Appendix B Derivation of the indices and properties of the EOI

Index construction begins by calculating coverage, defined as the proportion of infections of each type y in the basket (figure 1) that are susceptible to each available drug d (figure 2):

$$\underbrace{V_{y,d}}_{\text{Coverage of syndrome } y \text{ by drug } d} = \sum_{s \in S_y} (1 - \underbrace{\rho_{s,d}}_{\text{Resistance}}) \underbrace{\kappa_{s,y}}_{\text{Etiology}}, \tag{B.1}$$

where $\rho_{s,d}$ is the proportion of isolates of species s that are resistant to drug d as specified in the cumulative antibiogram (table 4) and $\kappa_{s,y}$ is the proportion of cases of syndrome y caused by species s in the basket (figure 1). S_y is the set of species associated with syndrome y. We assume that each infection is caused by a single species, and that treatment is informed by Gram stains.[18]

We define the Empiric Coverage Index (ECI) for common device-associate infections as the percentage of infections in the basket (figure 1) that are covered by empiric therapy, provided that each infection is treated with the drug that is most likely to provide coverage:

$$\text{ECI} = 100 \times \sum_{y \in Y} \alpha_y \max_{d=1}^{D_y} (V_{y,d}), \tag{B.2}$$

where α_y is the proportion of infections in the basket that are syndrome y (figure 1), Y is the set of syndromes in the basket, and D_y is the number of available drugs for treatment of syndrome y (figure 2).

The EOI is defined as the number of patients that can be covered by a set of drugs, relative to the number that can be covered by a single fully effective drug. To get the number of patients that can be covered by D_y drugs, we first label the drugs in order, so $V_{y,1}$ is the highest coverage, and V_{y,D_y} is the lowest coverage (figure 2).

Now assume that drug $d = 1$ is used exclusively until the second drug provides equal coverage. At that point both drugs 1 and 2 used until the third drug is equally effective, and so on. Define T_d as the time when use of drug d begins, and $\Delta T_d = T_{d+1} - T_d$ as the duration of time when drugs 1 to d are all used equally. It follows that the coverage provided by drug d at time T_{d+1} is equal to the initial coverage provided by drug $d + 1$; $V_{y,d}(T_{d+1}) = V_{y,d+1}$. At time 0 drug 1 is used, so $T_1 = 0$. Assume that the relationship between drug use and resistance does not differ among drugs, and that patients are treated at a constant rate n. Each drug is then used at a rate n/d.

We assume a simple linear decline in coverage with drug use, so that coverage by drug d of syndrome y at time t is (figure 3):

$$V_{y,d}(t) = \begin{cases} V_{y,d} - \dfrac{\beta f(d) n t}{d} \text{ if } T_d \leq t \leq T_{d+1}, \\ V_{y,d} \text{ if } t < T_d, \\ V_{y,d+1}(t) \text{ if } t > T_{d+1}, \end{cases} \tag{B.3}$$

where $V_{y,d}$ is the coverage provided by drug d at time 0, and $\beta f(d)$ is the decline in coverage with drug use. Setting $f(d) = 1$ implies that the only advantage of using multiple drugs is that we use less of each. Mixing or cycling antibiotics may additionally slow the spread of resistance,[43] which can be modelled by making $f(d)$ a decreasing function of d, with a value of 1 when $d = 1$, and a minimum value > 0. A simple exponential decay model $f(d) = (1 - \alpha)^(d - 1)$ is one possibility, but there are others so we retain the general form $f(d)$. The third equation indicates that once drug $d + 1$ comes into use at time T_{d+1}, coverage by drugs already in use (drugs 1 to d) declines with coverage by drug $d + 1$.

We can solve equation B.3 for the duration ΔT_d by noting that use of drug $d + 1$ begins when $V_{y,d}(t) = V_{y,d+1}$:

$$\Delta T_d = \frac{d[V_{y,d} - V_{y,d+1}]}{\beta f(d) n}. \tag{B.4}$$

The number of patients that can be treated in the interval T_d to T_{d+1} is:

$$S_{y,d} = \int_{t=T_d}^{T_{d+1}} nV_{y,d}(t)dt. \tag{B.5}$$

Substituting equations B.3 and B.4 into equation B.5 and simplifying gives us the number of patients covered in the interval T_d to T_{d+1} when all drugs from 1 to d are in use:

$$\begin{aligned} S_{y,d} &= \frac{n}{2}[V_{y,d}(T_d) + V_{y,d}(T_{d+1})]\Delta T_d \\ &= \frac{n}{2}[V_{y,d} + V_{y,d+1}]\frac{d[V_{y,d} - V_{y,d+1}]}{\beta f(d)n} \\ &= \frac{d}{2\beta f(d)}[V_{y,d}^2 - V_{y,d+1}^2]. \end{aligned} \tag{B.6}$$

Set $V_{y,D_y+1} = 0$ to get the number of patients covered in the final interval.

The total number of people covered is simply the sum of people covered in each interval:

$$S_y = \sum_{d=1}^{D_y} S_{y,d} = \frac{1}{2\beta f(d)} \sum_{d=1}^{D_y} d[V_{y,d}^2 - V_{y,d+1}^2]. \tag{B.7}$$

Setting $D_y = 1$ and $V_{y,1} = 1$ in equation B.7 gives us the number of people covered by a single fully effective drug: $F = 1/(2\beta)$. The value of the portfolio of D_y drugs for each syndrome relative to the value of a single fully effective drug then gives us an index of empiric options for each syndrome:

$$\begin{aligned} \mathrm{EOI}_y &= S_y/F \\ &= \sum_{d=1}^{D_y} d/f(d)[V_{y,d}^2 - V_{y,d+1}^2]. \end{aligned} \tag{B.8}$$

To get an EOI for the entire basket, we average over infection types:

$$\text{EOI} = \sum_{y \in Y} \alpha_y EOI_y, \tag{B.9}$$

where α_y is the proportion of infections in the basket that are syndrome y (figure 1).

The EOI has the following properties:

1. The index only reaches its minimum value when no drugs provide coverage $V_{y,d} = 0$.

2. The index reaches a maximum value of $D_y/f(D_y)$ when all options provide full coverage ($V_{y,d} = 1$).

3. All else being equal, large differences in resistance are reflected by large differences in the EOI (compare columns in figure 5).

4. All else being equal, and provided that $f(d) = 1$, a higher EOI is assigned when the best available coverage is high (compare rows in figure 5). Given cases with same number of available treatment options D_y and the same average coverage $\bar{V} = \sum_{d=1}^{D_y} V_{y,d}/D_y$, the lowest possible index value is assigned to the case where all drugs provide low coverage $\bar{V}$: $EOI_{\min} = D_y\bar{V}^2$. The highest possible index value is assigned to the case of $\lfloor \bar{V} D_y \rfloor$ drugs that provide full coverage, and one drug that provides the remaining coverage $\bar{V} D_y \ \% \ 1$. In this case, $EOI_{\max} = \lfloor \bar{V} D_y \rfloor + (\bar{V} D_y \ \% \ 1)^2$. TO DO: get the max and min when $f(d)$ is a declining function of d.