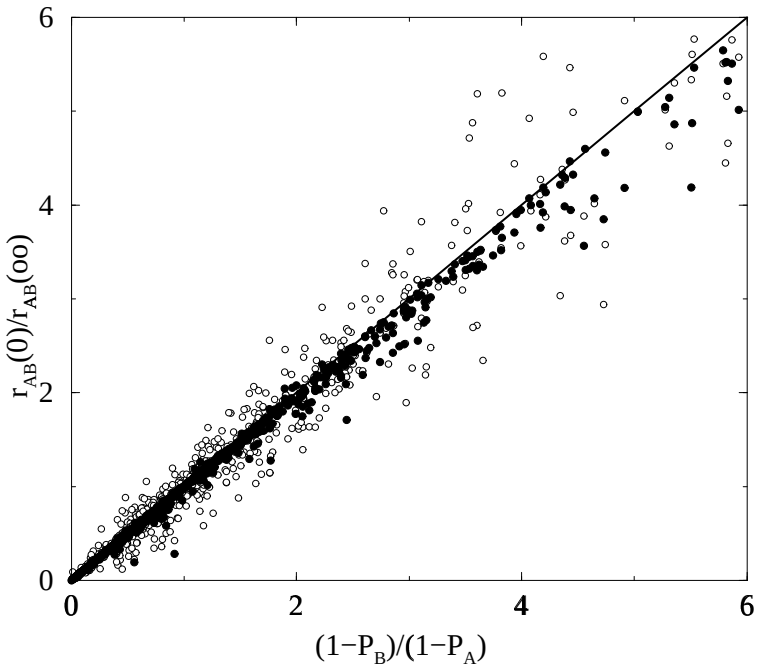

Figure 4: Dependence of the stationary outcome of mixed phage-mediated competition on the details of kinetic parameters. The bacterial strain with a Gm marker (filled circles) and the lysogens (open squares) were co-cultured with exogenously added lytic phage; the experimental data are the same as on Figure 5(a) in the main text. (a) The normalized initial concentration of the lytic phage, $\Phi^{(2)}(0)/I_A(0)$, varies from 0.1 (dashed line), 1 (long-dashed line) and 10 (dot-dashed line). (b) The infection-induced lysis rate λ changes from 0.0081 (dashed line), 0.081 (long-dashed line) and 0.81 (dot-dashed line). The other parameters used for the numerical simulations are the same as in Fig. 3(a).