Supporting Information

Ankomah and Levin 10.1073/pnas.1400352111

SI Text

1. The Null Case (Fig. S1). In the absence of an immune response and antibiotic treatment, the infecting bacterial population grows until its density is limited by the availability of resources (Fig. S1*A*). Under these conditions, the susceptible bacteria grow to densities that are high enough to produce a substantial density of refuge bacteria (BP_1). Intermediate-resistance bacteria (B_2) are generated but do not ascend due to resource restriction. With the parameters used, regardless of whether immune action is pathogen density-dependent (PDD) (Fig. S1*B*) or pathogen density-independent (PDI) (Fig. S1*C*), the innate immune response alone does not clear the infection over the 20-d period of the simulation.

2. Dosing Frequency (Fig. S2). In Fig. S2, we illustrate the dynamics of clearance with the same total dose of an antibiotic administered once daily (Fig. S2*A*) and when the administration of the drug is partitioned into eight equally spaced treatments daily (Fig. S2*B*).

3. Treatment Hiatuses (Fig. S3). In the body of the report, we note that, as the model is now developed, there are situations involving treatment hiatuses at "intermediate" density thresholds for adaptive treatment regimens that increase the term of and may prevent the clearance of normally self-limiting infections.

4. Pre-existing high level resistance and PDI immune dynamics (Fig. S4). In Fig. S4, we illustrate the dynamics of an infection with a minority population of resistant cells present before the initiation of therapy, and for which the immune response is pathogen density-independent.

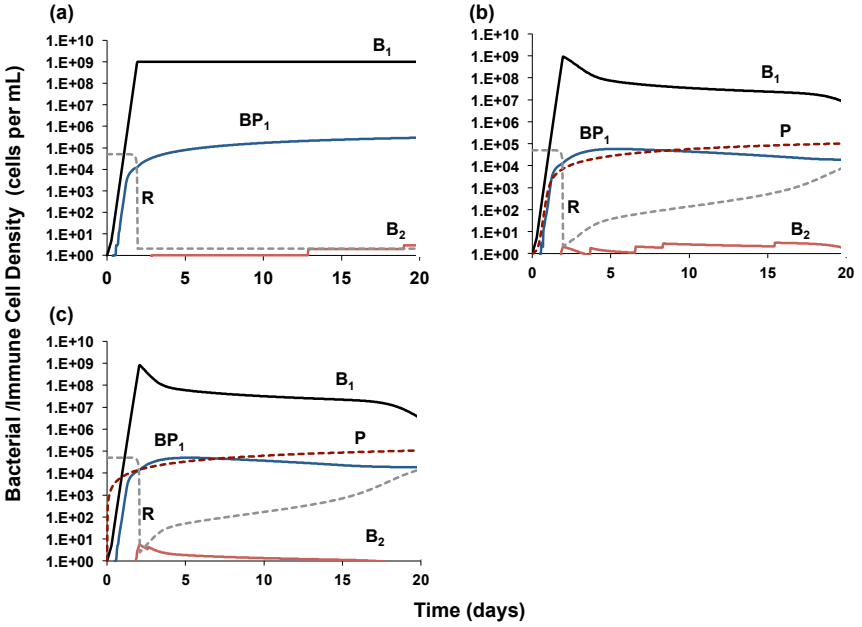

Fig. S1. Bacterial population dynamics of a self-limited infection with immune action and antibiotic treatment. Changes in the densities of the bacteria (B_1, antibiotic-susceptible, undergoing active growth; B_2, intermediate-resistant, undergoing active growth; BP_1, refuge bacteria), resources (R), and immune cells (P, innate immune cells) under the following conditions: (*A*) no immune response, no antibiotic treatment; (*B*) pathogen density-dependent (PDD) innate immune response; (*C*) pathogen density-independent (PDI) innate immune response. The parameter values used for the simulations are listed in Table S1.

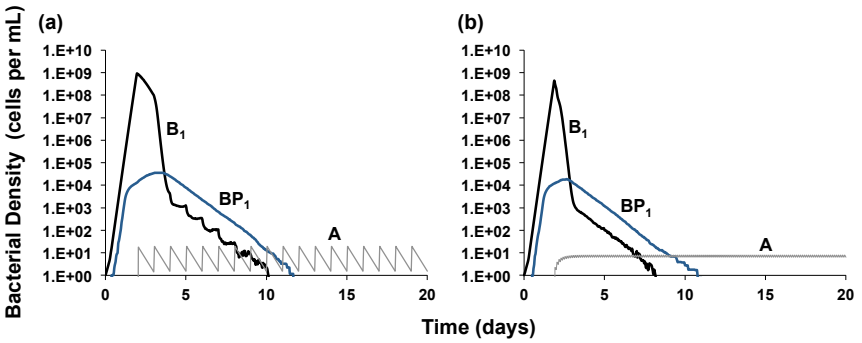

Fig. S2. Bacterial population dynamics of a self-limited infection with different frequencies of administration of a constant total daily dose. Changes in the densities of the bacteria (B_1, BP_1) and antibiotics (A) under the following conditions: (*A*) one antibiotic dose of 20 μg/mL per day; (*B*) eight doses of 2.5 μg/mL per day. The parameter values used for the simulations are listed in Table S1.

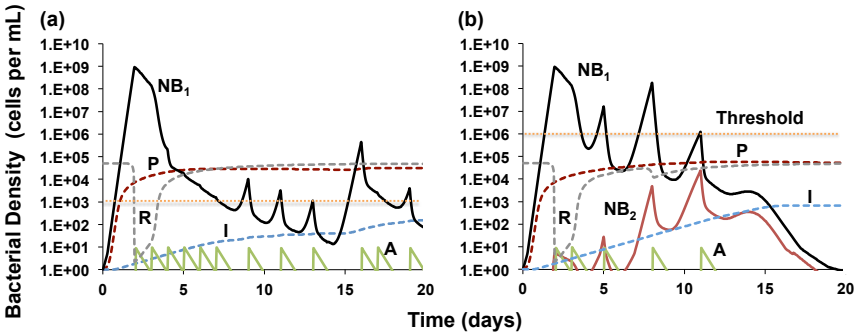

Fig. S3. Bacterial population dynamics of a self-limited infection with adaptive treatment regimens. Changes in the densities of the bacteria ($NB_1 = B_1 + BP_1$, $NB_2 = B_2 + BP_2$) under the following conditions: (*A*) adaptive treatment threshold, 10^3 bacteria per mL; (*B*) adaptive treatment threshold, 10^6 bacteria per mL. The parameter values used for the simulations are listed in Table S1.

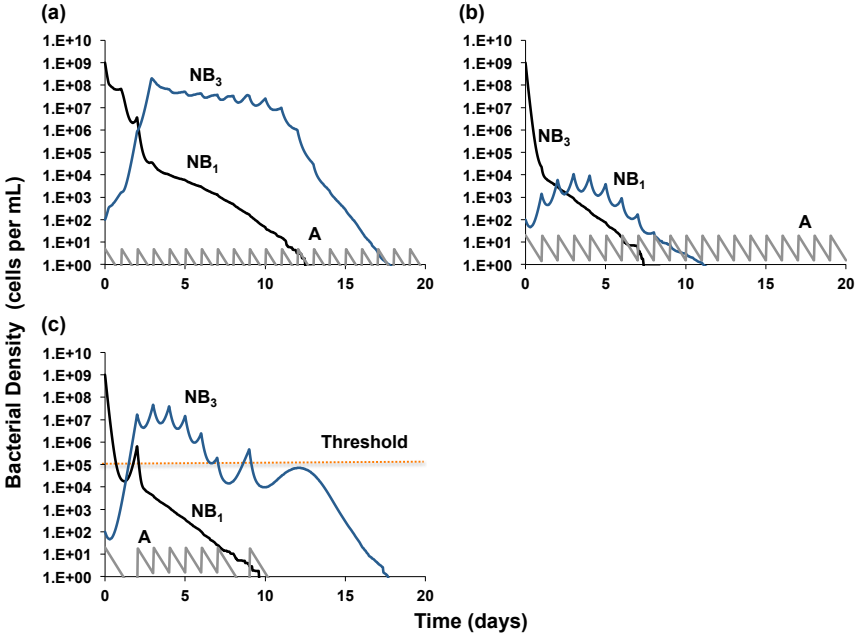

Fig. S4. Bacterial population dynamics of a self-limited infection with preexisting high-level resistant bacteria and PDI immune dynamics. Changes in the densities of the bacteria ($NB_1 = B_1 + BP_1$, $NB_2 = B_2 + BP_2$, $NB_3 = B_3 + BP_3$) under the following conditions: (*A*) dose of 5 μg/mL; (*B*) dose of 20 μg/mL; (*C*) dose of 20 μg/mL, adaptive treatment threshold of 10^5 bacteria per mL. The parameter values used for the simulations are listed in Table S1.

Table S1. Values and ranges for variables and parameters used for generating numerical solutions to the model

Variable/parameter	Description	Value or range considered*†
Variables		
A	Antibiotic concentration, μg/mL	0–40 [10]
B_i	Density of bacteria, cells per mL; population wholly susceptible to antibiotic action, $i = 1$; intermediate resistance, $i = 2$; high-level resistance, $i = 3$.	1–10^{10}
BP_i	Density of persisters, cells per mL; population wholly susceptible to antibiotic action, $i = 1$; intermediate resistance, $i = 2$; high-level resistance, $i = 3$.	1–10^{10}
R	Concentration of the limiting resource, μg/mL	0–500
Parameters		
V_{iMAX}	Maximum hourly growth rate of replicating bacteria	0.5 (1)
V_{iMIN}	Maximum hourly death rate generated by the antibiotic	−0.75 (1)
s_2, s_3	Fitness costs of resistance; assessed as decreases in maximum hourly growth rate for B_2 and B_3 populations	0–0.025 [0] (2)
V_{Pi}	Maximum hourly growth rate of persisters	0.001‡
MIC_i	Minimum inhibitory concentration of antibiotic A for population B_i, μg/mL	1, 2, 10, respectively§
κ	Hill coefficient	1 (3)
w	Hourly washout rate, rapidly replicating bacteria	0.2 (4)
w_2	Hourly washout rate, persisters	0.001¶
f_{SP}	Hourly rate at which B_i is converted into BP_i	0.005 (1, 5)
f_{PS}	Hourly rate at which BP_i is converted into B_i	0.05 (1, 5)
C	Reservoir resource concentration, μg/mL	500 (4, 6)
e	Efficiency of resource conversion into cells, μg/cell	5×10^{-7} (6)
k	Concentration of resource at half-maximal growth, μg/mL	1 (6)
A_{max}	Antibiotic concentration added at each dosing period, μg/mL	0–40 [10] (7, 8)
d	Antibiotic decay rate, h^{-1}	0.1 (9)
T	Time between doses, h	3–24 [24] (7, 8)
μ_1, μ_2	Mutation rate, mutations per cell division	10^{-8}, 10^{-9} (10)
k_I	Rate constant for adaptive immune-mediated clearance of replicating populations	5×10^{-4}‖**
k_P	Rate constant for innate immune-mediated clearance of replicating populations	5×10^{-6}**
j_I	Rate constant for adaptive immune-mediated clearance of persister populations	5×10^{-5}‖**
j_P	Rate constant for innate immune-mediated clearance of persister populations	5×10^{-8}**
η	Rate of innate immune cell recruitment	3×10^{-4}††
P_{MAX}	Innate immune reservoir, cells per mL	10^{6}††
γ	Rate of innate immune cell inactivation	10^{-3}††
α	Rate of increase, adaptive immune cells	0.01††
δ_I	Saturation density, adaptive immune cells	10^{3}‡‡
σ_I	Bacterial density at which adaptive immune response is at half-maximum activity, cells per mL	10^{3}‖**
σ_P	Constant that reflects the relationship between rate of recruitment of innate immune cells and bacterial density, cells per mL	10^{4}**

*When a range is considered, the values in brackets are the standard values used for numerical analysis of the model. Save for simulations in which parameters are varied, unless otherwise stated, the standard parameter values are used for all simulations.

†Where available, parameters used are within the range for *Escherichia coli* and *Staphylococcus aureus* and antibiotics used to treat infections with these organisms. However, the parameters are not specific for any antibiotic–species combination.

‡We use this very low growth rate to approximate the minimal to no-growth rate exhibited by persisters and other bacteria in physiological or spatial refuges.

§These values are within the range of clinical MIC breakpoints used for classifying bacteria as susceptible, intermediate-resistant, or fully (high-level) resistant to an antibiotic. See www.eucast.org/clinical_breakpoints/.

¶This low washout rate is used to approximate the relative stability of bacteria in spatial refuges.

‖As in ref. 11, we assume that the adaptive immune cells need to be at high densities to control the infection. Thus, we assume that the clearance rate constant, k_i, is less than the initial density of adaptive immune cells. In addition, we assume that the bacterial density at which the specific immune response grows at one-half its maximum rate will be intermediate between the initial bacterial density and the saturation density; i.e., k_i, $j_i << 1 << \sigma_i <<$ bacterial saturation density.

**We also assume that antigens that elicit specific immune responses are present at higher densities on bacterial surfaces than those that generate nonspecific (innate) responses (12), and that the adaptive immune response exhibits more effective bactericidal activity than the innate immune response; i.e., $\sigma_I < \sigma_P$, and $k_i > k_p$, $j_i > j_p$.

††These immune parameter values were chosen to generate an infection that would be self-limiting over a 20-d period.

‡‡To facilitate comparison between simulations with PDD and PDI immune dynamics, this parameter value for PDI dynamics was chosen to approximate the maximum density of the adaptive immune cells under PDD dynamics in the null case of no antibiotic treatment.

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