S1 Text: Aggressive treatment and/or containment may prevent treatment failure.

Immunity may increase with time for a variety of reasons. For example, the patient may have an adaptive response to an infection or their immune system may recover after being suppressed by certain cancer treatments. Because we allow for the possibility that immunity may increase with time, it is possible that aggressive treatment and/or containment will manage the infection indefinitely (i.e., completely prevent resistance emergence). In this case an infection has two distinct phases. During the first phase immunity is not strong enough to control the infection and the resistant density is increasing. During this phase of the infection our analysis from the main text holds. In the second phase, immunity is strong enough to control the resistant population and the resistant density is no longer increasing. During this phase both containment and aggressive treatment will prevent resistance emergence. Note that when the immune response is strong, containment (as defined in the main text) may not be possible since the sensitive density may also be decreasing. In this case withholding treatment is an effective strategy.

This means that any strategy that manages the infection until immunity is sufficiently strong will prevent resistance emergence. In general there will be scenarios where (i) aggressive treatment prevents treatment failure but containment does not, (ii) containment prevents resistance emergence but aggressive treatment does not, (iii) both aggressive treatment and containment prevent resistance emergence and (iv) neither aggressive treatment nor containment prevent resistance emergence. Our analysis applies to all of these scenarios.

S2 Text: Standard logistic formulation

Equation (1) from the main text is a standard logistic equation with a (possibly time-varying) carrying capacity. To see this note that,

$$\begin{aligned} \dot{R}(t) &= rR(t)(1-\delta R(t)) - \mu(t)R(t), \\ &= (r-\mu(t))R(t)(1-\frac{\delta r}{r-\mu(t)}R), \end{aligned}$$

and so the carrying capacity is $R_{Carry} = \frac{r-\mu(t)}{r\delta}$. If drug-resistance carries a fitness cost then the carrying capacity becomes

$$R_{Carry} = \frac{(1-c_I)r-\mu(t)}{(1-c_I)r(1+c_C)\delta} = \frac{1}{(1+c_C)\delta}\left(1-\frac{\mu(t)}{(1-c_I)r}\right)$$

where drug resistance reduces a pathogens intrinsic replication rate by a factor $(1-c_I)$ and increases its sensitivity to competition by a factor $(1+c_C)$. Finally note that if immunity

is constant then this carrying capacity is constant and becomes the self-limiting density described in the "Clinical gains" section of the main text

$$R_{lim} = \frac{1}{(1+c_C)\delta}\left(1 - \frac{\mu}{(1-c_I)r}\right).$$

S3 Text: Derivation of the balance threshold

The expansion rate for a purely resistant infection is described by (Equation (1) from the main text)

$$\dot{R}(t) = rR(t)\underbrace{(1-\delta R(t))}_{\substack{\text{reduction in}\\ \text{replication due}\\ \text{to competition}}} - \mu(t)R(t). \tag{S.1}$$

If the patient also harbours drug-sensitive pathogens then the resistant expansion rate will be modified by these sensitive pathogens. In particular, since we assume that all pathogens (regardless of drug sensitivity) contribute equally to competition, the reduction in replication will change from $(1-\delta R(t))$ to $(1-\delta P(t))$, where P is the total pathogen density (both drug sensitive and drug resistant). Additionally, the drug sensitive pathogens will be replicating and a proportion ϵ of their progeny will be drug-resistant (due to mutation). Since the replication process is similar for both drug-sensitive and drug-resistant pathogens, the term describing drug-sensitive replication is similar to the first term in Equation (1). Namely, drug-sensitive replication is described by $r(P(t)-R(t))(1-\delta P(t))$, where $P(t)-R(t)$ is the sensitive density at time t. The rate of mutational input is therefore $\epsilon r(P(t)-R(t))(1-\delta P(t))$. Therefore, in the presence of sensitive pathogen, the resistant expansion rate is given by

$$\dot{R}(t) = rR(t)(1-\delta P(t)) - \mu(t)R(t) + \epsilon r(P(t)-R(t))(1-\delta P(t)). \tag{S.2}$$

During containment the total pathogen density is maintained at the acceptable burden ($P(t) = P_{max}$) and so Equation (S.2) becomes,

$$\dot{R}(t) = \underbrace{rR(t)(1-\delta P_{max})}_{\text{first term}} - \mu(t)R(t) + \epsilon r(P_{max}-R(t))(1-\delta P_{max}). \tag{S.3}$$

Equation (S.3) can be rearranged to be written as the sum of three terms: the resistant expansion rate ignoring the effect of the sensitive density, the benefit of competitive suppression and the cost of mutational input. To see this, consider the first term in Equation (S.3) which describes the resistant replication rate:

$$\begin{aligned} rR(t)(1-\delta P_{max}) &= rR(t)\left[1-\delta R(t) - \delta(P_{max}-R(t))\right], \\ &= \underbrace{rR(t)\left[1-\delta R(t)\right]}_{\substack{\text{resistant replication rate}\\ \text{ignoring the effect of}\\ \text{sensitive pathogen}}} - \underbrace{rR(t)\delta\left[P_{max}-R(t)\right]}_{\substack{\text{competitive suppression}\\ \text{of resistant replication}\\ \text{due to sensitive pathogen}}}. \end{aligned}$$

Substituting this expression into Equation (S.3) results in

$$\dot{R}(t) = rR(t)\left[1-\delta R(t)\right] - rR(t)\delta\left[P_{max}-R(t)\right] - \mu(t)R(t) + \epsilon r(P_{max}-R(t))(1-\delta P_{max}),$$

which can be rearranged to produce Equation (2) from the main text:

$$\dot{R}(t) = \underbrace{rR(t)\left[1-\delta R(t)\right] - \mu(t)R(t)}_{\substack{\text{resistant expansion rate}\\ \text{ignoring the effect of}\\ \text{sensitive pathogen}}} - \underbrace{rR(t)\delta\left[P_{max}-R(t)\right]}_{\substack{\text{competitive suppression}\\ \text{(benefit of sensitive pathogen)}}} + \underbrace{\epsilon r(P_{max}-R(t))(1-\delta P_{max})}_{\substack{\text{mutational input}\\ \text{(cost of sensitive pathogen)}}}. \tag{S.4}$$

Adding the fitness costs of resistance to Equation (S.4), we recover Equation (3) from the main text which describes the expansion of the resistant population under containment:

$$\begin{aligned}\dot{R} &= (1-c_I)rR\left(1-(1+c_C)\delta R\right) - \mu(t)R \\ &\quad - \underbrace{(1-c_I)r(1+c_C)\delta R\left(P_{max}-R\right)}_{\substack{\text{competitive suppression}\\ \text{(benefit of sensitive pathogen)}}} + \underbrace{\epsilon r\left(P_{max}-R\right)\left(1-\delta P_{max}\right)}_{\substack{\text{mutational input}\\ \text{(cost of sensitive pathogen)}}}.\end{aligned}$$

Since the replication rate cannot be negative we assume that $P_{max} \leq \frac{1}{(1+c_C)\delta}$. If P_{max} is greater than $\frac{1}{(1+c_C)\delta}$ then containment at the lower burden $\frac{1}{(1+c_C)\delta}$ will prevent resistance expansion.

A sensitive density will be advantageous whenever benefit exceeds cost. In other words, whenever

$$(1-c_I)r(1+c_C)\delta R\left(P_{max}-R\right) > \epsilon r\left(P_{max}-R\right)\left(1-\delta P_{max}\right). \tag{S.5}$$

Rearranging Equation (S.5) gives,

$$R > \frac{\epsilon\left(1-\delta P_{max}\right)}{(1-c_I)(1+c_C)\delta} = R_{balance}.$$

S4 Text: Derivation of Equation 5 from main text

Maximizing the sensitive density will be advantageous whenever the resistant density exceeds the balance threshold. During the management period the resistant density is less than the acceptable burden P_{max}. This means that maximising the sensitive density will be advantageous only when,

$$P_{max} > R(t) > R_{balance} = \frac{\epsilon\left(1-\delta P_{max}\right)}{(1-c_I)(1+c_C)\delta}.$$

In paticular, this requires that the acceptable burden is greater than the balance threshold

$$P_{max} > R_{balance} = \frac{\epsilon\left(1-\delta P_{max}\right)}{(1-c_I)(1+c_C)\delta} \tag{S.6}$$

Rearranging Equation (S.6) we have that

$$P_{max} > \frac{\epsilon}{\delta\left(\epsilon + (1-c_I)(1+c_C)\right)}.$$

S5 Text: Distinguishing between the scenarios in Fig 2C and 2D of the main text

Consider any fixed set of parameter values where the balance threshold $R_{balance}$ is less than the acceptable burden P_{max}. We know that if the starting density $R(0)$ exceeds the balance threshold then containment is best (this is the scenario depicted in Figure 2B of the main text). If the starting density, however, is below the balance threshold then containment may or may not be better than aggressive treatment (we may either be in the case depicted by Figure 2C or the case depicted by Figure 2D of the main text). Here we show that while the resistant density is low we will be in the situation depicted by Figure 2C (i.e., aggressive treatment is best). Once the resistant density exceeds a certain value (denoted $R^*(0)$) then we will be in the scenario depicted in Figure 2D of the main text (i.e., containment is best). The precise value of $R^*(0)$ will depend on the parameter values. In the proof below we simply prove the existence of $R^*(0)$ (i.e., we do not provide an explicit expression for $R^*(0)$). In S6 Text we provide an equation which implicitly defines $R^*(0)$ in the case that the immune function μ is constant (i.e., does not change with time).

Claim 1. Let the dynamics of the resistant density be described by

$$\dot{R}_A(t) = (1-c_I)r(1-(1+c_C)\delta R_A(t))R_A(t) - \mu(t)R_A(t) \tag{S.7}$$

under aggressive treatment and by

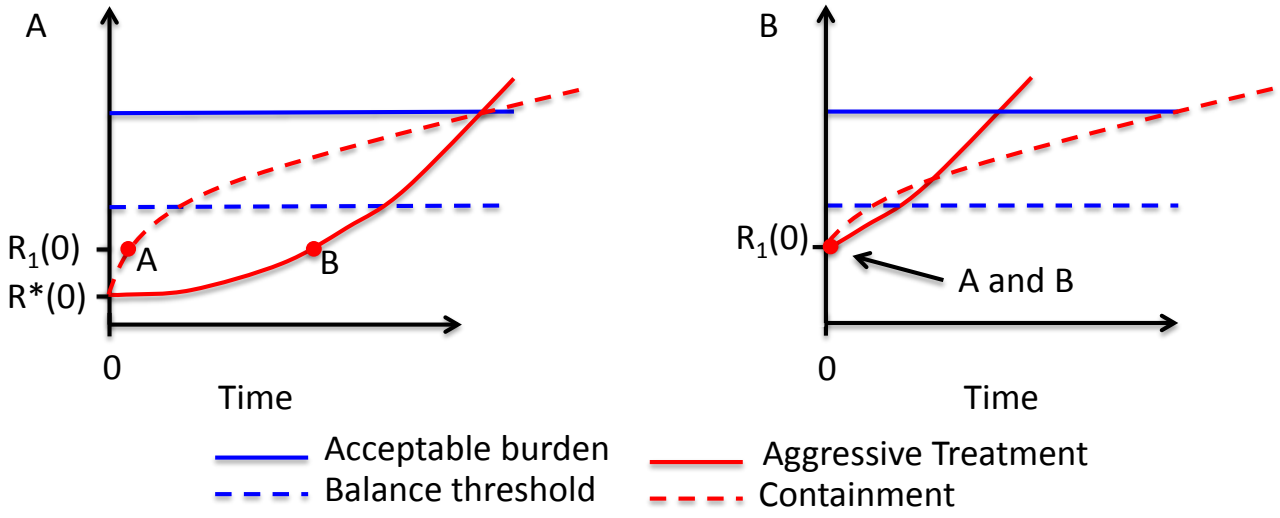
$$\dot{R}_C(t) = (1-c_I)r(1-(1+c_C)\delta P_{max})R_C(t) - \mu(t)R_C(t) + \epsilon r(1-\delta P_{max})(P_{max}-R_C(t)) \tag{S.8}$$

under containment, where the immune function μ is a non-decreasing function of time. Consider the scenario where the balance threshold is less than the acceptable burden ($R_{balance} < P_{max}$). Then there is a resistant density $R^*(0)$ such that

(i) if the starting resistant density is below $R^*(0)$ then aggressive treatment delays treatment failure longer than containment and

(ii) if the starting resistant density is above R_C then containment delays treatment failure longer than aggressive treatment.

Proof. We begin by proving this result for the case when the immune function μ is constant. Let t_A be the time to treatment failure under aggressive treatment and t_C the time to treatment failure under containment. In S6 Text we derive explicit closed form solutions for t_A and t_C for the case when μ is constant. These expressions are continuous functions of the



S1 Fig: **The effect of increasing the starting resistant density when the immune function μ is constant. Panel A:** The dynamics of the resistant density under containment (dashed red) and aggressive treatment (solid red). When the starting resistant density is $R^*(0)$, treatment failure occurs at the same time for both containment and aggressive treatment (the two curves intersect at the acceptable burden). The points A and B indicate the resistant density $R_1(0)$ on the containment curve and the aggressive treatment curve respectively. **Panel B:** This figure shows the curves in from Panel A translated to the left so that points A and B correspond to time $t = 0$. This shows the dynamics of the resistant density under containment (dashed red) and aggressive treatment (solid red) when the starting resistant density is $R_1(0)$. Because the aggressive treatment curve was shifted more than the containment curve the two curves now intersect below the acceptable burden. Containment delays treatment failure longer than aggressive treatment when the starting resistant density is greater than $R^*(0)$.

model parameters and the starting density $R(0)$. We also know that if $R(0) \geq R_{balance}$ then $t_C > t_A$ (this is the case depicted in Figure 2B of the main text). Additionally, if $R(0) = 0$ (and $\epsilon > 0$) then $t_A > t_C$. Then, since t_A and t_C are continuous functions of the starting resistant density, there is a starting resistant density $R_1(0)$ such that $R_1(0) < R_{balance}$ and $t_C = t_A$. This proves that there is at least one starting resistant density which is less than $R_{balance}$ and for which $t_C = t_A$. Let $R^*(0)$ be the smallest starting resistant density where $t_A = t_C$. S1 Fig, Panel A shows hypothetical curves for the resistant density starting at $R^*(0)$ under aggressive treatment and containment. Note that these curves intersect at the acceptable burden (i.e., $t_A = t_C$).

Now, since μ is constant the rate of change of the resistant density depends only on the resis-

tant density (i.e., Equation (S.7) and Equation (S.8) do not explicitly depend on time). This means that if the starting resistant density was some larger value $R_1(0)$ then the resistant density under containment would follow the same path (but shifted in time). Similarly the resistant density under aggressive treatment would also follow the same path (but shifted in time). In particular the containment curve in S1 Fig Panel A would be shifted to the left so that point A corresponds to time $t = 0$ and the aggressive treatment curve in S1 Fig Panel A would be shifted to the left so that point B corresponds to time $t = 0$. S1 Fig Panel B shows the shifted curves which describe the dynamics of the resistant density under containment and aggressive treatment when the starting density is $R_1(0)$. Since the curve for aggressive treatment must be shifted more (i.e., in S1 Fig Panel A point B is further to the right than point A) the two shifted curves intersect at a lower value than the two original curves (i.e., they intersect below the acceptable burden). In other words, containment takes longer to fail than aggressive treatment. This argument is true for any $R_1(0) > R^*(0)$ and hence containment will be best whenever the starting resistant density exceeds $R^*(0)$. Additionally, since $R^*(0)$ was chosen to be the minimum starting resistant density where $t_A \leq t_C$ (and $t_A > t_C$ when $R(0) = 0$) by continuity we also know that aggressive treatment will be best whenever the starting resistant density is below $R^*(0)$. This proves the claim for the case when μ is constant. S6 Text also contains an alternative proof of this claim.

Now consider the case when μ is a non-decreasing function of time. Let $R^*(0)$ be the smallest starting resistant density where $t_A = t_C$ in the case where μ is a non-decreasing function of time. S2 Fig Panel A shows the resistant density under containment and aggressive treatment when the starting resistant density $R^*(0)$. Recovering the resistant dynamics for the case when the starting resistant density is $R_1(0)$ requires two steps. The first step, which is depicted in S2 Fig Panel B, is to translate the curves to the left so that points A and B correspond to time $t = 0$. This step is identical to what was done for the case when μ is constant. The second step is to account for the fact that the immune response at any particular resistant density will be less than or equal to the immune response at the same resistant density in the unshifted curves (because μ is a non-decreasing function of time). This implies that the rate of change of the actual resistant density will be greater than that depicted in S2 Fig Panel B. Additionally, since the aggressive treatment curve was translated from a later time (i.e., point B in S2 Fig Panel A occurs at a later time than point A) the increase in its rate of change will be at least as great as for the containment curve. This means that the curves depicting the actual dynamics under containment and aggressive treatment will intersect at a lower resistant density (compare points C_2 and C_3 in S2 Fig Panel C). S3 Fig shows a magnified version of the curves in S3 Fig Panel C. Note that because the magnitude of the change in immune function will be greater for aggressive treatment the distance between the containment and aggressive treatment curve will be less in Panel C than in Panel B. This means that the two curves intersect at a lower resistant density (point C_3 is below point C_2). This argument is true for any $R_1(0) > R^*(0)$ and hence containment will be best whenever the starting resistant density exceeds $R^*(0)$. Additionally, since $R^*(0)$ was chosen to be the minimum starting resistant density where $t_A \leq t_C$ (and

$t_A > t_C$ when $R(0) = 0$) by continuity we also know that aggressive treatment will be best whenever the starting resistant density is below $R^*(0)$.

□

S6 Text: Supporting calculations for Fig 3 of main text.

Let R_A denote the resistant density under aggressive treatment and let R_C denote the resistant density under containment. Because we assume that aggressive treatment immediately removes the entire drug-sensitive population, the expansion of the resistant density under aggressive treatment is described by

$$\dot{R}_A = (1 - c_I) r R_A (1 - (1 + c_C)\delta R_A) - \mu R_A. \tag{S.9}$$

Assuming that the immune response μ is constant the solution to this equation is

$$R_A(t) = \frac{\left(1 - \frac{\mu}{(1-c_I)r}\right) R(0) \exp\left[((1 - c_I)r - \mu)t\right]}{\left(1 - \frac{\mu}{(1-c_I)r}\right) + R(0)(1 + c_C)\delta \left(\exp\left[((1 - c_I)r - \mu)t\right] - 1\right)}, \tag{S.10}$$

where $R(0)$ is the resistant density at the start of the management period. If aggressive treatment fails at time $t = t_A$ then $R_A(t_A) = P_{max}$. Substituting this equality into Equation (S.10) gives,

$$t_A = \frac{1}{((1 - c_I)r - \mu)} \ln\left[\frac{P_{max}}{R(0)} \frac{(1 - c_I)r(1 - R(0)(1 + c_C)\delta) - \mu}{(1 - c_I)r(1 - P_{max}(1 + c_C)\delta) - \mu}\right]. \tag{S.11}$$

Under containment the expansion of the resistant density is described by

$$\dot{R}_C = (1 - c_I) r R_C (1 - (1 + c_C)\delta P_{max}) - \mu R_C + \epsilon r \left(1 - \delta P_{max}\right)\left(P_{max} - R_C\right).$$

Assuming that the immune response μ is constant the solution to this equation is

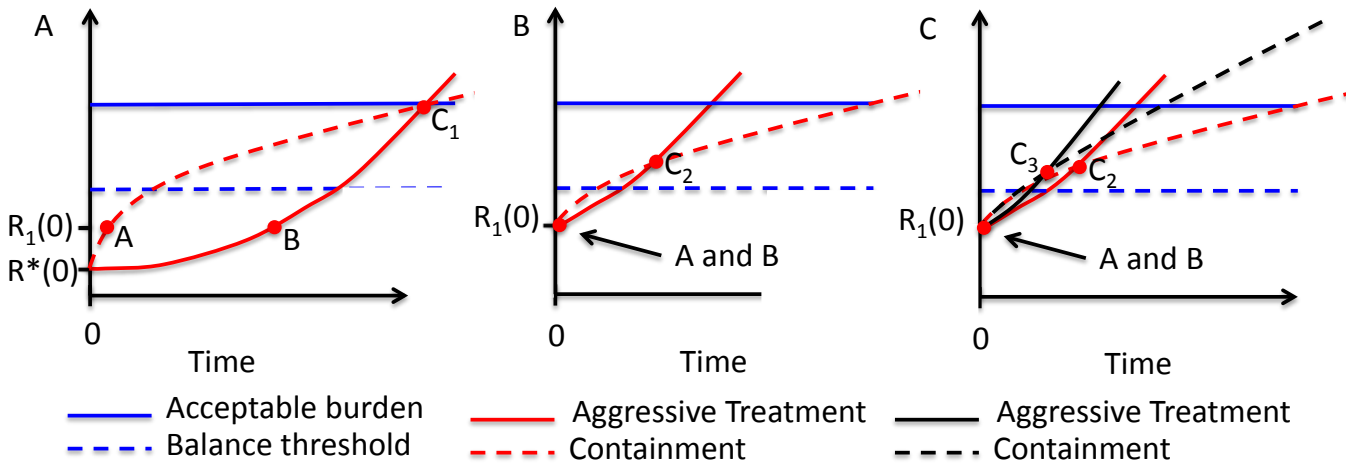
$$R_C(t) = (B + R(0)) \exp\left[((1 - c_I)r(1 - (1 + c_C)\delta P_{max}) - \epsilon r(1 - \delta P_{max}) - \mu)\, t\right] - B, \tag{S.12}$$

where $R(0)$ is the resistant density at the beginning of the management period and

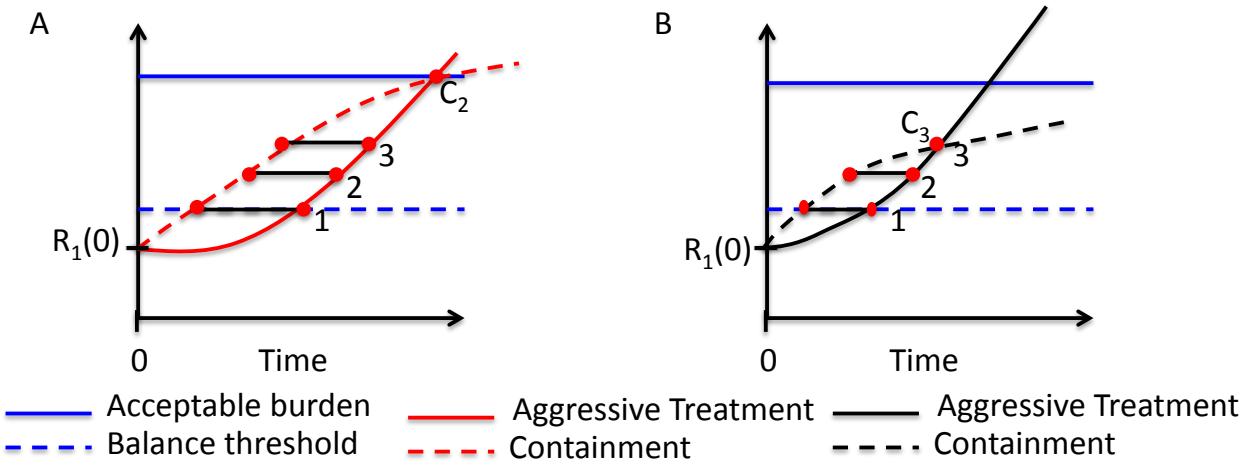
$$B = \frac{\epsilon r \left(1 - \delta P_{max}\right) P_{max}}{(1 - c_I)r(1 - (1 + c_C)\delta P_{max}) - \epsilon r(1 - \delta P_{max}) - \mu}.$$

If containment fails at time t_C then $R_C(t_C) = P_{max}$. Substituting this equality into Equation (S.12) gives,

$$t_C = \frac{1}{(1 - c_I)rD} \ln\left[\frac{P_{max}}{R(0)} \left(\frac{(1 - c_I)D + \epsilon\left(1 - \delta P_{max}\right)}{(1 - c_I)D + \epsilon\left(1 - \delta P_{max}\right)\frac{P_{max}}{R(0)}}\right)\right], \tag{S.13}$$



S2 Fig: **The effect of increasing the starting resistant density when the immune function μ is a non-decreasing function of time. Panel A:** The dynamics of the resistant density under containment (dashed red) and aggressive treatment (solid red). When the starting resistant density is $R^*(0)$ treatment failure occurs at the same time for both containment and aggressive treatment (the two curves intersect at the acceptable burden). The points A and B indicate the resistant density $R_1(0)$ on the containment curve and the aggressive treatment curve respectively. There are two steps involved in obtaining the actual resistance dynamics from these curves. **Panel B:** Step One. This figure shows the curves from Panel A translated to the left so that points A and B correspond to time $t = 0$. **Panel C:** Step Two. The rate of change of the actual containment curve (black dashed) will be greater than the one shown in Panel B (i.e., the black dashed curve is above the red dashed curve). This is because the immune response of the shifted curve will be less. This difference will increase in time. This is also true for the aggressive treatment curve (black solid), but the difference will be greater because the aggressive treatment curve involved a larger shift in time. This shows the dynamics of the resistant density under containment (dashed red) and aggressive treatment (solid red) when the starting resistant density is $R_1(0)$. Because the aggressive treatment curve was shifted more than the containment curve the two curves now intersect at an even lower resistant density (point C_3 is below point C_2). Containment delays treatment failure longer than aggressive treatment when the starting resistant density is greater than $R^*(0)$.



S3 Fig: **Magnified version of the curves in S2 Fig.** The black horizontal lines indicate the distance between the containment curve and the aggressive treatment curve at different resistant densities. **Panel A:** The red curves from Panel C of S2 Fig. **Panel B:** The black curves from Panel C of S2 Fig. Notice that the black horizontal lines in Panel B are shorter than the corresponding lines in Panel B. This indicates that accounting for the fact that the immune function is a non-decreasing function of time actually decreases the distance between the containment and aggressive treatment curves. This means that they will intersect at a lower resistant density.

where

$$D = 1 - \frac{\mu}{(1-c_I)r} - (1+c_C)\delta P_{max} - \frac{\epsilon}{(1-c_I)}\left(1-\delta P_{max}\right).$$

Therefore, from Equation (S.11) and (S.13) we have,

$$\frac{t_C}{t_A} = \frac{\frac{1}{(1-c_I)rD}\ln\left[\frac{P_{max}}{R(0)}\left(\frac{(1-c_I)D+\epsilon(1-\delta P_{max})}{(1-c_I)D+\epsilon(1-\delta P_{max})\frac{P_{max}}{R(0)}}\right)\right]}{\frac{1}{((1-c_I)r-\mu)}\ln\left[\frac{P_{max}}{R(0)}\frac{(1-c_I)r(1-R(0)(1+c_C)\delta)-\mu}{(1-c_I)r(1-P_{max}(1+c_C)\delta)-\mu}\right]}. \tag{S.14}$$

Now, from Equation (S.9), $\dot{R}_A = 0$ when $R_A = \frac{1}{(1+c_C)\delta}\left(1-\frac{\mu}{(1-c_I)r}\right)$. This is the self-limiting density discussed in the main text,

$$R_{lim} \doteq \frac{1}{(1+c_C)\delta}\left(1-\frac{\mu}{(1-c_I)r}\right).$$

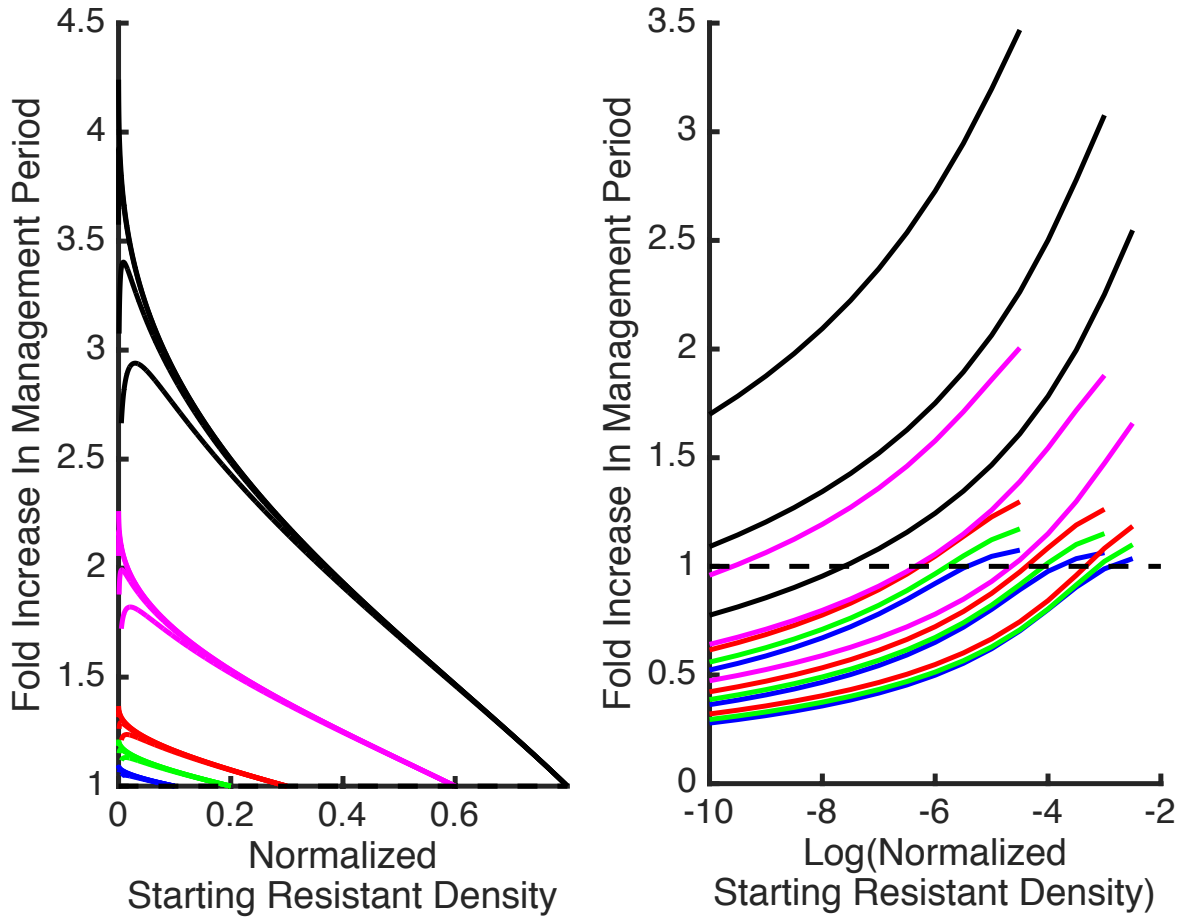
Now define the variables: $\tilde{R}_{balance} = \frac{R_{balance}}{R_{lim}}$, $\tilde{P}_{max} = \frac{P_{max}}{R_{lim}}$ and $\tilde{R}_0 = \frac{R(0)}{R_{lim}}$. Substituting these variables into Equation (S.14) allows us to express the ratio $\frac{t_C}{t_A}$ in terms of how the three pathogen densities $R(0)$, P_{max} and $R_{balance}$ compare to R_{lim}. That is,

$$\frac{t_C}{t_A} = \frac{1}{1-\tilde{P}_{max}-\tilde{R}_{balance}}\frac{\ln\left[\frac{\tilde{P}_{max}}{\tilde{R}_0}\left(\frac{\left(1-\tilde{P}_{max}\right)}{\left(1-\tilde{P}_{max}\right)+\tilde{R}_{balance}\left(\frac{\tilde{P}_{max}}{\tilde{R}_0}-1\right)}\right)\right]}{\ln\left[\frac{\tilde{P}_{max}}{\tilde{R}_0}\frac{\left(1-\tilde{R}_0\right)}{\left(1-\tilde{P}_{max}\right)}\right]}. \tag{S.15}$$

Equation (S.15) is the equation that was used to generate Fig. 3 of the main text. In Fig. 3 the acceptable burden was allowed to vary from 10% to 80% of R_{lim} (i.e, $\tilde{P}_{max} \in [0.1, 0.8]$) and the resistant density at the start of the management period was allowed to vary from the balance threshold to 80% of R_{lim} (i.e, $\tilde{R}_0 \in [\tilde{R}_{balance}, 0.8]$). Here we reproduce Fig. 3 from the main text (S4 Fig; Panel A) but also include the possibility that the starting resistant density is below the balance threshold (S4 Fig; Panel B). Together, Panel A and Panel B of S4 Fig allow the starting resistant density to vary from 10^{-8}% to 80% of R_{lim} (i.e, $\tilde{R}_0 \in [10^{-10}, 0.8]$). These choices cover a wide range of possibilities.

The chosen parameter range, $\tilde{R}_{balance} \in [0, 0.01]$ requires a bit more explanation. Note that,

$$\begin{aligned}
\tilde{R}_{balance} &= \frac{\epsilon\left(1-\delta P_{max}\right)}{(1-c_I)(1+c_C)\delta}\frac{(1+c_C)\delta}{\left(1-\frac{\mu}{(1-c_I)r}\right)}, \\
&= \frac{\epsilon\left(1-\delta P_{max}\right)r}{(1-c_I)r-\mu}, \\
&\leq \frac{\epsilon}{1-c_I}\frac{1}{1-\frac{\mu}{(1-c_I)r}}.
\end{aligned}$$



S4 Fig: Ratio of time to treatment failure under containment to time to treatment failure under aggressive treatment. Each color corresponds to a different acceptable burden (blue:10%, green: 20%, red: 30%, purple:60% and black:80% of R_{lim}). $\tilde{R}_{balance}$ is varied in the range of [0, 0.01]. For each color, the upper curve corresponds to $\tilde{R}_{balance} = 0$ and the lower curve to $\tilde{R}_{balance} = 0.01$. **Panel A:** Values are plotted for $\tilde{R}_0 \geq \tilde{R}_{balance}$. (The starting resistant density exceeds the balance threshold.) **Panel B:** The same as Panel A except for $\tilde{R}_0 < \tilde{R}_{balance}$. (The starting resistant density is below the balance threshold.) Note that the horizontal axis in Panel B is $\log \tilde{R}_0$.

The quantity $\frac{(1-c_I)r}{\mu}$ can be thought of as the expected number of progeny produced by an average resistant pathogen (assuming there is no competition). If $\frac{(1-c_I)r}{\mu} \geq 1.1$ and the reduction in intrinsic replication $(1-c_I) \geq 0.1$ then we have,

$$\tilde{R}_{balance} \leq \epsilon 110.$$

Under these assumptions $\tilde{R}_{balance}$ will be less than 0.01 provided the probability of mutation is not too large (i.e., $\epsilon < 9.1 \times 10^{-5}$). Alternatively, if $\frac{(1-c_I)r}{\mu} \geq 2$ and the reduction in intrinsic replication $(1-c_I) \geq 0.1$ then $\tilde{R}_{balance}$ will be less than 0.01 provided the mutation rate ϵ is less than 5×10^{-4}.

We can also use this example to gain some insight into the situation when $R(0) < R_{balance} < P_{max}$ (i.e., the cases depicted in Figure 2 C-D in the main text). In particular we will show that there is a resistant density $R^*(0)$ such that aggressive treatment is best whenever $R(0) < R^*(0)$ and containment is best whenever $R(0) > R^*(0)$.

Containment will be at least as good as aggressive treatment whenever $t_C \geq t_A$. By Equation (S.15) this will occur whenever

$$\tilde{R}_0 \leq f(\tilde{R}_0) \tag{S.16}$$

where

$$f(\tilde{R}_0) = \tilde{P}_{max}\left[\frac{\tilde{R}_0(1-\tilde{P}_{max})}{\tilde{P}_{max}(1-\tilde{R}_0)}\right]^A - \tilde{R}_{balance}\frac{(\tilde{P}_{max}-\tilde{R}_0)}{1-\tilde{P}_{max}}$$

and $A = 1 - \tilde{P}_{max} - \tilde{R}_{balance}$. We will now show that the equality in Equation (S.16) can hold for at most one value of $\tilde{R}_0 \in [0, \tilde{P}_{max})$. First note that if $\tilde{R}_0 = 0$ then $f(0) = -\frac{\tilde{R}_{balance}\tilde{P}_{max}}{1-\tilde{P}_{max}} < 0$ and hence (assuming that $\epsilon \neq 0$) Equation (S.16) is not satisfied when $\tilde{R}_0 = 0$. Additionally, when $\tilde{R}_0 = \tilde{P}_{max}$ we have that $f(\tilde{P}_{max}) = \tilde{P}_{max}$ and $\left.\frac{\partial f}{\partial \tilde{R}_0}\right|_{\tilde{P}_{max}} = 1$. Note also that if $\tilde{R}_0 = \tilde{P}_{max} - \epsilon$ then

$$f(\tilde{P}_{max}-\epsilon) = \tilde{P}_{max}\left[\frac{(\tilde{P}_{max}-\epsilon)(1-\tilde{P}_{max})}{\tilde{P}_{max}(1-\tilde{P}_{max}+\epsilon)}\right]^A - \tilde{R}_{balance}\left[\frac{\epsilon}{1-\tilde{P}_{max}}\right] \doteq T(\epsilon)$$

and

$$\frac{\partial T}{\partial \epsilon} = -\tilde{P}_{max}A\left[\frac{(\tilde{P}_{max}-\epsilon)(1-\tilde{P}_{max})}{\tilde{P}_{max}(1-\tilde{P}_{max}+\epsilon)}\right]^{A-1}\frac{1-\tilde{P}_{max}}{\tilde{P}_{max}(1-\tilde{P}_{max}+\epsilon)^2} - \frac{\tilde{R}_{balance}}{1-\tilde{P}_{max}} < 0$$

and so as $\tilde{R}_0$ approaches $\tilde{P}_{max}$ from the left, the function f decreases to approach $\tilde{P}_{max}$. This means that f must cross the $\tilde{R}_0 = \tilde{R}_0$ line an odd number of times.

If f crosses the $\tilde{R}_0 = \tilde{R}_0$ line only once then this proves the claim. In particular the crossing occurs when $R(0) = R^*(0)$. In other words, $R^*(0)$ is implicitly defined when $R(0) = R^*(0)$ and equality holds in Equation (S.16).

Suppose, on the other hand, that f crosses the $\tilde{R}_0 = \tilde{R}_0$ line more than once. Let $\tilde{R}_1$ and $\tilde{R}_2$ denote the values of $\tilde{R}_0$ at the first two crossings. Then we must have that $\frac{\partial f}{\partial \tilde{R}_0}\Big|_{\tilde{R}_1} > \frac{\partial \tilde{R}_0}{\partial \tilde{R}_0}\Big|_{\tilde{R}_1} = 1$ and $\frac{\partial f}{\partial \tilde{R}_0}\Big|_{\tilde{R}_2} < \frac{\partial \tilde{R}_0}{\partial \tilde{R}_0}\Big|_{\tilde{R}_2} = 1$. Since $\frac{\partial f}{\partial \tilde{R}_0}$ is continuous this means that there must be a $\tilde{R}_3 \in (\tilde{R}_1, \tilde{R}_2)$ such that $\frac{\partial f}{\partial \tilde{R}_0}\Big|_{\tilde{R}_3} = 1$.

In other words,

$$\frac{\partial f}{\partial \tilde{R}_0}\Big|_{\tilde{R}_3} = \tilde{P}_{max} A \left[\frac{\tilde{R}_3(1-\tilde{P}_{max})}{\tilde{P}_{max}(1-\tilde{R}_3)}\right]^A \left[\frac{1}{\tilde{R}_3(1-\tilde{R}_3)}\right] + \frac{\tilde{R}_{balance}}{1-\tilde{P}_{max}} = 1. \tag{S.17}$$

After some simplification Equation (S.17) becomes

$$\left[\frac{\tilde{P}_{max}}{\tilde{R}_3}\right]^{1-A} = \left[\frac{1-\tilde{R}_3}{1-\tilde{P}_{max}}\right]^{1+A}. \tag{S.18}$$

Substituting $\tilde{R}_3 = \gamma \tilde{P}_{max}$ for some $\gamma \in (0,1)$ into Equation (S.18) results in

$$\tilde{P}_{max} = \frac{1 - \left(\frac{1}{\gamma}\right)^{\frac{1-A}{1+A}}}{\gamma - \left(\frac{1}{\gamma}\right)^{\frac{1-A}{1+A}}} \doteq B(\gamma). \tag{S.19}$$

But

$$\frac{\partial B}{\partial \gamma} = \frac{\frac{1-A}{1+A}\left(\frac{1}{\gamma}\right)^{\frac{1-A}{1+A}}\left(1-\frac{1}{\gamma}\right) + \left(\frac{1}{\gamma}\right)^{\frac{1-A}{1+A}} - 1}{\left(\gamma - \left(\frac{1}{\gamma}\right)^{\frac{1-A}{1+A}}\right)^2} < 0,$$

which implies that there is at most one γ that will satisfy Equation (S.19). Therefore, f cannot cross the $\tilde{R}_0 = \tilde{R}_0$ line more than once.

S7 Text: Minimizing the resistant expansion rate will maximally delay treatment failure

Here we provide a condition which – when it is satisfied – guarantees that minimising the resistant expansion rate at each instant in time will maximally delay treatment failure. We then demonstrate that our main model of infection dynamics (Equation (3) in the main text)

satisfies this condition.

Statement of condition: If the minimum achievable resistant expansion rate at any instant of the infection depends only on (i) that instant t and (ii) the resistant density at that instant $R(t)$, then minimizing the resistant expansion rate at each instant will maximally delay treatment failure. More formally, if the minimum achievable resistant expansion rate at the point $(t, R(t))$ depends only on the point $(t, R(t))$ and not on other factors such as the path taken to reach that point, then minimizing the resistant expansion rate at each instant in time will maximally delay treatment failure. We will refer to this treatment regimen as the "minimizing regimen".

Explanation of condition: S5 Fig provides a pictoral explanation for why the above statement is true. Let R_M denote the resistant density trajectory that corresponds to the "**M**inimizing regimen". Let R_A be any other possible resistant density trajectory (any "**A**lternative regimen" that doesn't minimise the resistant expansion rate at every single instant). These two trajectories coincide at the start of the management period ($t = 0$). Suppose these trajectories start to differ at time $\bar{t}$. This implies that the resistant expansion rates of these two trajectories must differ at $\bar{t}$. In particular, it must be (by definition) that the resistant expansion rate of the minimizing regimen is less than that of the alternative regimen. If $\dot{R}$ denotes the resistant expansion rate then,

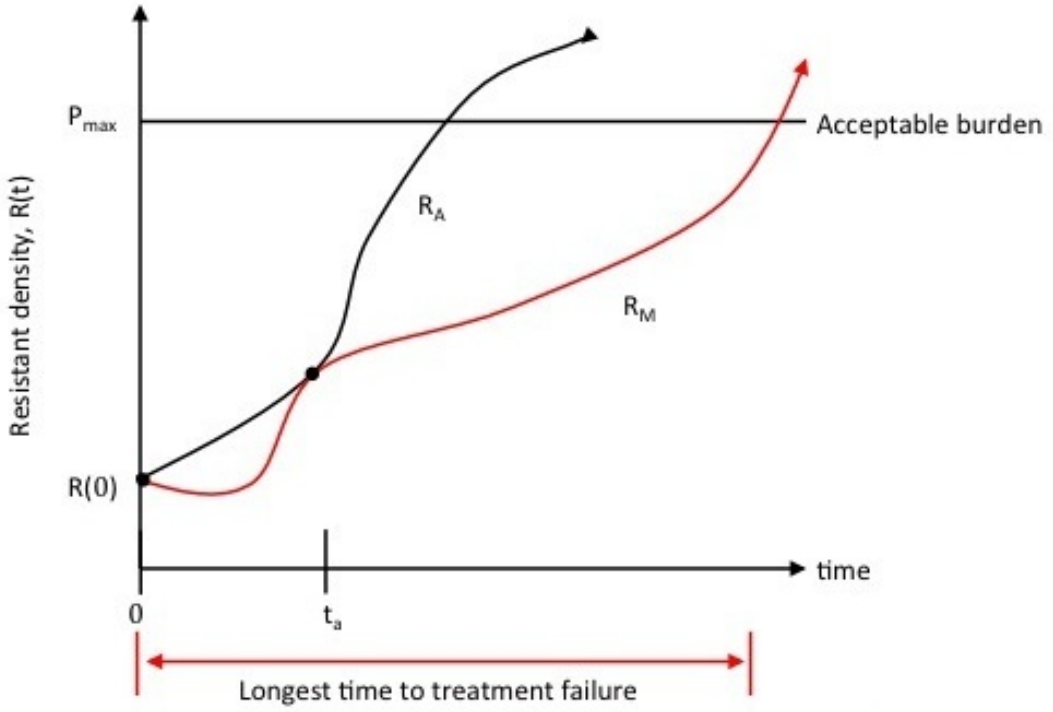
$$\dot{R}_M(\bar{t}) < \dot{R}_A(\bar{t}).$$

This means that at the instant $\bar{t}$, R_A is increasing more quickly (or decreasing more slowly) than R_M. Hence, R_M will never exceed R_A. Every time these two trajectories meet, they will either continue to coincide or R_M will be driven below R_A. Since the resistant density corresponding to the minimizing regimen is always less than or equal to the resistant density corresponding to the alternative regimen, it cannot exceed the acceptable burden before R_A. The minimizing strategy will delay treatment failure at least as long as the alternative regimen. Since this argument holds for any alternative regimen, the minimizing strategy will maximally delay treatment failure.

Model specific comments: We now show that the conceptual model used in our main analysis (Equation (3) of the main text) satisfies the above mentioned condition. For our main model, the resistant expansion rate is

$$\dot{R}(t) = (1 - c_I)r\left(1 - (1 + c_C)\delta P(t)\right)R(t) - \mu(t)R(t) + \epsilon r\left(1 - \delta P(t)\right)\left(P(t) - R(t)\right), \quad \text{(S.20)}$$

where the total pathogen density $P(t)$ lies in the range of $[R(t), P_{max}]$. When $P(t) = R(t)$ the sensitive population has been removed and when $P(t) = P_{max}$ the sensitive density is at its maximum clinically acceptable value (i.e., $P_{max} - R(t)$). For a fixed set of model parameters, the resistant expansion rate (Equation (S.20)) depends only on the time t (which will determine the immune response $\mu(t)$), the resistant density $R(t)$ and the total pathogen



S5 Fig: **Minimizing the resistant expansion rate at each instant in time will maximally delay treatment failure.** The minimizing regimen chooses the sensitive density that minimizes the resistant expansion rate at each instant in time (red curve). This curve will never exceed the curve resulting from any other alternative strategy (for example, the black curve). In this particular example, the two trajectories initially coincide at the beginning of the management period ($t = 0$) and at one other time t_a (indicated by black dot). In both cases the curve corresponding to the minimizing regimen (red curve) is driven below the alternative curve (black curve).

density $P(t)$. For a fixed point $(t, R(t))$, the resistant expansion rate can be modified by changing the sensitive density (which amounts to picking total pathogen densities $P(t)$ in the range $[R(t), P_{max}]$). The allowed range of pathogen densities depends only on $R(t)$. Hence the achievable range of resistant expansion rates at the point $(t, R(t))$ is completely determined by the point $(t, R(t))$.

This tells us that, if at every instant t of the infection, we are free to choose any pathogen density in the range of $[R(t), P_{max}]$ then the time to treatment failure will be maximally delayed by choosing the sensitive density that minimises the resistant expansion rate. In particular, the analysis in the main text, indicates that the resistant expansion rate will be minimized by removing the sensitive pathogen (i.e., choosing $P(t) = R(t)$) when the resistant density is less than the balance threshold and maintaining the maximum clinically acceptable sensitive density (i.e., choosing $P(t) = P_{max}$) when the resistant density exceeds the balance threshold. Note that, if the resistant density is below the balance threshold at the start of the management period then this "minimizing regimen" requires deliberately increasing the sensitive density if the resistant density eventually reaches and exceeds the balance threshold.

S8 Text: Slowing resistance emergence: immediate versus future effects of the sensitive population

If the resistant expansion rate depends on the current sensitive and resistant densities but not on previous pathogen densities, then maximizing the sensitive density is advantageous whenever it slows the expansion of the resistant population and detrimental whenever it increases it. In particular, this statement is true when the resistant expansion rate is described by Equation (3) from the main text and also the alternative models discussed in S9 Text.

If, on the other hand, previous pathogen densities are important then determining whether or not maximizing sensitive pathogen is advantageous is more complicated. Previous pathogen densities may be important if, for example, they affect the current immune response or the current resource availability. Here we discuss, in the context of our main model (Equation (3) from main text), how these generalities can change the results.

Immunity with history dependence

It may be advantageous to temporarily elevate the resistant expansion rate if this will lead to an improved immune response later in the infection. Suppose the patient's immune response is determined by the accumulated pathogen burden he has experienced during his infection. In particular, suppose that the greater the accumulated pathogen burden – the stronger the immune response.

If the immunity is an increasing function of total experienced pathogen burden $P_{Bur}(t) = \int_0^t P(\tau)\mathrm{d}\tau$, then the model for containment used in our main analysis becomes,

$$\begin{aligned}\dot{R} &= (1-c_I)r\left(1-(1+c_C)\delta R\right)R - \mu(P_{Bur}(t))R \\ &\quad -(1-c_I)r(1+c_C)\delta R(P_{max}-R) + \epsilon r\left(1-\delta P_{max}\right)(P_{max}-R),\end{aligned}$$

where $\frac{\mathrm{d}\mu}{\mathrm{d}P_{Bur}} > 0$.

In this case, the immediate effect of sensitive pathogen on the resistant expansion rate is unchanged. That is, the instantaneous expansion of the resistant population is minimised by (i) removing the entire sensitive population if $R(t) < R_{balance}$ and by (ii) maximising the sensitive density if $R(t) > R_{balance}$. These assumptions about immunity, however, will increase the number of scenarios where containment is better than aggressive treatment. To see this, consider the four possibilities depicted in Fig. 2 of the main text:

Possibility A: If $R_{balance} > P_{max}$ then maximising the sensitive density will always increase the expansion rate of the resistant population. In this case, however, containment may still be better than aggressive treatment if it sufficiently augments the immune response.

Possibility B: If $P_{max} > R(0) > R_{balance}$ then maximising the sensitive density will decrease the expansion rate of the resistant population whenever the resistant density is increasing. In this case, containment minimises the instantaneous expansion of the resistant density AND maximizes the immune response – containment is better than aggressive treatment.

Possibilities C-D: If $P_{max} > R_{balance} > R(0)$ then maximising the sensitive density initially increases the resistant expansion rate and then later (i.e., when the resistant density exceeds the balance threshold) decreases the resistant expansion rate. If immunity increases with P_{Bur} then there will be an increased number of scenarios where containment out performs aggressive treatment because of augmented immunity.

Opposite assumptions about immunity lead to opposite conclusions. If the immune response is a decreasing function of total past pathogen burden (which can occur, for example, with immune exhaustion, then elevating the resistant expansion rate may be advantageous if it leads to decreased pathogen burden. This assumption about immunity will decrease the number of scenarios where containment is better than aggressive treatment. To see this, let immunity be a decreasing function of total experienced pathogen burden (i.e., $\frac{\mathrm{d}\mu}{\mathrm{d}P_{Bur}} < 0$) and consider the four possibilities depicted in Fig. 2 of the main text:

Possibility A: If $R_{balance} > P_{max}$ then maximising the sensitive density will always increase the expansion rate of the resistant population. In this case, aggressive treatment will minimize the instantaneous resistant expansion rate and maximize immunity. Aggressive

treatment is best.

Possibility B: If $P_{max} > R(0) > R_{balance}$ then maximising the sensitive density will always decrease the expansion rate of the resistant population while the resistance is increasing. In this case, containment minimises the instantaneous resistant expansion rate but also minimises the immune response. Aggressive treatment may be better than containment if it leads to a sufficiently large immune response.

Possibilities C-D: If $P_{max} > R_{balance} > R(0)$ then maximising the sensitive density initially increases the resistant expansion rate and then, when the resistant density exceeds the balance threshold, decreases the resistant expansion rate. If immunity decreases with P_{Bur} then there will be an increased number of scenarios where aggressive treatment outperforms containment because of augmented immunity.

Resource dynamics with history effects

If competition is mediated through a resource then changing resource levels (due to pathogen use) during the management period will change the strength of competition. If the availability of resources is a decreasing function of total experienced pathogen burden $P_{Bur}(t) = \int_0^t P(\tau)\mathrm{d}\tau$, this can be captured in our original model (Equation (3) in main text) by assuming that the effect of competition (as determined by the coefficient δ) is an increasing function of $P_{Bur}(t)$. With this assumption, the model used in our main analysis becomes,

$$\begin{aligned}\dot{R} &= (1-c_I)r\left(1-(1+c_C)\delta(P_{Bur}(t))R\right)R-\mu(t)R \\ &\quad -(1-c_I)r(1-c_C)\delta(P_{Bur}(t))R(P_{max}-R)+\epsilon r\left(1-\delta(P_{Bur}(t))P_{max}\right)(P_{max}-R),\end{aligned}$$

where $\frac{\mathrm{d}\delta}{\mathrm{d}P_{Bur}} \geq 0$.

In this case, the immediate effect of sensitive pathogen on the resistant expansion rate is still unchanged. That is, the instantaneous expansion of the resistant population is minimised by (i) removing the entire sensitive population if $R(t) < R_{balance}$ and by (ii) maximising the sensitive density if $R(t) > R_{balance}$. The balance threshold $R_{balance}$ does, however, depend on δ. In particular,

$$\frac{\partial}{\partial\delta}R_{balance} = \frac{-\epsilon}{(1-c_I)(1-c_C)\delta^2} < 0. \tag{S.21}$$

Hence, as P_{Bur} increases, δ will increase and $R_{balance}$ will decrease. In other words, $R_{balance}$ will decrease as the infection progresses. This means that once $R > R_{balance}$ this will continue to be true while the resistance density in increasing.

Let $R_{balance}(0)$ denote the balance threshold at the start of the management period and consider the four possibilities depicted in Fig. 2 of the main text:

Possibility A: If $R_{balance}(0) > P_{max}$ then maximising the sensitive density initially increases the expansion rate of the resistant population. In this case, however, containment may still be better than aggressive treatment if it can sufficiently augment the effect of competition and adequately (and rapidly) lower the balance threshold.

Possibility B: If $P_{max} > R(0) > R_{balance}(0)$ then maximising the sensitive density will always decrease the expansion rate of the resistant population while resistance emergence is a threat. In this case, containment minimises the instantaneous expansion of the resistant density AND maximizes the effect of competition – containment is better than aggressive treatment.

Possibilities C-D: If $P_{max} > R_{balance}(0) > R(0)$ then maximising the sensitive density initially increases the resistant expansion rate and then, when the resistant density exceeds the balance threshold, decreases the resistant expansion rate. If the effect of competition increases with P_{Bur} then there will be an increased number of scenarios where containment out performs aggressive treatment because of enhanced competition.

So far we have assumed that resources are continually depleted through-out the infection. If the patient is able to replenish resources before treatment failure occurs, then this will not be true. For example, if the patient's physiological response is to rapidly replenish resources once they become too low then maximizing the sensitive density even if the resistant density exceeds the balance threshold may be detrimental. In this case maintaining a lower sensitive density may be preferable if it can prevent the resource level from becoming too low and triggering a sudden influx of resources.

In general, the details of the patient's response to resource depletion are important and need to be evaluated on a case by case basis. Here we consider an extremely simple response to resource depletion in order to see how results can differ from the case where there is no appreciable replenishment of resources. Suppose the patient responds to even the slightest resource depletion with an immediate, large influx of new resources. In this extreme case the presence of pathogen in the patient will actually cause the resource level to increase. In particular, we will assume that as P_{Bur} increases, δ will decrease (sensitivity to competition decreases). By Equation (S.21) this means that $R_{balance}$ will increase as the infection progresses.

Possibility A: If $R_{balance}(0) > P_{max}$ then sensitive pathogen will always increase the expansion rate of the resistant population. Aggressive treatment is best.

Possibility B: If $P_{max} > R(0) > R_{balance}(0)$ then sensitive pathogen will initially decrease the expansion rate of the resistant population. In this case, containment will initially minimize the instantaneous resistant expansion rate but, since the balance threshold is increasing, it is possible that there will be a period of time later in the infection when $R < R_{balance}$ and

sensitive pathogen actually increases the resistant expansion rate. If treatment failure occurs before $R < R_{balance}$ then containment is best. On the other hand, if containment causes the balance threshold to exceed the resistant density before treatment failure then it is possible that aggressive treatment is better than containment. This will depend, in part, on how much containment accelerates the increase in $R_{balance}$.

Possibilities C-D: If $P_{max} > R_{balance}(0) > R(0)$ then sensitive pathogen initially increases the resistant expansion rate and then, when the resistant density exceeds the balance threshold, decreases the resistant expansion rate. If the effect of competition decreases with P_{Bur} then there will be an increased number of scenarios where aggressive treatment out performs containment because of the decreases effect of competition.

In summary temporarily elevating the resistant expansion rate may be advantageous if it will lead to either a stronger immune response or allow low resource levels to be sustained for extended periods of time.

S9 Text: Alternative ways to model competition

Here we detail the analysis of cost and benefit for two alternative models of competition.

General Lotka-Volterra competition

If we include the possibility that intra-specific and inter-specific competition may differ, then our original model (Equation (3) from the main text) becomes

$$\begin{aligned}\dot{R} &= (1-c_I)rR\left(1-\delta_{RR}R-\delta_{RS}\left(P_{max}-R\right)\right)-\mu(t)R \\ &\quad +\epsilon r\left(P_{max}-R\right)\left(1-\delta_{SR}R-\delta_{SS}(P_{max}-R)\right), \end{aligned} \tag{S.22}$$

where δ_{RR} and δ_{RS} are the competition coefficients describing how resistant replication is suppressed by resistant and sensitive pathogens, respectively. Similarly, δ_{SR} and δ_{SS} are the competition coefficients describing how sensitive replication is suppressed by resistant and sensitive pathogens, respectively. Since the replication rate is non-negative we assume that $\delta_{SR}P_{max} < 1$, $\delta_{SS}P_{max} < 1$, $\delta_{RR}P_{max} < 1$ and $\delta_{RS}P_{max} < 1$.

We can rewrite Equation (S.22) to separate out the contribution of the sensitive density to get:

$$\begin{aligned}\dot{R} &= \underbrace{(1-c_I)rR\left(1-\delta_{RR}R\right)-\mu(t)R}_{\substack{\text{resistant expansion}\\ \text{with no sensitives}}}-\underbrace{(1-c_I)rR\left(P_{max}-R\right)\delta_{RS}}_{\substack{\text{benefit of}\\ \text{maximizing sensitives}}} \\ &\quad +\underbrace{\epsilon r(P_{max}-R)\left(1-\delta_{SR}R-\delta_{SS}\left(P_{max}-R\right)\right)}_{\substack{\text{cost of}\\ \text{maximizing sensitives}}}. \end{aligned} \tag{S.23}$$

Maximizing the sensitive density will be advantageous whenever the benefit exceeds the cost. That is, whenever

$$(1-c_I)rR\left(P_{max}-R\right)\delta_{RS} > \epsilon r(P_{max}-R)\left(1-\delta_{SR}R-\delta_{SS}\left(P_{max}-R\right)\right). \tag{S.24}$$

There are two possibilities:

Possibility 1: $(1-c_I)\delta_{RS}-\epsilon(\delta_{SS}-\delta_{SR})>0$
In this case, rearranging Equation (S.24) gives,

$$R > \frac{\epsilon r(1-\delta_{SS}P_{max})}{(1-c_I)r\delta_{RS}+\epsilon r(\delta_{SR}-\delta_{SS})}.$$

In other words, the balance threshold for the general Lotka-Volterra competition (Equation (S.23)) is given by

$$R_{balance} = \frac{\epsilon r(1-\delta_{SS}P_{max})}{(1-c_I)r\delta_{RS}+\epsilon r(\delta_{SR}-\delta_{SS})}.$$

In this case the equivalent of Equation (5) in the main text is

$$P_{max} > \frac{\epsilon}{\epsilon\delta_{SR}+(1-c_I)\delta_{RS}}.$$

Possibility 2: $(1-c_I)\delta_{RS}-\epsilon(\delta_{SS}-\delta_{SR})<0$
In this case, rearranging Equation (S.24) gives,

$$R < \frac{\epsilon r(1-\delta_{SS}P_{max})}{(1-c_I)r\delta_{RS}+\epsilon r(\delta_{SR}-\delta_{SS})} < 0,$$

which is never possible and so maximising the sensitive density is never advantageous. If $(1-c_I)\delta_{RS}-\epsilon(\delta_{SS}-\delta_{SR})<0$, then aggressive treatment should be used. Note that this can occur only if sensitive replication is more strongly impacted by the presence of a sensitive pathogen than a resistant pathogen ($\delta_{SS}>\delta_{SR}$). Even if $\delta_{SS}>\delta_{SR}$, however, the difference would have to be substantial

$$\delta_{SS}-\delta_{SR} > \frac{(1-c_I)\delta_{RS}}{\epsilon}.$$

In particular, since $1\geq\delta_{SS}>\delta_{SR}>0$, this can occur only if $\epsilon>(1-c_I)\delta_{RS}$. In this case the cost of mutational input is so great that it is never advantageous to maintain sensitive pathogen in the patient.

Gompertz competition
If competition is modelled with a Gompertz function then the expansion of a purely resistant

infection is described by the following equation (for simplicity assume there are no fitness costs associated with resistance):

$$\dot{R} = rR\log\left(\frac{1}{\delta R}\right) - \mu(t)R. \tag{S.25}$$

Adding sensitive pathogen to Equation (S.25), the expansion of the resistant density under containment is described by,

$$\dot{R} = rR\log\left(\frac{1}{\delta P_{max}}\right) - \mu(t)R + \epsilon r\left(P_{max} - R\right)\log\left(\frac{1}{\delta P_{max}}\right).$$

We can rewrite this equation to separate out the contribution of the sensitive density to get:

$$\dot{R} = \underbrace{rR\log\left(\frac{1}{\delta R}\right) - \mu(t)R}_{\substack{\text{resistant expansion}\\ \text{with no sensitives}}} - \underbrace{rR\log\left(\frac{P_{max}}{R}\right)}_{\substack{\text{benefit of}\\ \text{maximizing sensitives}}} + \underbrace{\epsilon r(P_{max} - R)\log\left(\frac{1}{\delta P_{max}}\right)}_{\substack{\text{cost of}\\ \text{maximizing sensitives}}}. \tag{S.26}$$

Sensitive pathogen will be advantageous whenever the benefit exceeds the cost. In other words, whenever

$$rR\log\left(\frac{P_{max}}{R}\right) > \epsilon r(P_{max} - R)\log\left(\frac{1}{\delta P_{max}}\right). \tag{S.27}$$

Rearranging Equation (S.27) gives,

$$R > \frac{\epsilon P_{max}}{\epsilon\log\left(\frac{1}{\delta P_{max}}\right) + \log\left(\frac{P_{max}}{R}\right)}. \tag{S.28}$$

Note that the resistant density R is present on both sides of Equation (S.28). The right-hand side of Equation (S.28), however, satisfies

$$\frac{\partial}{\partial R}\frac{\epsilon P_{max}}{\epsilon\log\left(\frac{1}{\delta P_{max}}\right) + \log\left(\frac{P_{max}}{R}\right)} = \frac{\epsilon P_{max}}{\epsilon\log\left(\frac{1}{\delta P_{max}}\right) + \log\left(\frac{P_{max}}{R}\right)}\frac{1}{R\left(\epsilon\log\left(\frac{1}{\delta P_{max}}\right) + \log\left(\frac{P_{max}}{R}\right)\right)}.$$

Therefore, whenever $R = \frac{\epsilon P_{max}}{\epsilon\log\left[\frac{1}{\delta P_{max}}\right]+\log\left[\frac{P_{max}}{R}\right]}$, we have

$$\frac{\partial}{\partial R}\frac{\epsilon P_{max}}{\epsilon\log\left[\frac{1}{\delta P_{max}}\right] + \log\left[\frac{P_{max}}{R}\right]} = \frac{1}{\left(\epsilon\log\left[\frac{1}{\delta P_{max}}\right] + \log\left[\frac{P_{max}}{R}\right]\right)} < 1.$$

This means that whenever $R = \frac{\epsilon P_{max}}{\epsilon\log\left[\frac{1}{\delta P_{max}}\right]+\log\left[\frac{P_{max}}{R}\right]}$, R will increase more rapidly than $\frac{\epsilon P_{max}}{\epsilon\log\left[\frac{1}{\delta P_{max}}\right]+\log\left[\frac{P_{max}}{R}\right]}$. Hence, once Equation (S.28) holds, it will continue to hold provided resistance emergence is a threat. This means that once R is sufficiently large the sensitive

pathogens will be advantageous.

Although this establishes a threshold condition, we can not explicitly write an analytic expression for the balance threshold. We can, however, provide an upper bound. Namely, since

$$\frac{\epsilon P_{max}}{\epsilon \log\left(\frac{1}{\delta P_{max}}\right) + \log\left(\frac{P_{max}}{R}\right)} \leq \frac{\epsilon P_{max}}{(1-\epsilon)\log\left(P_{max}\right) - \epsilon \log\left(\delta\right)},$$

we know that

$$R_{balance} \leq \frac{\epsilon P_{max}}{(1-\epsilon)\log\left(P_{max}\right) - \epsilon \log\left(\delta\right)}.$$

This also means that the balance threshold is guaranteed to be below the acceptable burden if

$$P_{max} > \exp\left[\frac{\epsilon}{1-\epsilon}\left(1 + \log(\delta)\right)\right].$$

Note that this is an upper bound and that the acceptable burden does not need to be this high in order to exclude the possibility shown in Fig. 2 (Panel A) of the main text.

S10 Text: Further complexities

Here we augment our original model (Equation (3) from the main text) to include horizontal gene transfer and derive the balance threshold for this new model. We will also consider the possibility that the immune response inhibits pathogen function instead of actively clearing pathogen from the patient and briefly discuss the possibility that the phenotype of drug-resistance occurs on a continuum.

Horizontal gene transfer: One possible disadvantage of maintaining sensitive pathogen in the patient is that these pathogens could acquire resistance genes. These resistance genes could be acquired from either the existing resistant population or possibly the patient's microbiota.

We begin by considering resistant gene transfer from the resistant population to the sensitive population. We consider two possibilities. The first is that the rate of gene transfer is density dependent. In this case we model the rate of transfer of resistant genes from the resistant pathogen population to the sensitive population as $\epsilon_{HD} R(t)(P(t) - R(t))$. The other possibility is that gene transfer is not density dependent. In this case, we model the transfer rate of resistant genes from the resistant pathogen population to the sensitive population as $\epsilon_{HND} \frac{R(t)}{P(t)}(P(t) - R(t))$.

Similarily, for gene transfer from the microbiota to sensitive pathogen, we will use

$$\delta_{HD} B_R(t)(P(t) - R(t))$$

for the density dependent rate and $\delta_{HND}\frac{B_R(t)}{B(t)}(P(t)-R(t))$ for the density independent rate. Here, $B(t)$ is some relevant measure of total microbiota density. Similarly, $B_R(t)$ is some relevant measure of resistant microbiota density.

Computing the new balance threshold: With these additional terms, the expansion of the resistant population under containment is now defined by,

$$\begin{aligned}\dot{R}(t) &= (1-c_I)\,r\,(1-(1+c_C)\delta P_{max})\,R(t)-\mu(t)R(t)\\ &\quad +\epsilon r\,(1-\delta P_{max})\,(P_{max}-R(t))\\ &\quad +\epsilon_{HD}R(t)(P_{max}-R(t))+\epsilon_{HND}\frac{R(t)}{P_{max}}(P_{max}-R(t))\\ &\quad +\delta_{HD}B_R(t)(P_{max}-R(t))+\delta_{HND}\frac{B_R(t)}{B(t)}(P_{max}-R(t)).\end{aligned} \tag{S.29}$$

Depending on the assumptions about horizontal gene transfer some of the constants ϵ_{HD}, ϵ_{HND}, δ_{HD}, δ_{HND} may be zero. For example, if horizontal gene transfer between the resistant and sensitive pathogen is density dependent then $\epsilon_{HD}>0$ and $\epsilon_{HND}=0$. We will continue to carry all of the terms to maintain full generality.

Equation (S.29) can be written as the sum of three parts. The first part is the resistant expansion rate in the absence of sensitive pathogen, the second part is the benefit of sensitive pathogen and the third part is the cost of sensitive pathogen:

$$\begin{aligned}\dot{R}(t) &= \underbrace{(1-c_I)\,r\,(1-(1+c_C)\delta R(t))\,R(t)-\mu(t)R(t)}_{\text{no sensitive pathogen}}-\underbrace{(1-c_I)\,r(1+c_C)\delta R(t)(P_{max}-R(t))}_{\text{benefit of sensitive pathogen}}\\ &\quad +\underbrace{\left[\epsilon r\,(1-\delta P_{max})+\epsilon_{HD}R(t)+\epsilon_{HND}\frac{R(t)}{P_{max}}+\delta_{HD}B_R(t)+\delta_{HND}\frac{B_R(t)}{B(t)}\right](P_{max}-R(t))}_{\text{cost of sensitive pathogen}}.\end{aligned}$$

In order for the instantaneous effect of sensitive pathogen to be positive, sensitive pathogen must decrease the resistant expansion rate. A comparison of cost and benefit tells us that the benefit will exceed the cost whenever,

$$R(t)\left[(1-c_I)r(1+c_C)\delta-\epsilon_{HD}-\frac{\epsilon_{HND}}{P_{max}}\right]>\epsilon r\,(1-\delta P_{max})+\delta_{HD}B_R(t)+\delta_{HND}\frac{B_R(t)}{B(t)}.$$

The right-hand side of the above inequality is always positive. This means that if the left-hand side is negative then sensitive pathogen is detrimental. In other words, if

$$\left[(1-c_I)r(1+c_C)\delta-\epsilon_{HD}-\frac{\epsilon_{HND}}{P_{max}}\right]<0$$

then the instantaneous effect of sensitive pathogen is detrimental. This will occur whenever the rate of horizontal gene transfer from the resistant population exceeds the benefit of competitive suppression due to sensitive pathogen.

If

$$\left[(1-c_I)r(1+c_C)\delta - \epsilon_{HD} - \frac{\epsilon_{HND}}{P_{max}}\right] \tag{S.31}$$

is always negative then the cost of gene transfer from the resistant pathogen population always outweighs the benefit of competitive suppression. In this case, sensitive pathogen is always detrimental and aggressive treatment should be used.

On the other hand, if expression (S.31) is always positive then the benefit of sensitive pathogen always outweighs the cost of gene transfer from the resistant pathogen population. In this case, we still need to consider the effect of gene transfer from the microbiota and also the effect of mutational input, before we can determine if sensitive pathogen is advantageous. We do this by examining the balance threshold:

$$R_{balance} = \frac{\epsilon r\left(1-\delta P_{max}\right) + \delta_{HD}B_R(t) + \delta_{HND}\frac{B_R(t)}{B(t)}}{\left[(1-c_I)r(1+c_C)\delta - \epsilon_{HD} - \frac{\epsilon_{HND}}{P_{max}}\right]}. \tag{S.32}$$

Whenever the resistant density exceeds the balance threshold the instantaneous effect of the sensitive density is advantageous. Whenever the resistant density is below the balance threshold this instantaneous effect is detrimental. Because the balance threshold depends on the density of microbiota ($B(t)$ and $B_R(t)$) it may change as the infection progresses. We now make some simplifying assumptions about the microbiota in order to continue this analysis.

First, we assume that if a narrow spectrum antibiotic is used then $B(t)$ and $B_R(t)$ are constant during the infection. In this case the balance threshold (Equation (S.32)) is constant and sensitive pathogen will be advantageous whenever the resistant density is large enough. That is, the cases described in Fig. 2 of the main text characterise the different possibilities.

Second, we assume that if a broad spectrum antibiotic is used then $B(t)$ will decrease and $B_R(t)$ will increase. In particular, if we assume that $B(t)$ is monotonically decreasing and $B_R(t)$ is monotonically increasing during treatment, then the balance threshold will increase during the management period. In particular, this means that the resistant density may exceed the balance threshold at one time during the infection and then later be below the balance threshold even though the resistant density is increasing the entire time. In other words, the scenarios depicted in Fig. 2 of the main text do not cover all possible scenarios.

These assumptions, do however allow us to make some general observations about the use of broad spectrum antibiotics. First, if aggressive treatment is best when a narrow spectrum drug is used (i.e., $B(t)$ and $B_R(t)$ are constant) then it will also be best when a broad spectrum drug is used. This is because, in this model, the only effect of choosing a broad-spectrum drug over a narrow spectrum drug is that it increases the cost of horizontal gene

transfer. Conversely, if containment is better than aggressive when a narrow spectrum is used, aggressive treatment may still be better if a broad spectrum antibiotic is used. Finally, all else being equal, a narrow spectrum drug will always delay resistance emergence at least as long as a broad spectrum drug.

Modifications to immune response: To this point we have assumed that immunity increases pathogen clearance. Here we consider the possibility that instead of increasing the rate of pathogen clearance, immunity acts to impair pathogen function. We will assume that this type of immunity is an increasing function of time and model it by assuming that either the intrinsic replication rate r or the competition coefficient δ decrease with time. Note that, since the intrinsic replication rate and competition coefficient of the resistant pathogen are defined relative to r and δ, this type of immune response will affect both drug-sensitive and drug-resistant pathogens.

Under this assumption, the term representing the benefit of competitive suppression (i.e., the first term in expression (S.31)) will change as the infection progresses. If immunity only inhibits a pathogen's ability to compete then the first term in expression (S.31) will increase with time. This means that expression (S.31) could be negative at the start of the management period but eventually become positive. This indicates that initially, when the immune response is low the benefit of competitive suppression is not enough to outweigh the cost of gene transfer from the resistant population. As the immune response increases and strengthens competitive suppression this will change. Therefore, even if expression (S.31) is initially negative, containment may still be better than aggressive treatment. Now consider the effect of immunity on the balance threshold:

$$\frac{\partial}{\partial \delta} R_{balance} = \frac{-\left[\epsilon r P_{max} + R_{balance}(1-c_I) r (1+c_C)\right]}{\left[(1-c_I) r (1+c_C)\delta - \epsilon_{HD} - \frac{\epsilon_{HND}}{P_{max}}\right]} < 0.$$

Therefore if immunity causes δ to increase then the balance threshold will decrease during the infection. This will increase the number of scenarios where containment is better than aggressive treatment.

Finally, consider the case where immunity reduces the intrinsic replicative ability. In this case the first term in expression (S.31) will decrease with time. This means that expression (S.31) could be positive at the start of the management period but eventually become negative. If immunity acts to decrease the intrinsic replicative ability, this will increase the number of scenarios where aggressive treatment is better than containment. Now consider how increasing immunity will change the balance threshold:

$$\frac{\partial}{\partial r} R_{balance} = \frac{\left[\epsilon\left(1-\delta P_{max}\right) - R_{balance}(1-c_I)(1+c_C)\delta\right]}{\left[(1-c_I) r (1+c_C)\delta - \epsilon_{HD} - \frac{\epsilon_{HND}}{P_{max}}\right]} < 0,$$

where the last inequality is due to the fact that $\frac{\epsilon(1-\delta P_{max}}{(1-c_I)(1+c_C)\delta} < R_{balance}$. Therefore if immunity causes r to decrease then the balance threshold will increase during the infection –

increasing the number of scenarios where containment is better than aggressive treatment. Note that this is only true when there is horizontal gene transfer. If there is no horizontal gene transfer the balance threshold does not depend on r (see Equation 4 in main text). In this case, this type of immunity will not impact the results in the main text.

In summary, if the immune response inhibits pathogen function rather than simply killing pathogens, then it matters how this inhibition occurs. If the effect augments the benefit of competitive suppression then sensitive pathogen is more likely to be advantageous. If the effect reduces the benefit of competitive suppression (by reducing the intrinsic replicative ability) then sensitive pathogen is less likely to be advantageous. These relationships are similar to those discussed in Fig. 4 of the main text (see S12 Text for details).

Modeling drug-resistance as a continuous phenotype: A major assumption in all of our models is that pathogens are either completely drug-sensitive or completely drug-resistant. Here we provide some general comments of how our analysis could be adjusted to accommodate the possibility that pathogens exhibit an entire range of drug sensitivities.

First we assume that the main clinical concern are pathogens that are completely drug resistant. In other words, we assume that – by adjusting drug concentrations – we are able to control any pathogen that exhibits at least partial drug-sensitivity. Under these assumptions we can still model the total pathogen density as the combination of the drug-resistant density R and the drug-sensitive density $P - R$. But now, the drug sensitive density also includes pathogens with only partial drug-sensitivity. The important difference between this model and the one used in the main text is that, now the characteristics of the drug sensitive density will change through-out the infection. Since we are interested in understanding how these changes impact the analysis, we rewrite Equation (3) from the main text using the resistant characteristics as the reference:

$$\begin{aligned}\dot{R} &= rR(1-\delta R) - \mu(t)R \\ &\quad - \underbrace{r R \delta (P_{max} - R)}_{\substack{\text{benefit} \\ \text{of maximizing} \\ \text{sensitive density}}} + \underbrace{\epsilon(1+b_I) r \left(1 - (1-b_C)\delta P_{max}\right)(P_{max} - R)}_{\substack{\text{cost} \\ \text{of maximizing} \\ \text{sensitive density}}},\end{aligned} \tag{S.33}$$

where the intrinsic replication rate of sensitive pathogens is a factor $(1+b_I)$ greater than that of drug resistant pathogens and drug sensitive pathogens are a factor $(1 - b_C)$ less sensitive to competition than drug-resistant pathogens. With this notation the balance threshold becomes

$$R_{balance} = \frac{\epsilon\,(1+b_I)}{\delta}\left(1 - (1-b_C)\delta P_{max}\right).$$

Now, if we assume that exposure to drug causes the average characteristics of the drug sensitive population to become more like the characteristics of the drug resistant population

then, as the infection progresses, we would expect b_I and b_C to decrease to zero. Decreasing b_I and b_C will cause $R_{balance}$ to decrease. Therefore, if the only changes to the sensitive population are decreases in b_I and b_C then accounting for the possibility that there is a range of drug-sensitivities will increase the number of scenarios where containment is better than aggressive treatment. It is likely, however, that as the sensitive population becomes more like the resistant population the probability of mutation to full resistance will increase. Increasing ϵ has the opposite effect on the balance threshold. If the change in epsilon trumps the change in b_I and b_C then we would expect aggressive treatment to be better in a wider range of scenarios. This case also suggests the possible utility of using a delayed aggressive strategy – namely following containment until the probability of mutation becomes too large and then switching to aggressive treatment. A proper understanding of this situation requires a separate analysis.

S11 Text: Containment can be effective even if the total pathogen density is below the acceptable burden

If containment is better than aggressive treatment then it is highly desirable to keep the pathogen density at the acceptable burden. Gains will accrue, however, even if treatment does not perfectly achieve this target. In particular, for the dynamics described by Equation (3) of the main text, sensitive pathogen will be advantageous whenever $R(t) > \frac{\epsilon(1-\delta P(t))}{(1-c_I)(1+c_C)}$. In other words, whenever

$$P(t) \in [\frac{1}{\delta} - \frac{(1-c_I)(1+c_C)R(t)}{\epsilon}, P_{max}].$$

Since $\frac{1}{\delta} - \frac{(1-c_I)(1+c_C)R(t)}{\epsilon}$ decreases as the resistant density increases, this range expands as the resistant density increases, so that as the infection progresses, the total pathogen density can be lower and gains will still accrue. Thus, from a practical perspective, it is not necessary to keep the total cell population at precisely the allowable burden. This will make successful implementation of containment easier.

S12 Text: Supporting calculations for Fig 4 of main text

Let R_A denote the resistant density under aggressive treatment. Because we assume that aggressive treatment immediately removes the entire drug-sensitive population, the expansion of the resistant density under aggressive treatment is described by

$$\dot{R}_A = (1-c_I)rR_A(1-(1+c_C)\delta R_A) - \mu R_A. \tag{S.34}$$

Let R_C denote the resistant density under containment. Under containment the expansion of the resistant density is described by

$$\begin{aligned}\dot{R}_C &= (1-c_I)rR_C(1-(1+c_C)\delta R_C)-\mu(t)R_C \\ &\quad -\underbrace{(1-c_I)rR_C(1+c_C)\delta(P_{max}-R_C)}_{\text{Benefit}}+\underbrace{\epsilon r\,(1-\delta P_{max})\,(P_{max}-R_C)}_{\text{Cost}}. \quad \text{(S.35)}\end{aligned}$$

Amplifying competition for both resistant and sensitive pathogens: An alternative intervention that amplifies the effect of competition equally for both drug-sensitive and drug-resistant pathogens will increase the competition coefficient δ. The derivatives of cost and benefit with respect to δ are:

$$\frac{\partial \text{Cost}}{\partial \delta} = -\epsilon r P_{max}\,(P_{max}-R_C) < 0$$

and

$$\frac{\partial \text{Benefit}}{\partial \delta} = (1-c_I)rR_C(1+c_C)(P_{max}-R_C) > 0.$$

Therefore, increasing δ will increase the benefit and reduce the cost of sensitive pathogen.

The derivative of the resistant expansion rate with respect to δ under containment is:

$$\frac{\partial \dot{R}_C}{\partial \delta} = -(1-c_I)rR_C(1+c_C)P_{max} - \epsilon r P_{max}\,(P_{max}-R_C) < 0,$$

and under aggressive treatment is

$$\frac{\partial \dot{R}_A}{\partial \delta} = -(1-c_I)rR_A(1+c_C)R_A < 0.$$

Therefore, increasing δ reduces the expansion rate of the resistant population and thus extends the amount of time that the infection can be managed with both containment and aggressive treatment.

Finally,

$$\frac{\partial R_{balance}}{\partial \delta} = \frac{-\epsilon}{(1-c_I)(1+c_C)\delta^2} < 0,$$

and so increasing δ will decrease the balance threshold.

Amplifying competition for only resistant pathogens: An alternative intervention that amplifies the effect of competition for only drug-resistant pathogens will increase the competitive fitness cost c_C. The derivatives of cost and benefit with respect to c_C are:

$$\frac{\partial \text{Cost}}{\partial c_C} = 0$$

and

$$\frac{\partial \text{Benefit}}{\partial c_C} = (1 - c_I) r R_C \delta (P_{max} - R_C) > 0.$$

Therefore, increasing c_C will increase the benefit and have no effect on the cost of sensitive pathogen.

The derivative of the resistant expansion rate with respect to c_C under containment is:

$$\frac{\partial \dot{R}_C}{\partial c_C} = -(1 - c_I) r R_C \delta P_{max} < 0$$

and under aggressive treatment is

$$\frac{\partial \dot{R}_A}{\partial c_C} = -(1 - c_I) r R_A \delta R_A < 0.$$

Therefore, increasing c_C reduces the expansion rate of the resistant population and thus extends the amount of time that the infection can be managed with either containment or aggressive treatment.

Finally,

$$\frac{\partial R_{balance}}{\partial c_C} = \frac{-R_{balance}}{(1 + c_C)} < 0,$$

and so increasing c_C will decrease the balance threshold.

Amplifying competition for sensitive pathogens only: Assessing the impact of this intervention requires a modification of Equation (S.34) and Equation (S.35). Note that Equation (S.34) and Equation (S.35) can be written in terms of fitness benefits associated with drug sensitivity instead of fitness costs associated with drug resistance. Doing this yields,

$$\dot{R}_A = r R_A (1 - \delta R_A) - \mu R_A, \tag{S.36}$$

and

$$\begin{aligned} \dot{R}_C &= r R_C (1 - \delta R_C) - \mu(t) R_C \\ &\quad - \underbrace{r R_C \delta (P_{max} - R_C)}_{\substack{\text{benefit} \\ \text{of maximizing} \\ \text{sensitive density}}} + \underbrace{\epsilon (1 + b_I) r \left(1 - (1 - b_C) \delta P_{max}\right) (P_{max} - R_C)}_{\substack{\text{cost} \\ \text{of maximizing} \\ \text{sensitive density}}}, \end{aligned} \tag{S.37}$$

where the intrinsic replication rate of sensitive pathogens is a factor $(1 + b_I)$ greater than that of drug resistant pathogens and drug sensitive pathogens are a factor $(1 - b_C)$ less sensitive to competition than drug-resistant pathogens.

An alternative intervention that amplifies the effect of competition for only drug-sensitive pathogens will decrease the competitive fitness benefit b_C. The derivatives of cost and benefit with respect to b_C are:

$$\frac{\partial \text{Cost}}{\partial b_C} = \epsilon(1+b_I)r\delta P_{max}\left(P_{max} - R_C\right) > 0$$

and

$$\frac{\partial \text{Benefit}}{\partial b_C} = 0.$$

Therefore, decreasing b_C will decrease the cost and have no effect on the benefit of sensitive pathogen.

The derivative of the resistant expansion rate with respect to b_C under containment is:

$$\frac{\partial \dot{R}_C}{\partial b_C} = \epsilon(1+b_I)r\delta P_{max}\left(P_{max} - R_C\right) > 0$$

and under aggressive treatment is

$$\frac{\partial \dot{R}_A}{\partial b_C} = 0.$$

Therefore, under containment, decreasing b_C reduces the expansion rate of the resistant population and thus extends the amount of time that the infection can be managed. Under aggressive treatment, decreasing b_C has no effect on the resistant expansion rate.
Finally, if the balance threshold is written in terms of fitness benefits then

$$R_{balance} = \frac{\epsilon(1+b_I)}{\delta}\left[1 - (1-b_C)\delta P_{max}\right]$$

and so

$$\frac{\partial R_{balance}}{\partial b_C} = \frac{\epsilon(1+b_I)}{\delta}\delta P_{max} > 0.$$

Therefore, decreasing b_C will decrease the balance threshold.

Now we consider alternative interventions which change the pathogens' intrinsic ability to replicate.

Reducing intrinsic replication for both resistant and sensitive pathogens: An alternative intervention that reduces intrinsic replication equally for both drug-sensitive and drug-resistant pathogens will decrease r. The derivatives of cost and benefit with respect to r are:

$$\frac{\partial \text{Cost}}{\partial r} = \epsilon\left(1 - \delta P_{max}\right)\left(P_{max} - R_C\right) > 0$$

and

$$\frac{\partial \text{Benefit}}{\partial r} = (1 - c_I)R_C(1 + c_C)\delta(P_{max} - R_C) > 0.$$

Therefore, decreasing r will decrease both the cost and the benefit of sensitive pathogen.

The derivative of the resistant expansion rate with respect to δ under containment is:

$$\frac{\partial \dot{R}_C}{\partial r} = (1 - c_I)R_C(1 - (1 + c_C)\delta P_{max}) + \epsilon\left(1 - \delta P_{max}\right)\left(P_{max} - R_C\right) > 0,$$

and under aggressive treatment is

$$\frac{\partial \dot{R}_A}{\partial r} = (1 - c_I)R_A(1 - (1 + c_C)\delta R_A) > 0.$$

Therefore, decreasing r reduces the expansion rate of the resistant population and thus extends the amount of time that the infection can be managed with both containment and aggressive treatment.
Finally,

$$\frac{\partial R_{balance}}{\partial r} = 0,$$

and so decreasing r has no effect on the balance threshold.

Reducing intrinsic replication for resistant pathogens only: An alternative intervention that reduces the intrinsic replication of only the drug-resistant pathogen will increase the intrinsic fitness cost c_I. The derivatives of cost and benefit with respect to c_I are:

$$\frac{\partial \text{Cost}}{\partial c_I} = 0$$

and

$$\frac{\partial \text{Benefit}}{\partial c_I} = -rR_C(1 + c_C)\delta(P_{max} - R_C) < 0.$$

Therefore, increasing c_I will decrease the benefit and have no effect on the cost of sensitive pathogen.

The derivative of the resistant expansion rate with respect to c_I under containment is:

$$\frac{\partial \dot{R}_C}{\partial c_I} = -rR_C(1 - (1 + c_C)\delta P_{max}) < 0$$

and under aggressive treatment is

$$\frac{\partial \dot{R}_A}{\partial c_I} = -rR_A(1 - (1 + c_C)\delta R_A) < 0.$$

Therefore, increasing c_I reduces the expansion rate of the resistant population and thus extends the amount of time that the infection can be managed with either containment or aggressive treatment.

Finally,

$$\frac{\partial R_{balance}}{\partial c_I} = \frac{R_{balance}}{(1 - c_I)} > 0,$$

and so increasing c_I will increase the balance threshold.

Reducing intrinsic replication for sensitive pathogens only: An alternative intervention that reduces the intrinsic replication of only the drug-sensitive pathogens will decrease the fitness benefit b_I. From Equation (S.37), the derivatives of cost and benefit with respect to b_I are:

$$\frac{\partial \text{Cost}}{\partial b_I} = \epsilon r \left(1 - (1 - b_C)\delta P_{max}\right)\left(P_{max} - R_C\right) > 0$$

and

$$\frac{\partial \text{Benefit}}{\partial b_I} = 0.$$

Therefore, decreasing b_I will decrease the cost and have no effect on the benefit of sensitive pathogens.

The derivative of the resistant expansion rate with respect to b_I under containment is:

$$\frac{\partial \dot{R}_C}{\partial b_I} = \epsilon r \left(1 - (1 - b_C)\delta P_{max}\right)\left(P_{max} - R_C\right) > 0$$

and under aggressive treatment is

$$\frac{\partial \dot{R}_A}{\partial b_I} = 0.$$

Therefore, under containment, decreasing b_I reduces the expansion rate of the resistant population and thus extends the amount of time that the infection can be managed. Under aggressive treatment, decreasing b_I has no effect on the resistant expansion rate.

Finally, if the balance threshold is written in terms of fitness benefits then

$$R_{balance} = \frac{\epsilon(1 + b_I)}{\delta}\left[1 - (1 - b_C)\delta P_{max}\right]$$

and so

$$\frac{\partial R_{balance}}{\partial b_I} = \frac{R_{balance}}{(1 + b_I)} > 0.$$

Therefore, decreasing b_I will decrease the balance threshold.