Appendix S: Supplementary Information: Epidemiological and evolutionary consequences of periodicity in treatment coverage

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S.1 Typical behaviour of the heterogeneous model for various types of treatments

(a) Anti-infection ($r_1$)

(b) Anti-transmission ($r_3$)

(c) Anti-toxin ($r_4$)

Figure S.1: Dynamics of the model with anti-infection (a), anti-transmission (b) and anti-infection (c) treatments. $v$ takes the value 1 during $pT$ (all newborns are treated), and the value 0 during $(1 - p)T$ (no newborn is vaccinated). Left panels: Dynamics for the densities of susceptible naive (plain grey), susceptible treated (plain black), infected naive (dotted grey) and infected treated hosts (dotted black). Right panels: Corresponding periodic attractors. Parameters: $r_i = 0.8$, $p = 0.6$, $T = 30$, $\alpha = 1$, $b = 2$, $d = 1$. 
S.2 Basic reproduction number $R_0$

S.2.1 Basic reproduction number in a constant environment

Omitting time dependency, we have the following equations for the densities of infected:

\[
\begin{align*}
\dot{I}_N &= (\beta_N(z)I_N + \beta_T(z)I_T)S_N - (d + \alpha_N + \gamma_N(z))I_N, \\
\dot{I}_T &= (\beta_N(z)I_N + \beta_T(z)I_T)\sigma S_T - (d + \alpha_T + \gamma_T(z))I_T.
\end{align*}
\]

In matrix form, the densities of infected hosts are associated to the Jacobian matrix $A(t)$ at equilibrium, like:

\[
A(t) = \begin{pmatrix}
S_N^0(t)\beta_N & S_T^0(t)\beta_T \\
\sigma S_T^0(t)\beta_N & \sigma S_T^0(t)\beta_T
\end{pmatrix}
\]

(S.1)

The Jacobian matrix $A$ can be written as $F - V$, with $F$ the birth matrix and $V$ the death matrix:

\[
\begin{align*}
F(t) &= \begin{pmatrix}
S_N^0(t)\beta_N & S_T^0(t)\beta_T \\
\sigma S_T^0(t)\beta_N & \sigma S_T^0(t)\beta_T
\end{pmatrix} \\
V &= \begin{pmatrix}
d + \alpha_N + \gamma_N & 0 \\
0 & d + \alpha_T + \gamma_T
\end{pmatrix}
\end{align*}
\]

Since the elements of $V^{-1}$ and $F$ are positive and $-V$ has strictly negative eigenvalues, we can apply the Next Generation Theorem, which states that the basic reproduction number in a constant environment correspond to the dominant eigenvalue of $FV^{-1}$. Straightforward algebra then leads to:

\[
R_0 = \frac{\beta_N(z)}{d + \alpha_N + \gamma_N} \hat{S}_N + \frac{\beta_T(z)}{d + \alpha_T + \gamma_T} \hat{S}_T.
\]

S.2.2 Basic reproduction number in a periodic environment for anti-infection ($r_1$) and anti-transmission ($r_3$) treatments

Omitting time dependency, we have the following equations for densities of infected for anti-infection ($r_1$) and anti-transmission ($r_3$) treatments:

\[
\begin{align*}
\dot{I}_N &= (\beta(z)I_N + (1 - r_3)\beta(z)I_T)S_N - (d + \alpha + \gamma(z))I_N, \\
\dot{I}_T &= (\beta(z)I_N + (1 - r_3)\beta(z)I_T)(1 - r_1)S_T - (d + \alpha + \gamma(z))I_T,
\end{align*}
\]

Setting $Z = I_N + (1 - r_3)I_T$ the weighted total density of infected hosts, we obtain from system S.2 the scalar equation:

\[
\dot{Z} = B(t)Z - D(t)Z
\]

(S.3)

with $B(t) = \beta(\alpha)(S_N(t) + (1 - r_1)(1 - r_3)S_T(t))$ and $D(t) = (d + \alpha + \gamma(z))$. In this case, Bacaër & Guernaoui [1] have shown that in a periodic environment $R_0$ can be calculated as:

\[
R_0 = \frac{\int_0^T B(t) dt}{\int_0^T D(t) dt}
\]

(S.4)

Gathering eq. (S.3) and eq. (S.4), we obtain the expression of the basic reproduction number for anti-infection and anti-transmission treatments, which corresponds to eq. (3.3) in the main text:

\[
R_0 = \frac{\beta(z)}{d + \alpha + \gamma(z)} \left( \langle S_N^0 \rangle + (1 - r_1)(1 - r_3)\langle S_T^0 \rangle \right),
\]

where $\langle S_N^0 \rangle$ and $\langle S_T^0 \rangle$ are calculated in Appendix S.3. For anti-infection ($r_1$) and anti-transmission ($r_3$) treatments, the basic reproduction number in a periodic environment with average coverage $\bar{\nu}$ is equal to the basic reproduction number in an environment with constant coverage $\bar{\nu}$, as verified in figure S.2.
Note also that \( r_1 \) and \( r_3 \) play the same role in the expression, hence the pathogen has the same \( R_0 \) in both cases, for a fixed treatment efficacy.

The densities of infected hosts can be written in matrix form:

\[
\frac{d}{dt} \begin{pmatrix} I_N \\ I_T \end{pmatrix} = A(t) \begin{pmatrix} I_N \\ I_T \end{pmatrix},
\]

with

\[
A(t) = \begin{pmatrix} S_N^0(t) \beta_N(z) - (d + \alpha_N + \gamma_N(z)) & S_N^0(t) \beta_T(z) \\ \sigma S_T^0(t) \beta_N(z) & \sigma S_T^0(t) \beta_T(z) - (d + \alpha_T + \gamma_T(z)) \end{pmatrix}
\]

The Jacobian matrix \( A(t) \) can be written as \( A(t) = F(t) - V \), with \( F(t) \) the periodic fecundity matrix and \( V \) the mortality matrix:

\[
F(t) = \begin{pmatrix} S_N^0(t) \beta_N(z) & S_N^0(t) \beta_T(z) \\ \sigma S_T^0(t) \beta_N(z) & \sigma S_T^0(t) \beta_T(z) \end{pmatrix}, \quad V = \begin{pmatrix} d + \alpha_N + \gamma_N & 0 \\ 0 & d + \alpha_T + \gamma_T \end{pmatrix}
\]

To compute \( R_0 \), we follow Bacaër [2] and we solve the following matrix ODE over one period of the disease-free attractor:

\[
\frac{dX}{dt} = \frac{F(t)}{R_0} X - V X, \quad (S.5)
\]

with initial condition \( X(0) = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix} \). We numerically calculate the dominant eigenvalue of \( X(T) \), \( \rho \), which is the Floquet multiplier, for values of \( R_0 \) varying by dichotomy. The value of \( R_0 \) that corresponds
to ρ = 1 is the value of the basic reproduction number of the population [2]. This gives the invasion threshold on figure S.3.

(a) Anti-growth (r₂)  (b) Anti-toxin (r₄)

Figure S.3: Invasion boundaries (R₀ = 1 lines) as a function of the transmission rate β and the virulence α, for (a) anti-growth (r₂) and (b) anti-toxin (r₄) treatments, with T = 2 and p = 0.5. The efficacy of treatments are shown in different colours: in shades of orange for anti-growth (r₂) and in shades of black for anti-toxin (r₄). The efficacy takes the values r₁ = 0.1, 0.3, 0.5, 0.7, 0.9, represented in a gradient of transparency, from light to dark. The periodic treatment coverage (solid line) is compared to the constant treatment coverage (dotted line).

S.2.4 Invasion threshold as a function of r and p

(a) Anti-infection (r₁)  (b) Anti-growth (r₂)  (c) Anti-transmission (r₃)

Figure S.4: Conditions of persistence of the pathogen in hosts populations according to the efficacy of the treatment (r), and the proportion of maximal treatments (p), for (a) anti-infection, (b) anti-growth and (c) anti-transmission treatments, with a periodic coverage (solid lines) or a constant coverage (dotted lines) The pathogen goes extinct above the curves (top right corner) and persist under. Anti-toxin is not shown because in this case, the pathogen persist in the population. Here b = 2, d = 1, T = 10, α = 1.
S.3 Disease-free dynamics

The dynamics of susceptible hosts in the absence of disease are such that:

\[
\begin{align*}
\dot{S}_N(t) &= (1 - \nu(t))b - dS_N(t), \\
\dot{S}_T(t) &= \nu(t)b - dS_T(t).
\end{align*}
\]  

(S.6)

Let \(S^0_N(t)\) and \(S^0_T(t)\) be the (periodic) solutions of the system on the disease-free attractor. For a function \(f\) on the attractor, we define \(\langle f \rangle = \int_0^T f(t) \, dt\). On the attractor, we have \(\langle \dot{S}_N \rangle = \langle \dot{S}_T \rangle = 0\), which leads to:

\[
\begin{align*}
\langle S^0_N \rangle &= \frac{b}{d} \int_0^T (1 - \nu(t)) \, dt = (1 - \bar{\nu})b, \\
\langle S^0_T \rangle &= \frac{b}{d} \int_0^T \nu(t) \, dt = \bar{\nu}b.
\end{align*}
\]  

(S.7)

Equations (S.6) can be written as \(\dot{X}(t) = A(t)X + b(t)\), where

\[
X = \begin{pmatrix} S_N(t) \\ S_T(t) \end{pmatrix}, \quad A(t) = \begin{pmatrix} -d & 0 \\ 0 & -d \end{pmatrix}, \quad \text{and} \quad b(t) = \begin{pmatrix} (1 - \nu(t)) \\ \nu(t) \end{pmatrix}.
\]

As shown by Perko [3], for \(A(t)\) a \((n \times n)\) matrix and \(b(t)\) a vector of continuous functions, the solutions of the nonhomogeneous linear system has the form \(X(t) = e^{A(t)} + \left( X(0) + \int_0^t e^{A(s)}b(s) \, ds \right) \). Applied to our system, the periodical solution of the system on the disease free periodic attractor is:

\[
\begin{align*}
S^0_N(t) &= e^{-dt} \left( S_N(0) + \int_0^t e^{ds} (1 - \nu(s))b \, ds \right), \\
S^0_T(t) &= e^{-dt} \left( S_T(0) + \int_0^t e^{ds} \nu(s)b \, ds \right).
\end{align*}
\]  

(S.8)

S.4 Evolutionary dynamics

S.4.1 Resident-mutant dynamics

The full model including the mutant dynamics is

\[
\begin{align*}
\frac{dS_N}{dt} &= (1 - \nu(t))b - (d + h_N + h'_N)S_N + (\gamma_N + \gamma'_N)S_N, \\
\frac{dS_T}{dt} &= \nu(t)b - (d + h_T + h'_T)S_T + (\gamma_T + \gamma'_T)S_T, \\
\frac{dI_N}{dt} &= (\beta_N(z)I_N + \beta_T(z)I_T)S_N - (d + \alpha_N + \gamma_N(z))I_N, \\
\frac{dI_T}{dt} &= (\beta_N(z)I_N + \beta_T(z)I_T)\sigma S_T - (d + \alpha_T + \gamma_T(z))I_T, \\
\frac{dI'_N}{dt} &= (\beta_N(z')I_N + \beta_T(z')I_T)S_N - (d + \alpha'_N + \gamma_N(z'))I'_N, \\
\frac{dI'_T}{dt} &= (\beta_N(z')I_N + \beta_T(z')I_T)\sigma S_T - (d + \alpha'_T + \gamma_T(z'))I'_T.
\end{align*}
\]  

(S.9)

with \(\alpha'_T = (1 - r_2)(1 - r_4)z', \quad \alpha'_N = z'\).
S.4.2 Analytical derivation for the selection gradient using time-dependent reproductive values

We start with equation (23) in [4], which gives the selection gradient for a class-structured population on a periodic attractor. For our model, this gives

\[ S = \left< v^\top \frac{dA'}{dz'} \bigg| z' = z \right> f^\top \]  \hfill (S.10)

where \( v(t) \) is the vector of reproductive values at time \( t \), \( f(t) \) is the vector of class frequencies at time \( t \), and \( A'(t) \) is the matrix given by (S.22). Equation (23) in [4] can be derived by computing the dynamics of the reproductive-value weighted mean trait, then assuming that the trait distribution is tightly clustered around its mean (weak selection), so that the dynamics of the mean trait is approximately proportional to the neutral variance times \( v^\top \frac{dA'}{dz'} f^\top \). Since the neutral variance is constant on the periodic attractor, the sign of \( S \) is sufficient to predict the direction of selection. Expanding the right-hand side of eq. (S.10) yields after some rearrangements

\[ S = \left< c_N \left( \beta_N(z) \frac{v_N \hat{S}_N(t)}{v_N} + v_T \sigma \hat{S}_T(t) \right) - \alpha'_N(z) \right> + c_T \left( \beta_T(z) \frac{v_N \hat{S}_N(t) + v_T \sigma \hat{S}_T(t)}{v_T} - \alpha'_T(t) \right) \]  \hfill (S.11)

where \( c_N(t) = v_N(t)f_N(t) \) is the class reproductive value of parasites in naive hosts, and \( c_T(t) = v_T(t)f_T(t) \) is the class reproductive values in treated hosts. Note that the class reproductive values are normalised so that \( c_N(t) + c_T(t) = 1 \).

In eq. (S.11), the reproductive values and class frequencies are computed in a neutral (or monomorphic) population. In matrix form, the dynamics of the densities of infected hosts in the resident population can be written as

\[ \frac{d}{dt} \begin{pmatrix} I_N \\ I_T \end{pmatrix} = A(t) \begin{pmatrix} I_N \\ I_T \end{pmatrix} \]  \hfill (S.12)

with

\[ A(t) = \begin{pmatrix} \beta_N S_N(t) - (d + \alpha_N) & \beta_T S_N(t) \\ \beta_N \sigma S_T(t) & \beta_T \sigma S_T(t) - (d + \alpha_T) \end{pmatrix}. \]  \hfill (S.13)

Following [4], the vector of class frequencies \( f = (f_N \quad f_T)^\top \) has dynamics

\[ \frac{df}{dt} = A(t)f - r(t)f \]  \hfill (S.14)

where \( r(t) = 1^\top A(t)f \) is the total growth rate of the population, while the dynamics of the vector of reproductive values, \( v \), is given by the adjoint equation

\[ \frac{dv^\top}{dt} = -v^\top A(t) + r(t)v^\top \]  \hfill (S.15)

(note that \( v^\top \) is a row vector). The reproductive values \( v_N(t) \) and \( v_T(t) \) give the “value” of a parasite in class \( N \) and \( T \) respectively, at time \( t \), i.e. how much future descendance this parasite can expect at time \( t \).

In general, the reproductive values on the periodic attractor can only be calculated numerically, but even without calculating the reproductive values, we can make some analytical progress by noting that

\[ \frac{1}{v_N} \frac{dv_N}{dt} = -\beta_N \omega_N + (d + \alpha_N + r(t)) \]  \hfill (S.16)

where, for \( k = N \) or \( T \),

\[ \omega_k = \frac{v_N \hat{S}_N(t) + v_T \sigma \hat{S}_T(t)}{v_k}. \]  \hfill (S.17)
Integrating eq. (S.16) over one period, we obtain
\[ \langle \omega_N \rangle = \frac{d + \alpha_N}{\beta_N}. \] (S.18)

From the dynamics of \( v_T(t) \), we similarly obtain
\[ \langle \omega_T \rangle = \frac{d + \alpha_T}{\beta_T}. \] (S.19)

Hence \( \omega_N \) and \( \omega_T \) fluctuate around \( (d + \alpha_N)/\beta_N \) and \( (d + \alpha_T)/\beta_T \) respectively. An interpretation of \( \omega_k \) is as follows: the numerator indicates the average value of an “offspring”, i.e. a parasite propagule landing on a new host (either a naive host, with “probability” \( S_N \), in which case the propagule has value \( v_N \), or a treated host, with “probability” \( S_T \), in which case the propagule has value \( v_T \)), and the denominator gives the value of the “adult” parasite in class \( k \). So \( \omega_k \) gives the relative value of an offspring relative to the value of an adult in class \( k \).

We can use this result and the definition of a covariance to simplify eq. (S.11) as
\[ S = \langle c_N \rangle \left( \beta_N(z) \frac{d + \alpha_N}{\beta_N} - \alpha_N(z) \right) + \langle c_T \rangle \left( \beta_T(z) \frac{d + \alpha_T}{\beta_T} - \alpha_T(z) \right) + \beta_N(z) \text{Cov}(c_N, \omega_N) + \beta_T(z) \text{Cov}(c_T, \omega_T). \] (S.20)

The second line depends on the temporal covariances between the class reproductive values \( c_k(t) \) and the relative offspring values \( \omega_k(t) \). To obtain our final approximation, we simply neglect these terms, which can be expected to be of second order for small fluctuations, so that the selection gradient can be written as
\[ S = \langle c_N \rangle \left( \beta_N(z) \frac{d + \alpha_N}{\beta_N} - \alpha_N(z) \right) + \langle c_T \rangle \left( \beta_T(z) \frac{d + \alpha_T}{\beta_T} - \alpha_T(z) \right) \] (S.21)
as in the main text. Note that \( \langle c_N \rangle + \langle c_T \rangle = 1 \), so that \( S \) takes the form of a weighted sum of the class-specific selection gradients (the terms between brackets).

For the anti-toxin treatment, straightforward simplifications leads to eq. (4.5) in the main text.

Note that, with our periodic step function \( \nu(t) \), it is easy to see that, in the limit of large periods, \( c_T(t) \) tends towards \( \nu(t) \), and therefore \( \langle c_T \rangle = \bar{\nu} = p \). Indeed, when \( T \) is large, the system essentially behaves as a succession of homogeneous equilibrium populations with either \( \nu = 0 \) or \( \nu = 1 \). When \( \nu = 1 \) (i.e. during a fraction \( p \) of the period), only treated hosts are present, so that \( c_T = 1 \). When \( \nu = 0 \), only untreated hosts are present, so that \( c_T = 0 \). Hence, \( \langle c_T \rangle = p \). This can be confirmed numerically (results not shown).

### S.4.3 Numerical calculation of invasion fitness using Floquet’s theory

Invasion fitness can be numerically calculated as the dominant Floquet exponent associated with the matrix
\[ A'(t) = \begin{pmatrix} \hat{S}_N(t) \beta_N(z') - (d + \alpha_N(z') + \gamma_N(z')) & \hat{S}_N(t) \beta_T(z') \\ \sigma \hat{S}_T(t) \beta_N(z') & \sigma \hat{S}_T(t) \beta_T(z') - (d + \alpha_T(z') + \gamma_T(z')) \end{pmatrix} \] (S.22)
where \( \hat{S}_N(t) \) and \( \hat{S}_T(t) \) are the densities of susceptible hosts on the endemic attractor. That is, we use the same method as in Appendix S.2.3, but evaluate the invasion matrix on the endemic attractor instead of the disease-free attractor. As for the epidemiological \( R_0 \) in appendix S.2.3, the Floquet multiplier \( \rho \) is related to the invasion fitness \( R' \), through the relationship \( \rho > 1 \iff R' > 1 \). For anti-infection (\( r_1 \)) and anti-transmission (\( r_3 \)) treatments, this allows us to check that periodicity has no effect on the ES virulence (figure S.5), as predicted by our direct analytical calculation of the mutant’s basic reproduction number (equation (4.1) in the main text). The numerical calculations using Floquet’s theory for anti-growth and anti-toxin treatments are shown in figures S.6 and S.7, respectively according to the period \( T \) and the fraction of the period with treatment \( p \).
Figure S.5: Numerical calculation of the evolutionarily stable virulence for anti-infection ($r_1$) and anti-transmission ($r_3$) treatments.

Figure S.6: Numerical calculation of the evolutionarily stable virulence for (a) anti-growth treatment in shape of orange and (b) anti-toxin treatment in shape of black, with a periodic treatment coverage (solid lines) and different periods: $T = 2$ (lighter), $T = 5$, $T = 8$ (darker). Compared to a constant treatment coverage with $p = \bar{\nu} = 0.8$ (dotted line), with the extinction thresholds for anti-growth treatment with a periodic coverage (orange crosses) or constant coverage (orange circle).
Figure S.7: Numerical calculation of the evolutionarily stable virulence for (a) anti-growth treatment (orange) and (b) anti-toxin treatment (black), with a periodic treatment coverage (solid lines) and different values of $p$: $p = 0.3$ (lighter), $p = 0.5$ or $p = 0.8$ (darker), for $T = 5$. Compared to a constant treatment coverage with $\bar{\nu} = p$ (dotted line), with the extinction thresholds for anti-growth treatment with a periodic coverage (orange crosses) or constant coverage (orange circle).

S.5 Impact of recovery

To highlight the effect of a non-zero recovery on our study, we set $\gamma = \gamma_N = \gamma_T$, and we perform numerical simulations for different values of $\gamma$. On figure S.8 we see that a non-zero recovery affects the prevalence of the disease. For anti-infection, anti-growth and anti-transmission treatments we observe a lower extinction threshold, while for anti-toxin treatments, recovery increases the prevalence. The quantitative effect on virulence evolution appears small, except for near-perfect anti-growth treatments.
Figure S.8: Effect of a non-zero recovery on the prevalence and $p$ (first line), on the prevalence and $T$ (second line), the extinction threshold (third line) and the evolution of virulence (fourth line), for anti-infection (blue), anti-growth (orange), anti-transmission (green) and anti-toxin (black). Left panels: $\gamma = 0$ (as in the main text). Middle panels: $\gamma = 0.5$. Right panels: $\gamma = 0.8$. 
S.6 Impact of the shape of the coverage functions

To check the robustness of our results, we performed simulations with a different function for treatment coverage: $\nu(t) = \frac{1}{2} \left(1 + \frac{\arctan(\sin(2\pi \omega t)/\delta)}{\arctan(1/\delta)}\right)$, which approximates a square wave for $\delta \approx 0$, and a sine wave when $\delta$ becomes large. For all values of $\delta$, $\nu = 1/2$.

Figure S.9: Effect of (a) different shapes treatment coverage functions defined by $\delta$, on (b,c) the prevalence and (d,e) the evolutionarily stable virulence, for anti-infection (blue), anti-growth (orange), anti-transmission (green) and anti-toxin (black) treatments, associated to the periodic coverage (solid lines) or the respective average coverage (dotted lines). Here $p = 0.5$, $T = 10$. 
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