Model equations and description for Knowles et al. *'Temperate infection in a virus-host system previously known for virulent dynamics'*, Nature Communications.

We studied three versions of a host-virus interaction model:

i) Virulent model: A classic version in which the virus is purely virulent.

ii) Phenomenological temperate model: A modified version of the classic model in which a switch from temperate to virulent mode occurs at specific times, which are informed by the host physiological data obtained in our experiments.

iii) Self-regulated temperate model: A modified version of the phenomenological temperate model that includes suggested mechanisms for the self-regulation of the switch from temperate to virulent infection.

We explain below all the different assumptions and model terms behind each model version. For all versions, we monitored the dynamics of healthy hosts, infected hosts, and free/infective viruses.

To present the model equations in a compact way, let us write all the different versions of the model together and differentiate the elements contributed by each version with specific colors. The equations that represent the growth of the uninfected population are presented in black, the additions required to complete a model in which the virus is purely virulent are presented in red, and the additions required to represent temperate dynamics are presented in blue. In other words, the virulent, purely-lytic version of the model uses black and red terms, whereas the temperate versions use all three colors (additional conditions are imposed for the self-regulated model, see section *Self-regulated temperate version: dynamic switch*).

a) *Uninfected population growth rate*:

All versions of the model use a phenomenological implementation of the growth rate. Using as a reference the experimental data for the uninfected case, in which the host

follows an approximately logistic growth, we devised an expression for the growth rate that would produce a logistic curve resembling our population density data in the absence of viruses. The following expression provides a good approximation to how the uninfected population growth rate changed with time:

$$\mu(t) = \mu_{eff}(t)\left(1 - \frac{[H](t) + (1 - r_s)[I](t)}{K}\right) \quad (1)$$

where [*H*] represents the density of uninfected hosts, [*I*] the density of infected hosts (which contribute to resource uptake only before induction, see below), *K* the carrying capacity (see **Supplementary Table 2** in the article for parameter values and units), and:

$$\mu_{eff}(t) = \begin{cases} \mu_{max} & \text{if} \quad t < 2 \\ s_\mu t + n_\mu & \text{if} \quad 2 < t < t_\mu \\ \mu_{min} & \text{if} \quad t > t_\mu \end{cases} \quad (2)$$

that is, the growth rate stays at a maximum level for two days, then decreases linearly to reach a minimum level at t_μ. The parameters of the (decreasing) linear relationship are thus given by:

$$s_\mu = \frac{\mu_{min} - \mu_{max}}{t_\mu - 2}$$

$$n_\mu = \mu_{max} - 2s_\mu = \frac{t_\mu \mu_{max} - 2\mu_{min}}{t_\mu - 2} \quad (3)$$

Eqs.(1)-(3) aim to replicate as closely as possible the growth conditions for the uninfected host population, including unknown/uncharacterized sources of physiological stress for which we may have no information. Our results do not change qualitatively if we replace Equation (1) for a standard Monod growth function.

b) *Model equations*

If [*H*] represents the concentration of uninfected hosts, [*V*] the concentration of extracellular (infective) viruses, and [*I*] the concentration of infected hosts, all in units of individuals per liter, the dynamics of the system are described by:

$$\frac{d[H](t)}{dt} = \mu(t)[H] - m[H] - k[H][V] + \mu_I(t)[I] \quad (4)$$

$$\frac{d[V](t)}{dt} = r_s B k_L[I] - k([H] + [I])[V] - m_V[V] \quad (5)$$

$$\frac{d[I](t)}{dt} = k[H][V] - r_s k_L[I] - m[I] \quad (6)$$

In the first equation (dynamics of the uninfected host population), the first term represents population growth; the second term represents natural mortality; the third term represents infection events, which occur at a rate *k* (viral adsorption rate); and the last term the fact that infected hosts can reproduce if the infecting virus is temperate which, for simplicity, we assume results in new uninfected hosts. In the second equation (dynamics of the freely-diffusing viral population), the third term represents viral decay out of the host; the second term represents infection events (including the possibility of an infected host to be re-infected by other viral individuals *via* superinfection); and the first term represents the viral offspring resulting from lysis (which only occurs if the virus is purely virulent or has switched from temperate to virulent, see below); each virus produces *B* virions per host, and we assume here that the offspring is released at a lytic rate k_L (inverse of the latent period, *L*). The latter assumption, which implies that the offspring is continuously released to complete burst size release in *L* days, aims at capturing intraspecific variability in the exact timing of offspring release as well as the possibility of virion release via budding (a possibility for EhV). In the last equation (dynamics of infected hosts), the first term represents infection events; the second term represents lysis of hosts (by either purely viruses or temperate viruses that have switched to virulent mode); and the third term represents host natural mortality.

c) Induction of temperate viruses (i.e., switch from temperate to virulent mode):

The potential temperate mode for the virus is implemented in the equations above *via* a switch function:

$$r_s = \begin{cases} 1 & \text{if virus is virulent} \\ \square & \\ 0 & \text{if virus is temperate} \end{cases} \quad (7)$$

Following the experimental data, in the temperate versions of the model we assumed that the default mode of the virus is temperate, with a physiologically-dependent switch to virulent mode that we modeled in two different ways.

Simple temperate version: data-informed switch

In this version of the model, a data-informed switch determines the change from temperate to virulent. Specifically, we assumed that such a mode change was triggered by the physiological stress of host cells measured in our experiments. Understanding as stress the decline that healthy hosts show in the photosynthetic performance curve, we imposed in this simple temperate version that induction occur at a particular time, t_s, matching the beginning of the decline in the F_v/F_m curve.

Thus, in this version of the model, $r_s = 1$ for $t \geq t_s$, and zero otherwise. This implicitly assumes that the virus does not switch back to the temperate mode in the duration of the experiment, which is consistent with our experimental results for the phenomenology of interest, namely the initial increase and decline of the host population. The specific times, t_s, extracted from the F_v/F_m curve, depended on initial host density but did not depend considerably on experimental setup. Specifically, these times were: 14 days for initial concentration of 10^1 cells per mL, 11 days for 10^2 cells per mL, 8 days for 10^3 cells per mL, 5 days for 10^4 cells per mL, 2 days for 10^5 cells per mL, and 1 day for higher initial concentrations.

Self-regulated temperate version: dynamic switch

We further modified the temperate model to include mechanisms that could explain the timing at which viral pressure significantly decimates and causes declines in host populations. To this end, and based on our observations, we introduced several biologically-reasonable changes/assumptions that aimed at triggering induction through system self-regulation:

— The infection mode depends on the time that the virus spends in the extracellular *milieu* between lysis of prior hosts and finding and infecting the subsequent host (see main text). Specifically, we assumed that the infection is virulent if the typical time between infections is smaller than the average life span of the virus, measured as the typical viral decay rate.

Mathematically, this is equivalent to:

$$[H] > \frac{m_V}{k} \tag{8}$$

— We further scaled the number of infected cells that undergo induction by the fraction of cells that show a temperate infection within the population. Our results were not qualitatively affected by this choice (and barely affected in a quantitative way, results not shown). Autophagy did not occur in the experiments (and therefore induction did not occur in the model) for the lowest initial density in the 10:1 treatment, and it was negligible for that same initial density in the preinfected treatments.

— If the infection is temperate, induction and associated viral replication and host lysis occurs after the infection leads to host stress (see main text). This is motivated by our observation that host autophagy occurs only in experiments where viruses are present. Specifically, in this version of the model, induction is triggered when the following expression is *minimized*:

$$\frac{1}{\mu_I(t)} + \frac{1}{k[H]} = \frac{k[H] + \mu_I(t)}{\mu_I(t)k[H]} \quad (9)$$

From the point of view of the host, the expression is the result of adding the typical replication time of the infected host and time between infections. Thus, the expression considers the tradeoff between the need to replicate fast and the associated increase in infection risk (due to the consequent increase in the host density, which leads to higher encounter rates). From the point of view of the virus, the expression signifies the overall generation time while temperate (or time between infections, as the replication of the infected cell always translates into “moving” to a new host). Importantly, this expression indirectly takes into account host stress in two ways: through density-dependent factors (self-shading, competition for resources) and other physiological factors including the temperate infection itself.

As mentioned above, we assumed that induction of intracellular temperate viruses occurs when the expression in Equation (9) transitions from decreasing to increasing.

Note that the condition given by Equation (8) is a sufficient condition for the infection to be virulent from the outset, whereas Equation (9) is a sufficient condition for induction. In consequence, infections that should be temperate will immediately after adsorption become virulent if the host is stressed enough for Equation (9) to be fulfilled. The host population typically surpasses the threshold for the infection mode condition (Equation (8)) before the induction condition (Equation (9)) occurs and, therefore, the newly-released viruses will ultimately result in virulent infections.

— Viral infectivity decreases fast out of the host. We implemented this condition during the initial temperate phase of the viral population, in which no new viruses are being produced and therefore viral aging can be easily tracked. Specifically,

we imposed a higher mortality (or loss of infectivity) rate (2 d^{-1}) for the extra-cellular viral population once the typical viral life span, $1/m_V$, is surpassed. In addition, to avoid an artificial recovery of this (old) viral population, we set a lower threshold of 10^{-1} cells per mL below which we set the population to zero.

d) Infected-host replication:

We assume that, while the virus is temperate, infected host cells can continue their usual life cycle and, therefore, continue replicating. Thus, the growth rate of infected hosts is implemented as:

$$\mu_I(t) = (1 - r_s)\mu(t) \quad (10)$$

that is, infected hosts replicate at the same growth rate as healthy hosts while the virus is temperate, and do not replicate at all when the virus is virulent. The justification for the latter is that, when virulent, the virus utilizes the synthesis machinery of the host, which prevents host replication.

As explained above, we assumed that infected-host replication produces new healthy hosts. In our simulations, distributing these replications between healthy and infected hosts, which is plausible if there is more than one virus per host opeing the possibility of superinfection, introduces some initial lag in the growth of the population. Because we lack information regarding the exact ratio of the population offspring that is represented by cells with complete (temperate) infective viruses, our choice here of assuming a complete healthy offspring is based on the best qualitative match with our experimental data.

Extrapolation to intermediate initial densities

To extrapolate to initial densities beyond the ones we used for our experiments, we deduced phenomenological expressions that aimed to replicate how several of our parameters depended on the initial densities we sampled with the experiments.

For the timing at which the growth rate reaches its minimum value, t_μ , for example, we observed the following approximated behavior:

$$t_\mu = \begin{cases} -1.75\, log([Ehux]_0) + 25 & \text{if } [Ehux]_0 > 10^1 cells/mL \\ 19 & \text{otherwise} \end{cases} \quad (11)$$

in days, if the initial density expressed in cells per mL.

In addition, we deduced a phenomenological expression for t_s as a function of the initial host density:

$$t_s = \begin{cases} -1.3\, log([Ehux]_0) + 16 & \text{if } [Ehux]_0 < 10^4 cells/mL \\ 1 & \text{otherwise} \end{cases} \quad (12)$$

in days, with the initial concentration expressed in units of cells per mL. The expectation is that these times vary with different stress conditions.