Appendix: Supplementary Data

Data Read from Input Files

Let n_w represent the total number of wards in Great Britain (GB), with p_h^j and p_w^j representing the home (nighttime) and work (daytime) population of each ward where $j = 1..n_w$. Home ward populations and geographic ward centroids are provided within the 2001 GB census. The average ward population is 5,696 individuals (standard deviation = 3,898, range = {104, 35,102}), and the average ward area is 23.2 km^2 (standard deviation = 74.3, range = {0.1, 3,243.9}). Work populations are precalculated from the home populations and commuting data, also provided in the 2001 GB census. As a result of the assumed release of tularemia organisms, there is an open-air inhaled dose, d_o^j, associated with each ward. Each open-air dose is precalculated within the HPAC software at the geographic ward centroid and then converted to an inhaled dose via the breathing rate (see Table 2).

Initial Calculations

Let us assume that there is a building protective factor, b_p (see Table 2), resulting in a lower inhaled dose inside buildings, d_{in}^j, given by:

$$d_{in}^j = (1 - b_p) d_o^j \text{ where } j = 1..n_w$$

The total number of work wards considered exposed to the release, n_{ew}, is given by:

$$n_{ew} = \sum_{j=1}^{n_w} 1 - \delta(d_o^j) \text{ where } \delta(n) = \begin{cases} 1, n = 0 \\ 0, n \neq 0 \end{cases}$$

The population within work wards considered exposed to the release, p_e^k, is given by

$$p_e^k = (1 - \delta(d_o^j)) p_w^j \text{ where } k = 1..n_{ew}$$

Note that j and k are matched at this stage to ensure correct allocation. Therefore, the total number of individuals considered exposed to the release, n_{eq}, is given by:

$$n_{eq} = \sum_{k=1}^{n_{ew}} p_e^k$$

The probability of infection for individuals located outside during the hours following the release, f_o^k, is given by:

$$f_o^k = 1 - \exp(-r_f d_o^k) \text{ where } k = 1..n_{ew}$$

and where r_f is the infectious dose parameter (see Table 3). Similarly, the probability of infection for individuals located inside during the hours following the release, f_{in}^k, is given by:

$$f_{in}^k = 1 - \exp(-r_f d_{in}^k) \text{ where } k = 1..n_{ew}$$

The number of infected individuals in each work ward considered exposed to the release, p_f^k, is a random draw from a binomial distribution given by:

$$u(x) = \binom{p_e^k}{x} [(1 - b_{in}) f_o^k]^x (1 - (1 - b_{in}) f_o^k)^{p_e^k - x} + \binom{p_e^k}{x} [b_{in} f_{in}^k]^x (1 - b_{in} f_{in}^k)^{p_e^k - x}$$

ie, $p_f^k \sim Binomial(p_e^k, (1 - b_{in}) f_o^k) + Binomial(p_e^k, b_{in} f_{in}^k)$ where b_{in} is the proportion of individuals inside buildings (see Table 2). The total number of work wards where individuals were infected, n_{fw}, is given by:

$$n_{fw} = \sum_{k=1}^{n_{ew}} 1 - \delta(p_f^k)$$

and the total number of infected individuals is given by:

$$n_{fq} = \sum_{k=1}^{n_{ew}} p_f^k$$

The location, i_μ, and scale, i_σ, parameters of the log-normal distribution satisfy the equations:

$$E_i = \exp(i_\mu + 0.5 {i_\sigma}^2)$$

$$SD_i = E_i \sqrt{\exp({i_\sigma}^2) - 1}$$

where $E_i(d) = i_c \log_{10}(d) + i_m$, i_c is the incubation period gradient parameter (see Table 3), i_m is the incubation period intercept parameter (see Table 3), and SD_i is the incubation period standard deviation parameter (1 day, see main text). The location, s_μ, and scale, s_σ, parameters of the log-normal distribution satisfy the equations:

$$E_s = \exp(s_\mu + 0.5 {s_\sigma}^2)$$

$$SD_s = E_s \sqrt{\exp({s_\sigma}^2) - 1}$$

where E_s is the symptomatic period mean (see Table 3), SD_s is the symptomatic period standard deviation (see Table 3).

Individual Characteristics

Let q^l_C be a matrix where each row, $l = 1..n_{fq}$, represents a different infected individual and each column, $C = 1..10$, represents a different characteristic relating to that individual. Note that $q^l_{1..6}$ are static characteristics (ie, constant) and $q^l_{7..10}$ are dynamic characteristics (ie, variable) depending on the intervention strategy.

Static Characteristics

The work location of each individual, q^l_1, is given by:

$$q^l_1 = k \qquad \text{for} \qquad p_f^{k-1} < l \leq p_f^k \qquad (\text{define } p_f^0 = 0)$$

The home location for each infected individual, q^l_2, is a random draw from a multivariate hypergeometric distribution given by:

$$v^k(y) = \frac{\prod_{j=1}^{n_w} \binom{m_j}{y_j}}{\binom{p^j_w}{p^k_f}}$$

ie, $q^l_2 \sim Multi\text{ var }iateHypergeometric(\tilde{m}^k, p^k_f, n_w)$

where m^k_i represents the number of individuals that commute from k to i. The building location (inside = 1 or outside = 0) of each infected individual, q^l_3, is given by:

$$q^l_3 \sim Binomial(1, b_{in})$$

ie, $q^l_3 \sim Bernoulli(b_{in})$

The probability of death in the absence of antibiotic treatment of each infected individual, q^l_4, is given by:

$$q^l_4 = \begin{cases} 1 - \exp\left(-r_d d_o^{q^l_1}\right) & q^l_3 = 0 \\ 1 - \exp\left(-r_d d_{in}^{q^l_1}\right) & q^l_3 = 1 \end{cases} \quad \text{if}$$

where r_d is the lethal dose response parameter (see Table 3). The incubation period of each infected individual, q^l_5, is a random draw from a log-normal distribution given by:

$$\omega(z) = \frac{1}{z i_\sigma \sqrt{2\pi}} \exp\left(-\frac{(\ln(z) - i_\mu)^2}{2 {i_\sigma}^2}\right) \qquad \text{for} \quad z > 0$$

ie, $q^l_5 \sim LogNormal(i_\mu, {i_\sigma}^2)$ where $\begin{cases} d = d_o^{q^l_1} & q^l_3 = 0 \\ d = d_{in}^{q^l_1} & q^l_3 = 1 \end{cases}$ if

The time to the end of the symptomatic period of each infected individual, q^l_6, is given by:

$$q^l_6 \sim Lognormal(s_\mu, {s_\sigma}^2) + q^l_5$$

Dynamic Characteristics

The time of death of each infected individual, q^l_7, is initially allocated as:

$$q^l_7 = 10^{10}$$

The antibiotic treatment status (treated = 1, untreated = 0) of each infected individual, q^l_8, is initially allocated as:

$$q^l_8 = 0$$

In the Absence of Interventions

The time of death of each infected individual, q^l_7, is updated to:

$$q^l_7 \leftarrow \begin{cases} q^l_6 & Bernoulli(q^l_4) = 1 \\ q^l_7 & Bernoulli(q^l_4) = 0 \end{cases} \quad \text{if}$$

Under the Individual Strategy

The antibiotic treatment time of each infected individual, q^l_9, is given by:

$$q^l_9 = \begin{cases} t_g + t_s & order(q^l_5) < n_s \quad \text{and} \quad q^l_5 + t_s < t_g + t_s \\ q^l_5 + t_s & order(q^l_5) < n_s \quad \text{and} \quad q^l_5 + t_s \geq t_g + t_s \\ 10^{10} & order(q^l_5) > n_s \end{cases} \quad \text{if}$$

where t_g is the minimum time for outbreak detection (see Table 4), t_s is the self-reporting delay following symptom onset (see Table 4), n_s is the stockpile level (range of values, see main text). The probability of death of each infected individual, q^l_{10}, is given by:

$$q^l_{10} = \begin{cases} q^l_4[1 - \exp(-r_t(q^l_9 - q^l_5))] & Bernoulli(c) = 1 \\ q^l_4 & Bernoulli(c) = 0 \end{cases} \quad \text{if}$$

where r_t is the antibiotic treatment efficacy parameter (Table 4) and c is the antibiotic compliance for symptomatic individuals (see Table 4). The time of death of each infected individual, q^l_7, is updated to:

$$q^l_7 \leftarrow \begin{cases} q^l_6 & q^l_6 \leq q^l_9 & Bernoulli(q^l_4) = 1 \\ q^l_7 & q^l_6 \leq q^l_9 & Bernoulli(q^l_4) = 0 \\ & \text{if} & \text{and} \\ q^l_6 & q^l_6 > q^l_9 & Bernoulli(q^l_{10}) = 1 \\ q^l_7 & q^l_6 > q^l_9 & Bernoulli(q^l_{10}) = 0 \end{cases}$$

Let z_1 represent the vector of indices l where $q_9^l < 10^{10}$ (ie, the infected individuals who receive antibiotics). The antibiotic treatment status (treated = 1, untreated = 0) of each infected individual, q_8^l, is updated to:

$$q_8^{z_1} \leftarrow 1$$

Under the Collective Strategy

For each work ward, j, the start time for mass antibiotic distribution in each ward, t_a^j, is initially allocated as

$$t_a^j = 10^{10} \qquad \text{where} \qquad j = 1..n_w$$

Let n_t represent the trigger number of symptomatic individuals in a ward required for mass antibiotic distribution (see Table 4). For each *infected* work ward, $m = 1..n_{fw}$, the time that case n_t becomes symptomatic, t_f^m, is given by:

$$t_f^m = q_{5(n_t)}^l \qquad \forall \qquad q_1^l \equiv m$$

Note that the brackets in the equation above represent the order statistic of q_5 and that q_1^l and m are matched at this stage to ensure correct allocation. Let z_2 represent the vector of indices m where $t_f^m < 10^{10}$ (ie, the infected work wards that are identified for mass antibiotic distribution. Note that some infected work wards would not experience n_t cases.). The start time for mass antibiotic distribution in each ward, t_a^j, is updated to:

$$t_a^{z_2} \leftarrow \begin{matrix} t_f^{z_2} \\ \\ t_g \end{matrix} \quad \text{if} \quad \begin{matrix} t_f^{z_2} > t_g \\ \\ t_f^{z_2} < t_g \end{matrix}$$

The total number of individuals who have been identified for mass antibiotic distribution, T_M, is initially allocated as:

$$T_M = 0$$

Mass distribution of antibiotics to different wards is implemented via discrete event simulation by looping through the remaining equations in this section $\dim(z_2)$ times. Let z_3 represent the vector of indices l where $q_1^l = z_2^L$ (ie, infected individuals who, depending on the stockpile level, receive antibiotics during the current loop. Note that z_3 is equivalent to z_1 under the individual strategy.). The antibiotic treatment time of each infected individual during the current loop, $q_9^{z_3}$, is initially given by:

$$q_9^{z_3} \leftarrow \begin{cases} t_g + t_s & \text{if} \quad q_5^{z_3} + t_s < t_g + t_s \\ q_5^{z_3} + t_s & \quad\;\; q_5^{z_3} + t_s \geq t_g + t_s \end{cases}$$

Let t_u^n be a random draw from a uniform distribution given by:

$$\upsilon(\chi) = \begin{cases} \frac{1}{\beta - \alpha} & \text{for} \quad \alpha \leq \chi \leq \beta \\ 0 & \quad\;\; \chi < \alpha, \chi > \beta \end{cases}$$

ie, $t_u^n \sim Uniform(t_s, t_d)$

where $n = 1..\dim(z_3)$ and where t_d is the time to distribute antibiotics to an entire ward (see Table 4). To capture mass antibiotic distribution, the antibiotic treatment time of each infected individual during the current loop, $q_9^{z_3}$, is updated to:

$$q_9^{z_3} \leftarrow \begin{cases} t_a^{z_2^L} + t_u^n & \text{if} \quad t_a^{z_2^L} + t_u^n < q_9^{z_3} \\ q_9^{z_3} & \quad\;\; t_a^{z_2^L} + t_u^n \geq q_9^{z_3} \end{cases}$$

The probability of death of each infected individual during the current loop, $q_{10}^{z_3}$, is given by:

$$q_{10}^{z_3} \leftarrow \begin{cases} 0 \\ q_4^{z_3}[1 - \exp(-r_t(q_9^{z_3} - q_5^{z_3}))] \\ q_4^{z_3} \end{cases}$$

$$\text{if} \quad \begin{matrix} Bernoulli(c) = 1 \\ Bernoulli(c) = 1 \\ Bernoulli(c) = 0 \end{matrix} \quad \text{and} \quad \begin{matrix} q_9^{z_3} - q_5^{z_3} \leq 0 \\ q_9^{z_3} - q_5^{z_3} > 0 \\ \\ \end{matrix}$$

The total number of individuals who have been identified for mass antibiotic distribution during the current loop, T_z, is given by:

$$T_z = p_w^{z_2^L}$$

The stockpile level, n_s, is updated to:

$$n_s \leftarrow n_s - T_z$$

The total number of individuals who have been identified for antibiotic treatment, T_M, is updated to:

$$T_M \leftarrow T_M + T_z$$

The antibiotic treatment status (treated = 1, untreated = 0) of each infected individual during the current loop, q_8^l, is updated to:

$$q_8^{z_3} \leftarrow \begin{matrix} 1 \\ Bernoulli\left(\frac{n_s + T_z}{T_z}\right) \\ 0 \end{matrix} \quad \text{if} \quad \begin{matrix} n_s > 0 \\ n_s \leq 0 \\ n_s \leq 0 \end{matrix} \quad \text{and} \quad \begin{matrix} \\ n_s + T_z > 0 \\ n_s + T_z \leq 0 \end{matrix}$$

The time of death of each infected individual, $q_7^{z_3}$, is updated to:

if $n_s > 0$ then

$$q_7^{z_3} \leftarrow \begin{cases} q_6^{z_3} & q_6^{z_3} \le q_9^{z_3} & Bernoulli(q_4^{z_3}) = 1 \\ q_7^{z_3} & q_6^{z_3} \le q_9^{z_3} & Bernoulli(q_4^{z_3}) = 0 \\ & \text{if} \quad \text{and} & \\ q_6^{z_3} & q_6^{z_3} > q_9^{z_3} & Bernoulli(q_{10}^{z_3}) = 1 \\ q_7^{z_3} & q_6^{z_3} > q_9^{z_3} & Bernoulli(q_{10}^{z_3}) = 0 \end{cases}$$

if $n_s \le 0$ and $n_s + T_z > 0$ then

$$q_7^{z_3} \leftarrow \begin{cases} q_6^{z_3} & & & Bernoulli(q_4^{z_3}) = 1 \\ q_7^{z_3} & & & Bernoulli(q_4^{z_3}) = 0 \\ & \text{if} \quad \text{and} & \text{and} & \\ q_6^{z_3} & q_6^{z_3} > q_9^{z_3} & q_8^{z_3} \neq 0 & Bernoulli(q_{10}^{z_3}) = 1 \\ q_7^{z_3} & q_6^{z_3} > q_9^{z_3} & q_8^{z_3} \neq 0 & Bernoulli(q_{10}^{z_3}) = 0 \end{cases}$$

if $n_s \le 0$ and $n_s + T_z \le 0$ then:

$$q_7^{z_3} \leftarrow \begin{cases} q_6^{z_3} & \text{if} & Bernoulli(q_4^{z_3}) = 1 \\ q_7^{z_3} & & Bernoulli(q_4^{z_3}) = 0 \end{cases}$$

Note that given the length and complexity of the Appendix, equations describing the administration of antibiotic courses to those individuals who lived (but didn't work) in wards identified for mass antibiotic distribution have been omitted. Please contact the authors for further details.

Summary Statistics

The total number of infected individuals given antibiotic treatment, S_I, is given by:

$$S_I = \sum_{l=1}^{n_{fp}} q_8^l$$

The total number of infected individuals given antibiotic treatment who survived the disease, S_S, is given by:

$$S_S = \sum_{l=1}^{n_{fp}} \delta(q_7^l q_8^l - 10^{10})$$

The total number of deaths due to the disease, S_{dD}, is given by:

$$S_{dD} = \sum_{l=1}^{n_{fp}} 1 - \delta(q_7^l - 10^{10})$$

The total number of exposed individuals given antibiotic treatment, S_M, is given by:

$$S_M = \begin{cases} 0 & & under\_the\_individual\_strategy \\ n_s & \text{if} \quad n_s \le T_M & under\_the\_collective\_strategy \\ T_M & n_s > T_M & under\_the\_collective\_strategy \end{cases}$$

The total number of severe antibiotic adverse events (possibly resulting in death), S_{aD}, is given by:

$$S_{aD} \approx \begin{cases} acS_S & under\_the\_individual\_strategy \\ ac[S_M - (S_I - S_S)] & under\_the\_collective\_strategy \end{cases}$$

where a is the antibiotic adverse event rate (see Table 4). The total number of deaths, S_D, is given by:

$$S_D = S_{dD} + S_{aD} \approx S_{dD}$$