RESEARCH ARTICLE

Why sensitive bacteria are resistant to hospital infection control [version 2; peer review: 2 approved]

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Abstract

Background: Large reductions in the incidence of antibiotic-resistant strains of Staphylococcus aureus and Clostridium difficile have been observed in response to multifaceted hospital-based interventions. Reductions in antibiotic-sensitive strains have been smaller or non-existent. It has been argued that since infection control measures, such as hand hygiene, should affect resistant and sensitive strains equally, observed changes must have largely resulted from other factors, including changes in antibiotic use. We used a mathematical model to test the validity of this reasoning.

Methods: We developed a mechanistic model of resistant and sensitive strains in a hospital and its catchment area. We assumed the resistant strain had a competitive advantage in the hospital and the sensitive strain an advantage in the community. We simulated a hospital hand hygiene intervention that directly affected resistant and sensitive strains equally. The annual incidence rate ratio (IRR) associated with the intervention was calculated for hospital- and community-acquired infections of both strains.

Results: For the resistant strain, there were large reductions in hospital-acquired infections (0.1 ≤ IRR ≤ 0.6) and smaller reductions in community-acquired infections (0.2 ≤ IRR ≤ 0.9). These reductions increased in line with increasing importance of nosocomial transmission of the strain. For the sensitive strain, reductions in hospital acquisitions were much smaller (0.6 ≤ IRR ≤ 0.9), while community acquisitions could increase or decrease (0.9 ≤ IRR ≤ 1.2). The greater the importance of the community environment for the transmission of the sensitive strain, the smaller the reductions.

Conclusions: Counter-intuitively, infection control interventions, including hand hygiene, can have strikingly discordant effects on resistant and sensitive strains even though they target them equally, following differences in their adaptation to hospital and community-based transmission. Observed lack of effectiveness of control measures for sensitive strains does not provide evidence that infection control interventions have been ineffective for sensitive strains.
does not provide evidence that infection control interventions have been ineffective in reducing resistant strains.

**Keywords**
mathematical modelling, nosocomial infections, hospital infection control, Clostridium difficile, Staphylococcus aureus, MRSA, hand hygiene, antibiotic resistance

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Introduction

In England and Wales, rates of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia in hospitals showed a sharp decline following implementation of the national CleanYour-Hands campaign in 2004, with rates falling from 1.9 to 0.9 cases per 10 000 bed days between 2004 and 2008\(^1\). Over the same period, the methicillin-sensitive Staphylococcus aureus (MSSA) bacteraemia rate showed a small increase from 2.7 per 10 000 bed days in 2004 to 3.0 in 2008. Analysis of regional or hospital-level data from England reveals a similar picture: most hospital settings experienced sharp falls in rates of MRSA infection from 2004, while MSSA infection rates either did not fall or fell only in line with pre-existing trends\(^2\). A remarkably similar pattern has recently been reported for Clostridium difficile infection (CDI) in England\(^3\). CDI prevention policies, including infection control and antibiotic stewardship, were introduced in England in 2007; by 2013 the annual number of CDI had fallen by approximately 80 per cent. Genomic analysis revealed that this decline was accounted for by the elimination of fluoroquinolone-resistant strains. Rates of infection with fluoroquinolone-sensitive strains showed very little change following the interventions, and there was no change in the number of inferred secondary cases with or without hospital contact.

These diverging outcomes for antibiotic-resistant and antibiotic-sensitive variants of common nosocomial pathogens have led some researchers to argue that these data provide evidence against infection control measures having played a major role in these declines\(^4\). It is reasoned that non-specific infection control measures, such as improved hand hygiene or ward cleaning, would be expected to reduce hospital transmission of resistant and sensitive strains equally. The fact that we observe only declines in resistant strains indicates that other factors, i.e. those having a differential effect on resistant and sensitive strains, must have been the major causes for the reduction\(^4\). Here we develop a simple mechanistic mathematical model to assess the validity of this line of reasoning. Our model considers the carriage dynamics of two bacterial strains: one antibiotic-resistant and one antibiotic-sensitive. We assume that both strains are able to spread between individuals in the hospital and the community, but that the resistant strain transmits better in the hospital, while the sensitive strain transmits better in the community.

Since most bacterial hospital pathogens of clinical concern can be carried asymptotically over long periods, we account for movements of colonized individuals between the hospital and community\(^5\). We explicitly model a hospital hand hygiene intervention as an example of a non-specific infection control measure and evaluate the impact of this intervention on the incidence of hospital and community acquisitions of antibiotic-resistant and antibiotic-sensitive strains.

Methods

Model framework and assumptions

We developed a dynamic deterministic compartmental transmission model to track the number of people colonized with the resistant and sensitive strains in the hospital and community (Figure 1).

Transmission between patients in the hospital was assumed to occur via the transiently contaminated hands of healthcare workers. We modelled this process explicitly using a previously described host-vector approach\(^6,7\). Persistent carriage of bacteria such as MRSA has been reported among healthcare workers, though is commonly found to be transient\(^8\). Therefore, healthcare workers in turn were assumed to become transiently contaminated through patient contact. Hand hygiene performed by a contaminated healthcare worker was assumed to clear this contamination\(^9\). Individuals were considered to be either colonized with an antibiotic-sensitive strain (whether asymptotically or symptomatically), colonized with an antibiotic-resistant strain or uncolonized and susceptible to both.

Patients were tracked by their hospitalisation history so that recently discharged patients (those in population 2) experienced a transient period with a shorter expected time to their next hospital admission; i.e. a higher (re)admission rate than the general community population (population 3, Figure 1). We assumed frequency-dependent transmission\(^10\). The model allowed for the possibility of assortative mixing within populations 2 and 3, where the effective contact rate of strain \(i\) (\(\beta_i\)) between individuals within a population \(n\) was a fraction of the effective contact rate between individuals across populations:

\[
N_2 \begin{pmatrix} N_2 & N_3 \\ \beta_{22} & f_{23}\beta_{33} \end{pmatrix}
\]

The resistant strain was assumed to be better adapted to the hospital setting, meaning that in the absence of other colonized hosts, a patient colonized with a resistant strain admitted to the hospital would be expected to generate more secondary cases during their hospital episode than a patient colonized with a sensitive strain. In contrast, the sensitive strain was assumed to be better adapted to the community. Individuals could not be co-infected with resistant and sensitive strains, and we allowed for bacterial interference between the two strains so that colonization with one strain reduced the risk of acquisition of the other strain, with at baseline assuming 100% bacterial interference, i.e. no replacement infection\(^11,12\).

Model equations are given below. Variables are defined in Table 1 and parameter definitions and values in Table 2.
Figure 1. Flow diagram of model framework. In all three populations, individuals can reside in and move between the three carriage states (uncolonized, colonized with antibiotic-sensitive bacteria, and colonized with antibiotic-resistant bacteria). Movements between states are indicated by black arrows. Broken white lines indicate what variables influence transition rates between compartments. Transmission events between hospitalized patients are mediated by transiently contaminated healthcare workers (circles), and transient contamination is removed by hand hygiene events (an intervention which affects resistant and sensitive strains equally).

Table 1. Model variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$U_1$</td>
<td>Susceptible population 1: number of patients in hospital who are not colonized/infected with either the resistant or sensitive strain.</td>
</tr>
<tr>
<td>$U_2$</td>
<td>Susceptible population 2: number of individuals in community setting who have a short expected time to hospital admission who are colonized with neither the resistant nor the sensitive strain.</td>
</tr>
<tr>
<td>$U_3$</td>
<td>Susceptible population 3: number of individuals in community setting who have a long expected time to hospital admission who are colonized with neither the resistant nor the sensitive strain.</td>
</tr>
<tr>
<td>$R_1$</td>
<td>Resistant population 1: number of patients in hospital setting colonized with the resistant (hospital-adapted) strain.</td>
</tr>
<tr>
<td>$R_2$</td>
<td>Resistant population 2: number of individuals in community setting who have a short expected time to hospital admission who colonized with the resistant (hospital-adapted) strain.</td>
</tr>
<tr>
<td>$R_3$</td>
<td>Resistant population 3: number of individuals in community setting who have a long expected time to hospital admission who colonized with the resistant (hospital-adapted) strain.</td>
</tr>
<tr>
<td>$S_1$</td>
<td>Sensitive population 1: number of patients in hospital setting colonized with the sensitive (community-adapted) strain.</td>
</tr>
<tr>
<td>$S_2$</td>
<td>Sensitive population 2: number of individuals in community setting who have a short expected time to hospital admission who colonized with the sensitive (community-adapted) strain.</td>
</tr>
<tr>
<td>$S_3$</td>
<td>Sensitive population 3: number of individuals in community setting who have a long expected time to hospital admission who colonized with the sensitive (community-adapted) strain.</td>
</tr>
<tr>
<td>$hcw_R$</td>
<td>Number of hospital healthcare workers who are transiently colonized with the resistant (hospital-adapted) strain.</td>
</tr>
<tr>
<td>$hcw_S$</td>
<td>Number of hospital healthcare workers who are transiently colonized with the sensitive (community-adapted) strain.</td>
</tr>
</tbody>
</table>
### Table 2. Model parameters. *Defined by other parameters to give $R$ values of 1.5 for the resistant and 1.4 for the sensitive strain. Here $R_n$ is defined as the expected number of secondary cases in the hospital and community resulting from one colonised individual in a fully uncolonized and susceptible population at baseline hand hygiene rates of 40%, accounting for the possibility of readmissions while still colonized.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value (range)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_1$</td>
<td>Number of hospitalised patients</td>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>$N_{hcw}$</td>
<td>Number of healthcare workers (HCW)</td>
<td>100</td>
<td>13,14</td>
</tr>
<tr>
<td>$N_2$</td>
<td>Number of people in the community who have a short expected time to hospital admission (recently discharged people)</td>
<td>10,000</td>
<td></td>
</tr>
<tr>
<td>$N_3$</td>
<td>Number of people in the community who have a long expected time to hospital admission (not recently discharged people)</td>
<td>100,000</td>
<td></td>
</tr>
<tr>
<td>$\tau$</td>
<td>Hospital patient removal rate (reciprocal of mean hospital stay)</td>
<td>$1/10d^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$\nu$</td>
<td>Rate of transition from the community population with a high hospital admission rate to the community population with a low hospital admission rate (reciprocal of mean duration with a high admission rate)</td>
<td>$hN_3/N_2$</td>
<td></td>
</tr>
<tr>
<td>$\rho$</td>
<td>Ratio of hospital admission rate of the recently hospitalised to hospital admission rate for the general population</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>$h$</td>
<td>Admission rate to hospital of people in the general population</td>
<td>See methods</td>
<td></td>
</tr>
<tr>
<td>$r$</td>
<td>Admission rate to hospital of recently discharged people</td>
<td>See methods</td>
<td></td>
</tr>
<tr>
<td>$c$</td>
<td>Mean number of HCW contacts per patient day</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>$\gamma_{R_i}$</td>
<td>Carriage clearance rate of the resistant (hospital-adapted) strain in the hospital/community (reciprocal of mean carriage duration)</td>
<td>$1/400d^{-1}$</td>
<td>15</td>
</tr>
<tr>
<td>$\gamma_{S_i}$</td>
<td>As above for the sensitive (community-adapted) strain</td>
<td>$1/400d^{-1},1/400d^{-1},1/400d^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$\beta_{R_1}$</td>
<td>Transmission parameter for the resistant strain (from colonized HCW to a susceptible patient)</td>
<td>0.187 (0.035, 0.225) *</td>
<td></td>
</tr>
<tr>
<td>$\beta_{S_1}$</td>
<td>As above for the sensitive strain</td>
<td>0.100 (0.040, 0.216) *</td>
<td></td>
</tr>
<tr>
<td>$\lambda_{R_i}$</td>
<td>Rate at which uncolonized individuals become infected with the resistant strain per unit time in the hospital/community</td>
<td>See methods</td>
<td></td>
</tr>
<tr>
<td>$\lambda_{S_i}$</td>
<td>As above for the sensitive strain</td>
<td>See methods</td>
<td></td>
</tr>
<tr>
<td>$H$</td>
<td>Baseline hand hygiene compliance (probability of successful hand decontamination following patient contact)</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>$\eta$</td>
<td>Hand hygiene rate</td>
<td>See methods</td>
<td></td>
</tr>
<tr>
<td>$\omega_{R}$</td>
<td>Bacterial interference: risk ratio for acquiring the resistant strain if carrying the sensitive strain relative to a non-carrier</td>
<td>0 (0, 1)</td>
<td></td>
</tr>
<tr>
<td>$\omega_{S}$</td>
<td>As above for the sensitive strain</td>
<td>0 (0, 1)</td>
<td></td>
</tr>
<tr>
<td>$f_{23}$</td>
<td>The ratio of the effective contact rate in $N_i$ from someone in $N_j$ to the effective contact rate in $N_j$ from someone in $N_i$ (where 1 implies that on contact, someone in $N_i$ is causing new infections in $N_j$ and $N_j$ at the same rate). Of note, as $N_j &gt; N_i$, $f_{ij} = N_j/N_i$ assumes the same per capita infection rate, i.e. homogeneous mixing.</td>
<td>$N_j/N_i$ (0, $N_j/N_i$)</td>
<td></td>
</tr>
<tr>
<td>$f_{32}$</td>
<td>The ratio of the effective contact rate in $N_i$ from someone in $N_j$ to the effective contact rate in $N_j$ from someone in $N_i$.</td>
<td>1 (0, $N_j/N_i$)</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>Percentage of transmission events with the hospital-adapted strain (assuming an otherwise fully susceptible population, and that the hospital-adapted strain is initially acquired in the hospital)</td>
<td>25% (0%, 60%)</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>As above for the community-adapted strain</td>
<td>2.5% (0%, 15%)</td>
<td></td>
</tr>
</tbody>
</table>
Equations

\[ \frac{dU_1}{dt} = rU_1 + hU_3 - \lambda_{s_1} U_1 - \lambda_{r_1} U_1 + \gamma_{r_1} R_1 + \gamma_{s_1} S_1 \]  
(1)

\[ \frac{dU_2}{dt} = -rU_2 - \nu U_1 + tU_1 - \lambda_{s_2} U_2 - \lambda_{r_2} U_2 + \gamma_{r_2} R_2 + \gamma_{s_2} S_2 \]  
(2)

\[ \frac{dU_3}{dt} = -hU_3 + \nu U_1 - \lambda_{s_3} U_3 - \lambda_{r_3} U_3 + \gamma_{r_3} R_3 + \gamma_{s_3} S_3 \]  
(3)

\[ \frac{dR_1}{dt} = rR_1 + hR_3 - \lambda_{s_1} R_1 + \lambda_{r_1} U_1 + \omega_{\beta_1} h_1 S_1 - \omega_{\beta_1} R_1 \]  
(4)

\[ \frac{dR_2}{dt} = -rR_2 - \nu R_2 - tU_1 + \lambda_{r_2} U_2 + h_{\beta_2} h_2 s_2 \]  
(5)

\[ \frac{dR_3}{dt} = -hR_3 + \nu R_2 - \lambda_{s_3} R_3 + \omega_{\beta_3} h_3 S_3 - \omega_{\beta_3} R_3 \]  
(6)

\[ \frac{dS_1}{dt} = rS_1 + hS_3 - \gamma_{s_1} S_1 - \lambda_{r_1} U_1 + \omega_{\beta_1} h_1 S_1 - \omega_{\beta_1} R_1 \]  
(7)

\[ \frac{dS_2}{dt} = -rS_2 - \gamma_{s_2} S_2 + \lambda_{r_2} U_2 + \omega_{\beta_2} h_2 S_2 - \omega_{\beta_2} R_2 \]  
(8)

\[ \frac{dS_3}{dt} = -hS_3 + \gamma_{s_3} S_3 - \lambda_{r_3} U_3 + \omega_{\beta_3} h_3 S_3 - \omega_{\beta_3} R_3 \]  
(9)

\[ \frac{dhcw_k}{dt} = p_\beta_{s_1} R_1 (N_{hcw} - hcw_k) N_{hcw} - \eta hcw_k \]  
(10)

\[ \frac{dhcw_s}{dt} = p_\beta_{s_3} S_1 (N_{hcw} - hcw_k) N_{hcw} - \eta hcw_s \]  
(11)

\[ h = \frac{\theta N}{N + \rho} \]

\[ r = \rho h \]

\[ \lambda_{s_1} = \beta_{s_1} h_{cw_k} / N_{hcw} \]

\[ \lambda_{s_2} = \beta_{s_2} R_2 / N_2 + \beta_{s_2} R_1 / N_3 \]

\[ \lambda_{s_3} = \beta_{s_3} R_3 / N_3 + \beta_{s_3} R_1 / N_4 \]

\[ \lambda_{r_1} = \beta_{r_1} h_{cw_s} / N_{hcw} \]

\[ \lambda_{r_2} = \beta_{r_2} S_2 / N_2 + \beta_{r_2} S_1 / N_3 \]

\[ \lambda_{r_3} = \beta_{r_3} S_3 / N_3 + \beta_{r_3} S_1 / N_4 \]

\[ \eta = \frac{H c N / (N_{hcw}(1 - H))}{N_1 + R_1 + S_1} \]

\[ N_1 = U_1 + R_1 + S_1 \]

\[ N_2 = U_2 + R_2 + S_2 \]

\[ N_3 = U_3 + R_3 + S_3 \]

The net reproduction numbers \( R \) for both resistant and sensitive pathogens (1.5 and 1.4, respectively) were calculated as the dominant eigenvalues of the next generation matrix\(^{16} \). Here, \( R \) is defined as the expected number of secondary cases in the hospital and community resulting from one infected individual in a fully uncolonized and susceptible population at baseline hand hygiene rates of 40%, accounting for the possibility of readmissions while still colonized. The model was implemented by numerically solving the set of ordinary differential equations using R version 3.3.1 (Team R Development Core, website: https://cran.r-project.org/) and the package deSolve\(^{17} \). Model code is available online\(^{18} \).

Hospital infection control measures

We modelled a hospital infection control intervention to reduce secondary spread of bacterial pathogens in the hospital. This was achieved by a stepwise increase in hand hygiene compliance amongst health care workers from a baseline rate of 40% to a rate of 50%. We assumed the intervention was equally effective at decontaminating hands of healthcare workers transiently contaminated with resistant and sensitive strains.

Measuring the impact of hospital infection control

Annual incidence rate ratios (IRR) were calculated using simulated data for one year pre- and post-intervention \( (T_0 \) and \( T_1 \) respectively) after first running the model to equilibrium. To aid comparison with reported infection data\(^1 \), we assumed the number of new infections with and without a hospital link \( (Y) \) was proportional to the cumulative number of acquisitions \( (\Delta I) \) in the hospital or community, respectively, in each of the two time periods:

\[ \Delta I_i (t) = \int_{T_1}^{T_1+365} \lambda_i U_i dt \]

\[ \Delta I_i (t) = \int_{T_0}^{T_0+365} \lambda_i U_i dt \]

\[ \Delta I_{23} (t) = \int_{T_0}^{T_0+365} \lambda_{23} U_2 + \lambda_{23} U_1 dt \]

\[ \Delta I_{23} (t) = \int_{T_0}^{T_0+365} \lambda_{23} U_2 + \lambda_{23} U_1 dt \]

Confidence intervals were calculated using 1000 Monte Carlo replicates on the assumption that the actual number of observed infections of each strain \( Y_i \) followed a negative binomial distribution where \( \text{Var}(Y_i) = \mu + \theta \mu / \kappa \) with \( \kappa \) (the dispersion parameter) = \( \mu(\theta - 1) \), with \( \theta = 5 \), and assuming 1 in 10 carriage episodes acquired in hospital resulted in a reported infection. This was 1 in 50 for community-acquired episodes. Hence we allowed for differences in reporting rates as well as heterogeneity in case-mix between both settings, affecting the likelihood of developing an infection. Then the IRR\(_h\) corresponded to the ratio of the number of new observed infections of strain \( i \) in population \( n \) in the year pre-intervention to the number in the first year post-intervention:

\[ \text{IRR}_{h} = \sum_{n=1}^{T_0+365} \frac{Y_n (t)}{T_0+365} \]

Investigating the importance of environmental adaptation of competing pathogens

At baseline, the relative fraction of new cases acquired in hospital was 25% and 2.5% for the resistant and sensitive strains, respectively. To investigate the impact of hospital- and community-adaptation of both strains on our findings, we varied the level of transmission in both settings for each of the two strains, while keeping the overall net reproduction number for resistant and sensitive strains constant at 1.5 and 1.4, respectively. We investigated hospital acquisition fractions of 0.5–60%, for the resistant
strain, and 0.5–15% for the sensitive strain. Only scenarios where resistant and sensitive strains co-existed prior to the intervention were considered in this analysis, and we considered this to be the case when the equilibrium incidence rates for colonization were above one per 100,000 person years for both strains.

**Results**

**Impact of hospital infection control**

Improving hand hygiene compliance by 10% resulted in dramatic reductions in the incidence of infections with the resistant strain. These reductions were most pronounced for secondary cases that resulted from cross-infection within the hospital (IRR = 0.41 [95% CI: 0.32–0.52] under baseline parameters); they were also clearly observed for acquisitions that occurred in the community (IRR = 0.67 [0.59–0.76], Figure 2). Incidence rates of infections caused by the sensitive strain were markedly less affected by the intervention, though in the first year post-intervention there was a moderate reduction in infections linked to hospital transmission (IRR = 0.83 [0.55–1.22] Figure 2). In contrast, the reduced competition from the resistant strain resulted in moderate reductions in the incidence of infections caused by the sensitive strain.

**Figure 2. Distribution of predicted incidence rate ratios associated with the infection control intervention.** Predicted annual incidence rate ratios (IRRs) for infections with the resistant and sensitive bacterial strains associated with a 10% improvement in hand hygiene compliance from a baseline of 40%. Incidence rate ratios were calculated using simulated data one year pre- and post-intervention, where observed infections followed a negative binomial distribution with a mean proportional to the number of acquisitions in hospital and community in the deterministic model. Shaded areas represent distributions, and enclosed dots and lines represent medians and standard deviations. An IRR of 1 corresponds to no change (dotted line). Non-enclosed single dots and lines represent mean and 95% confidence intervals of observed IRRs for *C. difficile* fluoroquinolone-resistant (turquoise) and fluoroquinolone-sensitive (grey) strains, grouped according to presence or absence of a hospital link (data from 4).
increases in sensitive infections linked to community acquisitions (IRR = 1.10 [1.03–1.17], Figure 2). The net result was a small overall increase in the incidence of infections with the sensitive pathogen. These trends are exactly in line with reported data (Figure 2).

Dynamics after hospital infection control
The above results appear counterintuitive, but can be understood after consideration of the dynamics. First, the reduction in resistant infections linked to community transmission can be explained by a reduction in the number of patients colonized with resistant bacteria at hospital discharge. Reducing the efflux of these colonized patients into the community (a consequence of reduced transmission in the hospital) leads to a long-term decline in the prevalence and incidence of the resistant strain in this setting (Figure 3). These gradual changes in the community reservoir (which occur despite the sudden changes in the hospital transmission rate due to the intervention) in turn lead to reduced importations (and subsequent transmission) of the resistant strain into the hospital. This explains why we see a gradual decline in resistant infections in the hospital and community even following an intervention that occurs in a stepwise manner and which is restricted to the hospital.

For the sensitive pathogen strain, we also see an initial stepwise reduction in the hospital incidence of new patient acquisitions (Figure 3). However, the drop is smaller than for the resistant strain because the sensitive strain depends much less on hospital transmission for maintaining its hospital prevalence and much more on importations from the community. Despite this initial fall in hospital prevalence and incidence of the sensitive strain, over a period of several years there are modest increases in both - a consequence of reduced competition with the resistant strain. The net result is that the intervention has a discordant effect on new hospital acquisitions of the sensitive and resistance strains; the former marginally increases over a period of several years, while the latter declines to low levels.

**Figure 3.** Predicted incidence and prevalence trends of the sensitive and resistant bacterial strains following the introduction of enhanced infection control. Trends in the incidence of new acquisitions (symptomatic and asymptomatic) and carriage prevalence for resistant and sensitive bacterial strains following a 10% stepwise improvement in hand hygiene compliance after one year from a baseline of 40%. Incidence trends are depicted as transmission events following from community-to-community transmission (dashed line) and hospital-to-hospital transmission (dotted line). As prevalence in the hospital represents only a small fraction of the overall prevalence (in hospital and community populations combined), the latter is almost identical to the community prevalence for both the resistant and sensitive bacterial strains.
Broadly similar dynamics were observed for larger increases in hand hygiene compliance, and for sufficiently high compliance the intervention was capable of driving the resistant strain to extinction (Supplementary Figure S1 and Supplementary Figure S2). Thus, while the resistant strain was able to persist at a low level alongside the sensitive strain when hand hygiene compliance was 50% (Figure 3), increasing it further to >55% induced a more rapid decline in both the hospital and community reservoir and successfully eliminated the resistant strain within the five year time period simulated (Supplementary Figure S1 and Supplementary Figure S2).

Importance of the degree of strain adaptation to the hospital and community settings
With baseline parameters, 25% of acquisitions of the resistant strain occurred in hospital; the corresponding figure for the sensitive strain was 2.5%. Increasing adaptation of the resistant strain to the hospital environment (i.e. increasing the proportion of resistant transmission that occurs in hospital by changing the values of the transmission parameters ($\beta_h$) while keeping the net reproduction number and all other parameters constant), resulted in larger effect sizes for the hospital infection control intervention: $0.1 \leq IRR \leq 0.6$ for incidence linked to hospital transmission and $0.2 \leq IRR \leq 0.9$ for incidence related to community transmission (Figure 4). For the sensitive strain, secondary cases with a hospital link also declined in response to the intervention, though at lower rates than the resistant strain ($0.6 \leq IRR \leq 0.9$).

In contrast, incidence rates of the sensitive pathogen without a hospital link either remained unchanged or increased following the infection control intervention ($0.9 \leq IRR \leq 1.2$). The smaller the importance of the hospital environment for transmission of the

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**Figure 4.** Annual incidence rate ratios of new acquisitions (symptomatic and asymptomatic) associated with an infection control intervention under different levels of adaptation of sensitive and resistant strains to hospital and community settings. In all simulations, reproduction numbers for resistant and sensitive strains were held constant at 1.5 and 1.4, respectively. For corresponding transmission parameter values, see https://github.com/esthervankleef/two_strain_model_published/tree/v1.0.3. White spaces represent scenarios where no co-existence occurred. An IRR = 1 corresponds to no change.
sensitive strain, the larger the increase in its incidence rate in the community in response to the intervention (Figure 4). This increase became larger when the percentage of resistance strain acquisitions occurring in the community increased.

Discussion

Our analysis shows that discordant temporal changes in resistant and sensitive infections in response to intensified hospital-based control measures, as observed for *Staphylococcus aureus* and *C. difficile*, are consistent with an intervention that reduces transmission rates of resistant and sensitive bacteria equally. Under plausible assumptions (all of which have been used in previous models) our simulations were able to produce effect sizes that are similar to those observed with real data. Notably, we did not assume the existence of an intervention, such as antimicrobial stewardship, that has different direct effects on resistant and sensitive strains. Some aspects of our results (and of the real-world data) may be considered counterintuitive, but the modelling framework helps provide a simple intuitive explanation. In general, if two pathogen strains compete unequally in two environments, a transmission-reducing intervention that preferentially targets one environment will have a disproportionate effect on the strain better adapted to that environment. We have used a hand hygiene intervention as our motivating example; similar conclusions would have been reached with other non-specific hospital infection control measures, such as ward cleaning.

Previous modelling work has shown that hospital infection control measures can have a greater effect on resistant than on sensitive bacteria. This can be expected when the hospital influx of patients carrying sensitive bacteria is the dominant factor in maintaining their high hospital prevalence, while patient-to-patient spread is largely responsible for the high hospital prevalence of resistant bacteria. Our model has extended this work by explicitly accounting for transmission in the community reservoir. One motivation for doing this is to allow direct comparison with data from recent studies using whole genome sequencing to identify infections plausibly linked to recent hospital transmission. Consideration of hospital and community dynamics also enabled us to capture the observed long-term temporal changes in resistance in response to interventions, and to demonstrate that the prevalence of sensitive bacteria may in fact marginally increase following non-specific infection control measures. We have not attempted to quantify the relative contributions of infection control, antibiotic stewardship and other factors in the large reductions in nosocomial infections with *C. difficile* and *S. aureus* in England and Wales. Our analysis merely shows that the observed reductions in resistant infections without reductions in sensitive infections is not inconsistent with infection control playing a major role. There are other lines of evidence to suggest infection control may have made an important contribution. For example, in England and Wales strong negative associations between hospital-level usage of soap and *C. difficile* infection rates and between alcohol hand rub and MRSA infection rates have been reported. Similar associations have been reported elsewhere (e.g. Vernaz et al., 2009).

The intensification of hospital infection control is commonly multifaceted, complicating the quantification of the effectiveness of individual interventions. Our findings indicate further data, e.g. hospital-level antimicrobial consumption data and measures of the behavioural impact of infection control interventions, are required to more reliably quantify the relative contribution of different control measures to the reductions observed. The most detailed analysis to date comes from two long time series studies from northeast Scotland. These suggest that both antibiotic stewardship and infection control measures made important contributions to the decline in MRSA infections in this region, while an antibiotic stewardship intervention (restricting the use of fluoroquinolones, clindamycin, co-amoxiclav, and cephalosporins) was likely to have been the dominant factor in reducing *C. difficile* infections. A strong point of our work is the simple framework we used for considering generic pathogens. The flexibility of the model readily allows adaptation to specific pathogens. For example, assumptions about carriage duration, mixing of community populations, and the degree of bacterial interference between the two strains can easily be altered (and will not change our main conclusions, as shown in respectively, Figure S3, Figure S4). In addition, by capturing dynamic transmission in both hospital- and community-populations (something commonly ignored in mathematical models of nosocomial pathogens), and including a core group of recently discharged patients with higher readmission rates, we were able to capture the interaction between hospital and community more realistically. Of note, this core group is not an essential model requirement for our central result, which is that infection control interventions alone can account for the very different effects on sensitive and resistant strains.

Our work also has important limitations. All models are simplifications of reality. Hospitals and communities encompass complex networks of contact patterns; our model represents only a caricature of these networks. We did not allow for co-infection with resistant and sensitive strains. This is a reasonable approximation for *S. aureus*, and competition for ecological niches has been reported for *C. difficile* (e.g. Songer et al., 2007; Merrigan et al., 2003), but it is unclear how appropriate this assumption would be for other enteric pathogens. Clearly, our model also ignores a lot of host and pathogen heterogeneity, nor did we account for stochastic effects. In small populations of single hospitals, chance events are likely to play an important role in the transmission dynamics of pathogens. Moreover, for simplicity we chose to focus on what appears to be the dominant mode of transmission (at least for *S. aureus*, other organisms are less well studied). Since hospitalised patients are generally not mobile, patient-to-patient transmission events represent either hand-borne or air-borne transmission. Studies from the 1960s suggest that the latter plays a relatively minor role in *S. aureus* transmission in hospital settings. However, we can think of no plausible mechanism by which incorporation of more biological realism would in any way alter our primary conclusion. Though our framework allows for further complexity, the purpose here was to demonstrate that the divergent effects of infection control interventions on resistant and sensitive models could be explained even with a simple model. Therefore, no formal model fitting to data was conducted. However, we have presented a set of scenarios for different degrees of hospital-adaptation, making our findings generalizable to a wide variety of settings and pathogens.
Conclusions
Hospital-based infection control interventions, such as hand hygiene, that target sensitive and resistant bacteria equally, can result in diverging outcomes for strains which are differentially adapted to community and hospital transmission. While it is highly plausible that changing patterns of antibiotic usage have played an important role in some of the observed declines in *C. difficile* and *S. aureus* infections, the relative importance of antibiotic stewardship versus infection control interventions cannot be inferred from differential changes in infection rates with resistant and sensitive bacteria.

Software availability
Latest source code: https://github.com/esthervankleef/Two_strain_model_published/tree/v1.0.3.
Archived source code as at the time of publication: http://doi.org/10.5281/zenodo.1045530
License: MIT license

Author contributions
BSC and EvK wrote the model code, performed the analyses and wrote the manuscript. NL and MB reviewed model assumptions, critically analysed the work and reviewed the manuscript.

Competing interests
All authors declare to have no competing interest.

Grant information
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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Supplementary material
Figure S1: Predicted trends in incidence of new acquisitions of sensitive and resistant strains under varying improvements in hand hygiene compliance. Trends in the incidence of new acquisitions (symptomatic and asymptomatic) for resistant and sensitive bacterial strains following a 5%, 10%, 15% and 20% improvement respectively in hand hygiene compliance from a baseline of 40%.
Click here to access the data.

Figure S2: Predicted trends in prevalence of new acquisitions of sensitive and resistant strains under varying improvements in hand hygiene compliance. Trends in the prevalence of carriage (symptomatic and asymptomatic) for resistant and sensitive bacterial strains following a 5%, 10%, 15% and 20% improvement respectively in hand hygiene compliance from a baseline of 40%.
Click here to access the data.

Figure S3: Predicted trends in incidence of new acquisitions of sensitive and resistant strains under varying degrees of bacterial interference. Trends in the incidence of new acquisitions (symptomatic and asymptomatic) for resistant and sensitive bacterial strains following 10% improvement respectively in hand hygiene compliance from a baseline of 40%.
Click here to access the data.

Figure S4: Predicted trends in incidence of new acquisitions of sensitive and resistant strains under varying degrees of social mixing between community populations. Trends in the incidence of new acquisitions (symptomatic and asymptomatic) for resistant and sensitive bacterial strains following 10% improvement respectively in hand hygiene compliance from a baseline of 40%.
Click here to access the data.
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The authors have carefully addressed my comments and provided more details on the modelling aspects.

I do not have any further comment to make.

Just a minor typo in the amendment box: “interference” instead of “inference”.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical modelling, bacterial resistance, pathogens interactions

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

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✔ Chris Robertson
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This paper presents a very interesting transmission dynamic model of resistant and susceptible pathogens in both healthcare and community settings. It is constructed in such a way as to be able to explore potential reasons why antimicrobial resistant organisms have been declining recently while sensitive versions of the same organism have been increasing or, remaining constant. This elegant model has different rates of transmission depending on the setting and this is the aspect which leads to an explanation of the observed data on reducing rates of MRSA alongside increasing rates of MSSA.

I think that the key aspect of the model is that resistant strains are assumed to be better adapted to the hospital setting and so would be expected to generate more secondary cases in hospital than a non resistant strain. The opposite is assumed to happen in the community. When an intervention is targeted at reducing transmission in hospitals then this will interfere more with the transmission of resistant organisms in hospital and will have no impact on the transmission in the community. This crucial assumption is not really justified, nor does it need to be, as the model only seeks to provide a mechanism whereby the observed results can be explained.

The model equations are standard for this type of model. This model, like many others, relies on assigning values to a number of parameters. There are not justified other than to have an $R_0$ of 1.5 for resistant strains and 1.4 for susceptible strains. These are reasonable values and, as this model is an exercise to see if a model can explain the observed results, getting justified parameter estimates for one organism is not really required.

In some respects the model is similar to the some of the models in Lipsitch et al. 2009$^1$ though co existence of susceptible and resistant strains are not permitted in this model.

The authors do not claim that this is a model for a disease however I was a little surprising that the resistant strain is eliminated when hand hygiene compliance reaches 55% while coexistence was observed when compliance was 50%.

Minor points:

The model assumes each hospital is associated with a community of 110,000 – this is OK for Scotland with 42 acute hospitals and a population of 5.2 million. The average size of each hospital is just under 300 beds. What would be the impact of smaller hospitals and smaller numbers of health care workers per hospital?

Is the ratio of 100:1000 for health care workers to patients per hospital realistic?

1 in 10 carriage episodes results in an infection – justification This is the same in hospital and community. However you might expect that immune compromised individuals in hospital who carry a strain might be more likely to develop an infection.

References


Is the work clearly and accurately presented and does it cite the current literature?

Yes
Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Nov 2017

Esther van Kleef, Mahidol Oxford Tropical Medicine Research Unit, Thailand

This paper presents a very interesting transmission dynamic model of resistant and susceptible pathogens in both healthcare and community settings. It is constructed in such a way as to be able to explore potential reasons why antimicrobial resistant organisms have been declining recently while sensitive versions of the same organism have been increasing or, remaining constant. This elegant model has different rates of transmission depending on the setting and this is the aspect which leads to an explanation of the observed data on reducing rates of MRSA alongside increasing rates of MSSA.

I think that the key aspect of the model is that resistant strains are assumed to be better adapted to the hospital setting and so would be expected to generate more secondary cases in hospital than a non resistant strain. The opposite is assumed to happen in the community. When an intervention is targeted at reducing transmission in hospitals then this will interfere more with the transmission of resistant organisms in hospital and will have no impact on the transmission in the community. This crucial assumption is not really justified, nor does it need to be, as the model only seeks to provide a mechanism whereby the observed results can be explained.

The model equations are standard for this type of model. This model, like many others, relies on assigning values to a number of parameters. There are not justified other than to have an $R_0$ of 1.5 for resistant strains and 1.4 for susceptible strains. These are reasonable values and, as this model is an exercise to see if a model can explain the observed results, getting justified parameter estimates for one organism is not really required.

In some respects the model is similar to the some of the models in Lipsitch et al. 2009 though co existence of susceptible and resistant strains are not permitted in this model.
1. The authors do not claim that this is a model for a disease however I was a little surprising that the resistant strain is eliminated when hand hygiene compliance reaches 55% while coexistence was observed when compliance was 50%.

This is over the 5-year period modelled, as presented in Figure S1 and Figure S2. The lower the improvement in hand hygiene, the more gradual the decline in resistant bacteria. Running the model over a 10-year period shows that eventually elimination of the resistant strain will be reached under 50% hand hygiene compliance as well. However, we considered a 5-year time horizon sufficient to illustrate the underlying dynamics. We have added the following text to the result section:

“…increasing it further to 55% induced a more rapid decline in both the hospital and community reservoir and successfully eliminated the resistant strain within the five year time period simulated.”

Minor points:

2. The model assumes each hospital is associated with a community of 110,000 – this is OK for Scotland with 42 acute hospitals and a population of 5.2 million. The average size of each hospital is just under 300 beds. What would be the impact of smaller hospitals and smaller numbers of health care workers per hospital?

With smaller population sizes (and smaller hospitals), stochastic effects would become increasingly important and the relative magnitude of fluctuations in each hospital would increase (in proportion to the reciprocal of the square root of the population size). Such stochastic effects are not accounted for in our paper as the key intention was to shed light on how hospital interventions could lead to long-term trends in large populations. Stochastic models would lead to the same broad conclusions, but in any given simulation the trends might be obscured by stochastic fluctuations (particularly when populations are small). We have added the following sentence listed in bold to the discussion:

Our model also ignores a lot of host and pathogen heterogeneity, and we did not account for stochastic effects. In small populations of single hospitals, chance events are likely to play an important role in the transmission dynamics of pathogens. However, we can think of no plausible mechanism by which incorporation of more biological realism would in any way alter our primary conclusion. Though our framework allows for further complexity, the purpose here was to demonstrate that the divergent effects of infection control interventions on resistant and sensitive models could be explained even with a simple model.

3. Is the ratio of 100:1000 for health care workers to patients per hospital realistic?

The EU FP7 framework RN4cast study surveyed practicing nurses in nine European countries in 2012, and hence provided insight in acute Trust nursing staff ratios in these countries, including England[1,2]. For England, ~3000 nurses from 31 Trusts, 46 hospitals
participated in the study. Patient to nursing staff ratios were highly variable across the
sampled Trusts in England, with an overall average of per 1 one patient, 8.8 [Range: 5.5 –
11.5] registered nurses [2]. Moreover, levels of 1:8 were found during day time and 1:11
during night time on average[1]. Across all participating countries, the patient-to-nurse
ratio was 1:8.3 [2.4 – 17.9] [2]. We are aware that these figures include nurses only, while
not accounting for other healthcare workers. As nurses account for the largest fraction of
caring staff, we believe that our patient healthcare worker ratio of 1:10 is not unrealistic.
However, we wish to emphasise that lower patient-to-healthcare worker ratios would not
change our findings.

We have added the above listed references to Table 2.

4. 1 in 10 carriage episodes results in an infection – justification. This is the same in hospital and
community. However you might expect that immune compromised individuals in hospital who carry
a strain might be more likely to develop an infection.

Fundamentally, we have presented a model of carriage dynamics and the assumption is
that clinical infections increase in line with the number of carriers. The key results
presented do not depend on the proportion of colonized patients who develop an
infection. For example, in figure 3, incidence refers to the "incidence of new acquisitions
(symptomatic and asymptomatic) " and figure 4 also refers to changes in incidence of
acquisitions of both symptomatic and asymptomatic infection (apologies if this was not
clear). The exception is figure 2 where we are attempting to simulate something like the
incidence data we observe (i.e. samples submitted to the Oxford University Hospitals NHS
Trust that tested positive for C. difficile. This hospital does all the C. difficile testing in
Oxfordshire, including samples submitted by GPs, community hospitals and other
providers[3]), though in this case we report only changes in these incidence rates
associated with an intervention (i.e. incidence rate ratios) rather than absolute numbers to
aid comparison with reference 4. The net result is the expected values of these IRRs will
be insensitive to the risk of clinical infection given carriage in hospital and community,
but the absolute numbers (and therefore degree of dispersion) will be sensitive to this. We
agree that difference in case mix between hospitalised individuals and individuals
residing in the community might lead to a difference in likelihood of developing infection.
In addition, hospital-acquired C. difficile cases are probably more likely to be reported
than community-acquired cases. Indeed, this may explain why the simulations are giving
wider dispersion for the IRR for hospital linked cases than observed data but somewhat
narrower dispersion for the community linked cases (for which we may be overestimating
the proportion seen in hospital). To address this issue we allowed for different constants
of proportionality for hospital and community-linked infections, and, by default, assumed
that hospital-acquired cases were 5 times more likely to be reported as
community-acquired cases. Figure 2 has been updated accordingly.

In addition, the method section now reads:

“We assumed the number of new infections reported with a hospital link or a community was
proportional to the cumulative number of acquisitions in the hospital or community in each of the
two time periods”
In explaining our calculated observed infections we now say:

“…and assuming 1 in 10 carriage episodes acquired in hospital resulted in a reported infection. This was 1 in 50 for community-acquired episodes. Hence we allowed for differences in reporting rates in both settings as well as heterogeneity in case-mix affecting the likelihood of developing an infection.”

Moreover, we have changed the caption of Figure 4 in line with figure 3, the caption now reads:

“Annual incidence rate ratios of new acquisitions (symptomatic and asymptomatic) associated with an infection control intervention under different levels of adaptation of sensitive and resistant strains to hospital and community settings”

References:


**Competing Interests:** We declare no competing interest
resistant and sensitive strains, even if they do not target specifically one or the other.

This is a very clear and well written article and I really enjoyed reading it. The question addressed is of high importance in a context where antimicrobial resistance keeps increasing and limited number of drugs and interventions are available to control it. Understanding better the respective impact of control measures is therefore essential to optimize their implementations and also interpret the observed trends. However, to make the presented results more convincing and interpretable, some clarification about the model is needed, in addition to sensitivity analysis on the model parameters.

Main comments

1. Modelling health care workers (HCW) colonisation. An originality of the model is that it specifically formalizes the patient-HCW transmission. Here, HCWs are classified either as non-hand-carriers or as hand-carriers. In the model, hand hygiene is therefore assumed to directly impact to directly clear HCW carriage in compliant individuals (eg at a proportion of 50%). Several epidemiological studies have shown that, in the case of S. aureus at least, proper (nasal) colonization is frequent in HCW. I would expect that, for those HCW properly carrying the bacteria, efficient hand hygiene may impede transmission to others by clearing hand carriage, but would not clear colonisation. They would not need to be recolonized through contact with patients to become again S or R carriers the next day. On the contrary, for purely transient hand carriers HCWs, I would expect that hand hygiene completely removes the bacteria from the hand and entire body. In that case, new acquisition from patient would be necessary for them to become carrier again. Can the authors comment on that point? In particular, how is HCW’s duration of carriage handled in the model?

2. Parameters table. The table needs some clarifications and references. (1) I did not understand the values of the following rates: tau, gammaR, and gammaS: is the rate or the duration depicted in the last column? It looks more like the reciprocal duration, despite the unit is given in day⁻¹. (2) I think a % is lacking in the last raw of the table. (3) Can you please explain the calculation of f23, this is not clear to me. (4) If I understand well, carriage is assumed to last for 400 days. This is quite long and may have consequences on the resulting trends obtained in the simulations. Can the authors provide a justification for this value and carry out some sensitivity analysis on this parameter? (5) Can you provide some justification about the values of p set to 10?

3. Bacterial interference. This is not clear whether the authors finally assumed some competition for colonisation between the strains or not. On the schematic representation of the model, no “superinfection” is assumed, but this mechanism is described in the Methods section. If w=0 as indicated in Table2, then full competition is assumed between the strains. This hypothesis is strong and may have some influence on the resulting trends. My intuition is that this strong assumption may provide more chance to S strains to spread in hospitals when R strains are removed by intervention. Could the authors carry out some sensitivity analysis on the impact of that parameter?

4. Transmission rate. Could you provide more details about beta calculation for the different strains in the different settings according to R0? Also, in the section “Importance of the degree of strain adaptation…”, “when increasing the transmission that occurs in hospital”, could you provide the corresponding values for beta?

Similarly, when investigating the importance of environmental adaptation, how did you process to vary “the level of transmission in both settings for each of the two strains, while keeping the overall basic reproduction number for R and S strains constant…”?
5. Model equations. Frequency dependent hypothesis is assumed in the ward which looks realistic. However, in some equations, this rule does not apply; it would require some explanation. In equations describing the hcwS and hcwR derivatives, the denominator of the transmission term is for example Nhcw.

6. Community transmission. The expressions of the force of infections for patients are not totally clear to me either. In particular, I don’t understand the term beta_R3xR3xf23/N2. Given the definition of f23, this expression is actually equivalent to beta_R3xR3/N3, which makes more sense to me. In general, it would be good if more details were provided to explain the model community transmission. It was not clear to me what the authors meant by “the model allowed for the possibility of assortative mixing within population 2 and 3”. Could you provide a mixing matrix to make clear the transmission between the 3 (or 4) populations? Similarly, expressions of lambda_R3, lambda_S1, lambda_S2 and lambda_S3 would need some more explanation. Why is it divided respectively by N3, N2 and N3?

7. Annual incidence rate ratio. Could you provide an equation for the calculation of IRR as a function of the measured outputs from the results?

8. Interpretation of results about the dynamic after hospital infection control. To make the interpretation of Figure 3 more convincing, it would be important to disentangle what processes come from the community- to-community transmission, the hospital- to-community (ie community importations) transmission, the hospital- to-hospital transmission and the community-to-hospital (ie hospital importations) transmission. Could the authors present, in addition to Figure 3, the incident cases coming from these different processes?

9. The modelled hospital population is 1000 patients and 100 HCWs. The proposed model is deterministic. How would stochasticity impact the results?

Minor comments

1. Does R0 define the number of secondary cases of infection or colonisation? As transmission occurs through colonization my choice would go for that one but in the main text and Table 2 legend, the authors mention “infection”. In addition, as R0 is actually defined in a setting with already 40% hand hygiene at baseline, this is actually not the strict basic reproductive number of the bacteria. I therefore suggest naming it reproductive number (R) which seems more correct to me.

2. Table 1. hCWR and hCWS notations do not match with notations in the model depicted in fig1. Could the authors check they use the same notations?

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes
If applicable, is the statistical analysis and its interpretation appropriate?  
Partly

Are all the source data underlying the results available to ensure full reproducibility?  
Yes

Are the conclusions drawn adequately supported by the results?  
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Mathematical modelling, bacterial resistance, pathogens interactions

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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**Author Response 12 Nov 2017**

**Esther van Kleef,** Mahidol Oxford Tropical Medicine Research Unit, Thailand

This article aims at investigating the impact of implementing unspecific control measures, such as hand hygiene, on the spread of antibiotic resistant and antibiotic sensitive bacteria in hospitals, using mathematical modelling. In this theoretical study, a new deterministic model based on ODEs is numerically simulated under different hand hygiene scenarios. For each scenario, the resulting annual incidence ratio is calculated for hospital- and community-acquired infections with resistant and sensitive bacteria. The simulation results suggest that, counter-intuitively but in accordance to the observations from recent years, infection control interventions such as hand hygiene can have discordant effects on resistant and sensitive strains, even if they do not target specifically one or the other.

This is a very clear and well written article and I really enjoyed reading it. The question addressed is of high importance in a context where antimicrobial resistance keeps increasing and limited number of drugs and interventions are available to control it. Understanding better the respective impact of control measures is therefore essential to optimize their implementations and also interpret the observed trends. However, to make the presented results more convincing and interpretable, some clarification about the model is needed, in addition to sensitivity analysis on the model parameters.

**Main comments**

1. Modelling health care workers (HCW) colonisation. An originality of the model is that it specifically formalizes the patient-HCW transmission. Here, HCWs are classified either as non-hand-carriers or as hand-carriers. In the model, hand hygiene is therefore assumed to directly impact to directly clear HCW carriage in compliant individuals (eg at a proportion of 50%). Several epidemiological studies have shown that, in the case of S. aureus at least, proper (nasal) colonization is frequent in HCW. I would expect that, for those HCW properly carrying the bacteria, efficient hand hygiene may impede transmission to others by clearing hand carriage, but would not clear colonisation. They would not need to be recolonized through contact with patients to become again S or R carriers the next day. On the contrary, for purely transient hand carriers HCWs, I would expect that hand hygiene completely
removes the bacteria from the hand and entire body. In that case, new acquisition from patient would be necessary for them to become carrier again. Can the authors comment on that point? In particular, how is HCW's duration of carriage handled in the model?

We recognise that both types of carriage have been found among healthcare workers, at least in the case of MRSA. A review of the literature [4] revealed a wide array of studies with some finding persistent carriage to be more common, whereas other studies concluded transient carriage is the most frequent type of carriage among healthcare workers. The findings of these studies are likely to be setting dependent and, as concluded by Albrich and Harbarth [4], sensitive to misclassification bias (e.g. incorrectly defining transient carriage as persistent carriage), and are, in any case, not informative about the significance of longer-term staff carriage for hospital transmission dynamics. In this model, we assumed that persistent carriage by healthcare workers does not play a significant role in hospital transmission and can be neglected. Clearly, as with other model assumptions, this is a simplification, and we acknowledge that there are case reports of outbreaks with a plausible link to long-term staff carriers. However, our assumption is supported by a prospective carriage study of MRSA in adult and paediatric ICUs using whole genome sequencing to determine possible transmission pathways [5]. This study showed frequent patient acquisition events of MRSA with closely related strains shared between overlapping patients, strongly suggesting patient-to-patient transmission. In contrast, while MRSA was recovered from nasal swabs from four healthcare workers, there was only a single patient MRSA acquisition that could have been plausibly related to known staff carriage (based on the whole genome sequencing data). Since patients were not mobile, patient-to-patient transmission events are likely to represent either hand-borne or air-borne transmission. Studies from the 1960s suggest that the latter plays a relatively minor role in S. aureus transmission in hospital settings (see, for example, [6,7]). Since the purpose of our model is to illustrate the potential differential effects of infection control measures on sensitive and resistant strains (and not to make strong claims for potential impact of different control measures), for simplicity we chose to focus on what appears to be the dominant mode of transmission (at least for S. aureus, other organisms are less well studied) rather than adding non-essential complexity by accounting for other transmission pathways. Therefore, following hand hygiene, healthcare worker carriage is cleared and new contact with contaminated patients is required for healthcare workers to become carriers again. Persistent colonization such as the nasal colonization the reviewer is referring to is not included in this model. Hence no explicit colonization time for healthcare workers is assumed. We have now added the following sentence to our methods:

"Persistent carriage of bacteria such as MRSA has been reported among healthcare workers, though is commonly found to be transient". Followed by the text already present: “Therefore, healthcare workers in turn were assumed to become transiently contaminated through patient contact. Hand hygiene performed by a contaminated healthcare worker was assumed to clear this contamination”

In addition, we have added the following text to our discussion:
Moreover, for simplicity we chose to focus on what appears to be the dominant mode of transmission (at least for S. aureus, other organisms are less well studied). Since hospitalised patients are generally not mobile, patient-to-patient transmission events represent either hand-borne or air-borne transmission. Studies from the 1960s suggest that the latter plays a relatively minor role in S. aureus transmission in hospital settings [24,25].”

2. Parameters table. The table needs some clarifications and references. (1) I did not understand the values of the following rates: tau, gammaR, and gammaS: is the rate or the duration depicted in the last column? It looks more like the reciprocal duration, despite the unit is given in day-1. (2) I think a % is lacking in the last raw of the table. (3) Can you please explain the calculation of f23, this is not clear to me. (4) If I understand well, carriage is assumed to last for 400 days. This is quite long and may have consequences on the resulting trends obtained in the simulations. Can the authors provide a justification for this value and carry out some sensitivity analysis on this parameter? (5) Can you provide some justification about the values of p set to 10

1. We thank the author for spotting this error, the last column should indeed depict the rates for tau, gammaR and gammaS. We have now changed the values to reflect the reciprocal duration.

2. The % sign is now added to the last row of table 2

3. See comment 6

4. We believe 400 days of carriage is a plausible value to represent the dynamics of MRSA. For example, Scanvic et al, CID 2001 found a median duration of carriage of 8.5 months among patients readmitted to hospital, following an exponential distribution[8]. This would result in an average duration of: \( y_{\text{in}} = (8.5/12)*365*1/\log(2) = 373 \) days.

For other major pathogens this is less well known, but, in the case of for example C. difficile, likely to be shorter. Our key results however, are not affected by this; in Van Kleef et al LID 2017[9] we show an example where we assumed a shorter duration of carriage (200 days) and were able to produce similar findings and conclusions. We feel that presenting additional sensitivity analysis here would make the paper harder to read and potentially obscure the key message.

However, we have added a reference to our analysis using different parameter values, including a shorter duration of carriage [9] to the discussion:

“For example, assumptions about carriage duration, mixing of community populations, and the degree of bacterial interference between the two strains can easily be altered (and will not change our main conclusions, as shown in respectively [20], Figure S3, Figure S4)” Furthermore, we added the reference of Scanvic et al to table 2.
5. The rational behind the different transmission probabilities of patients and healthcare workers relates to our assumption explained under comment 1. We assume that healthcare workers were transiently hand-carriers of bacterial pathogens, whereas patients were fully colonised. For patients, this could be e.g. on the skin, wounds or nasal carriage. We translated these different degrees of carriage in different risks of transmission. We fully agree with the reviewer that a justified value for $p$ based on scientific evidence would be important if we were interested in quantifying effects of hand hygiene interventions specifically. However, we are just using hand hygiene as a specific example of an intervention that interrupts transmission in the hospital but not the community for resistant and sensitive strains equally. To make the latter clearer, we have added the following in bold to our introduction:

“We explicitly model a hospital hand hygiene intervention as an example of a non-specific infection control measure and evaluate the impact of this intervention on the incidence of hospital and community acquisitions of antibiotic-resistant and antibiotic-sensitive strains.”

3. Bacterial interference. This is not clear whether the authors finally assumed some competition for colonisation between the strains or not. On the schematic representation of the model, no “superinfection” is assumed, but this mechanism is described in the Methods section. If $w=0$ as indicated in Table 2, then full competition is assumed between the strains. This hypothesis is strong and may have some influence on the resulting trends. My intuition is that this strong assumption may provide more chance to S strains to spread in hospitals when R strains are removed by intervention. Could the authors carry out some sensitivity analysis on the impact of that parameter?

We apologies that we did not make our assumptions regarding bacterial inference clear in our manuscript. We do assume competition for colonization between strains. This is specified by the parameters $w_s$ and $w_r$ (see table 2) which by default were set to 0 (implying carriage of one strain completely blocks acquisition of another i.e. complete bacterial interference). In response to this comment we have now conducted an additional sensitivity analysis where we assume $w_s, w_r = 0.25, 0.5, 0.75$ and 1 respectively. The results are presented in Figure S3.

We find that at lower levels of bacterial interference (i.e. higher $\omega_s$ and $\omega_r$), the incidence of the resistant strain in both the hospital and the community is higher compared to baseline, whereas the incidence of the sensitive strain is lower in both settings (Figure S3). This relates to the higher $R_n$ of the resistant strain, giving it a competitive advantage over the sensitive strain, which is further enhanced when replacement infection is allowed for. At $w_s, w_r = 1$, this means the sensitive strain does not coexist with the resistant at baseline hand hygiene levels of 40%. However, after implementation of the hand hygiene intervention, the sensitive strain will emerge even under these conditions. Thus, what is shown is that regardless of the level of bacterial interference, the overall conclusions remain unchanged: hospital infection control can have discordant effects on resistant and sensitive bacteria provided heterogeneity is present in their respective environmental
adaptations.

Just to clarify, while we do consider competition we do not consider superinfection (i.e. co-infection with both sensitive and resistant strains[10]) and we state this in the methods section “Individuals could not be co-infected with resistant and sensitive strains”. Including this would greatly add to the complexity of the model, reduce readability and, we feel, obscure the key messages.

We have added the following text in bold to the discussion section:

“For example, assumptions about carriage duration and the degree of bacterial interference between the two strains can easily be altered (and will not change our main conclusions, Lancet ID paper, Figure S3, Figure S4)”

Moreover, we have added the term ‘replacement infection’ to our methods, which now reads:

“we allowed for bacterial interference between the two strains so that colonization with one strain reduced the risk of acquisition of the other strain, i.e. replacement infection”.

4. Transmission rate. Could you provide more details about beta calculation for the different strains in the different settings according to R0? Also, in the section “Importance of the degree of strain adaptation…”, “when increasing the transmission that occurs in hospital”, could you provide the corresponding values for beta? Similarly, when investigating the importance of environmental adaptation, how did you process to vary “the level of transmission in both settings for each of the two strains, while keeping the overall basic reproduction number for R and S strains constant…”?

We varied the values of beta_R_n (where n = population 1, population 2, population 3) to give values of R0 = 1.5 an beta_R_s to give values of R0 = 1.4 keeping all other parameter values constant and ran the model at equilibrium. If at model equilibrium, the strain adaptation to each of the respective environments was at the desirable level, these values were chosen for model parameterisation. Here, the degree of strain adaptation was defined as the fraction of new acquisitions of strain i occurring in setting n (hospital or community) respectively on each day t.

The corresponding values for all beta_i_n used to produce figure 4 are available at https://github.com/esthervankleef/Two_strain_model_published. We have added the following text in bold to the method section:

“Increasing adaptation of the resistant strain to the hospital environment (i.e. increasing the proportion of resistant transmission that occurs in hospital by changing the values of the transmission parameters (beta_i_n) while keeping the basic reproduction number and all other parameters constant),

Also, we added the following text to the legend of Figure 4.

“For corresponding transmission parameter values see
Model equations. Frequency dependent hypothesis is assumed in the ward which looks realistic. However, in some equations, this rule does not apply; it would require some explanation. In equations describing the hcwS and hcwR derivatives, the denominator of the transmission term is for example Nhcw.

The reason why the denominator for hcwS and hcwR derivatives is Nhcw follows from the structure of our model, which assumes healthcare workers are the pathogen vectors. Similar to Cooper et al (1999)[11] we assume that in hospital, all transmission events between patients is caused by a contact from a transiently colonized HCW. Similarly, HCW acquire transient hand-contamination only by touching colonized patients.

In our model, beta_R1 = the probability that an uncolonized patient becomes colonized on contact with a colonized healthcare worker, whereas p*beta_R1 = the probability that an uncolonized healthcare worker becomes colonized with a resistant strain on contact with a colonized patient (where rho = ratio of probability of patient-to-HCW transmission vs HCW-to-patient transmission).

Hence, the rates at which contacts are made which can potentially result in colonization with a resistant strain is beta_R1*U1 for patients (i.e. a function of beta_R1 and the number of uncolonized patients U1), and p*beta_R1*R1 for healthcare workers (i.e. a function of p, beta_R1 and the number of colonized patients R1). Only a fraction of these contacts will result in transmission. For patients this is the fraction of contacts which are with colonized healthcare workers (hcw-R/Nhcw). For healthcare workers, it is those contacts in which the healthcare worker is uncolonized that will result in transmission (Nhcw – hcw – hcw/R)/Nhcw).

As a result, the rate of colonization for patients and healthcare workers is beta_R1*U1*hcw_R/Nhcw and p*beta_R1*R1(Nhcw – hcw_R – hcw_S)/Nhcw respectively.

In the community we do assume direct transmission between individuals, hence here the population size of the susceptible hosts is used as a denominator while following the assumption of frequency dependent transmission of Otto and Day[12], further explained under comment 6.

Of note: the parameter p was left out of equations 10 and 11, and has now been added.
This is a good point. We recognize that our baseline assumptions regarding the mixing of our population need further clarification. In our description of the force of infection, we followed the definition of Otto and Day, who decompose the frequency dependent incidence rate, i.e. the rate at which new infections occur, in three components [12]:

The rate of contact with other individuals in the population ($c$) which are of an appropriate type for transmission to be possible if one of the hosts is infectious

The probability that the contact is indeed with a susceptible host $U$ ($p$, assumed to be $U(t)/N(t)$)

The probability that a contact between an infectious and susceptible host leads to successful transmission ($v$)

In the case of frequency dependent transmission, $c$ is assumed constant, hence the effective contact rate or transmission coefficient $\beta = cv$. Assuming frequency dependent transmission, and the definition of Otto and Day, the mixing matrix for the community population should be as follows, where the beta terms are equivalent to the effective contact rates, and e.g. $f_{23}/\beta_{R3}$ reflects that the effective contact rate between individuals of population 2 and population 3 is a fraction of the effective contact rate between individuals in population 3.

Equation 1

Multiplying these by the number of infected individuals in each population and the probability $p_j$ that the contact is indeed with a susceptible host ($U_{Ri}/N_i$) would result in the following incidence rates:

Equation 2

As our lambdas represent the force of infections, i.e. the rate at which a susceptible individual becomes infected, we replaced $p_j$ of the incidence rates with the probability that the contact is with one specific susceptible host, i.e. and , resulting in:

Equation 3

The same logic applies to $\lambda_{S2}$ and $\lambda_{S3}$.

We realise our description of the $f_{23}$ and $f_{32}$ in table 2 was not entirely correct and would be better described as given below. Moreover, the reference of our frequency dependent transmission has been added to the method section, which now reads:
“We assumed frequency-dependent transmission [10]. The model allowed for the possibility of assortative mixing within populations 2 and 3, where the effective contact rate of strain i (\(\beta_{in}\)) between individuals within a population is a fraction of the effective contact rate between individuals across populations: “

Equation 4

We have changed the description of \(f_{23}\) and \(f_{32}\) in Table 2 to:

\[f_{23} = \text{The ratio of the effective contact rate in N2 from someone in N3 to the effective contact rate in N3 from someone in N3 (where 1 implies that on contact, someone in N3 is causing new infections in N3 and N2 at the same rate. Of note, as N3 > N2, }f_{23} = N2/N3\text{ assumes the same per capita infection rate, i.e. homogenous mixing.}\]

\[f_{32} = \text{The ratio of the effective contact rate in N3 from someone in N2 to the successful contact rate in N2 from someone in N2 (where 1 implies that on contact, someone in N2 is causing new infections in N2 and N3 at the same rate. Of note, as N3 > N2, }f_{32} = N3/N2\text{ assumes the same per capita infection rate, i.e. homogenous mixing.}\]

With regards to our assortative mixing assumption, as described in the above definitions, by defining \(f_{23} = N2/N3\) and \(f_{32} = 1\), we assume that individuals in N3 are equally likely to infect an individual in N2 as they are to infect a given individual in N3, whereas setting \(f_{32}\) to 1 implies a higher per capita rate of infection in N2, given \(N2 < N3\), thus individuals in N2 are more likely to infect an individual in N2 than an individual in N3. Baseline values of these parameters were chosen to reflect perceived heterogeneities in contacts (e.g. assuming a scenario of LTCFs (N2) vs the general population (N3) where those in N2 will be exposed preferentially to those in N2, but, considering some in N3 will be carers to N2, N3 will mix equally with N2 and N3. These assumptions are not critical to our results, as shown by a sensitivity analysis, where we modelled the following additional scenarios:

- Fully homogenous mixing (\(f_{23} = N2/N3, f_{32} = N3/N2\))
- Fully assortative mixing (\(f_{23} = f_{32} = 0\))

The results of this analysis are presented in Figure S4. We have added the following text to the discussion section:

“For example, assumptions about carriage duration and the degree of bacterial interference between the two strains can easily be altered (and will not change our main conclusions, Lancet ID paper, Figure S3, Figure S4)”

7. Annual incidence rate ratio. Could you provide an equation for the calculation of IRR as a function of the measured outputs from the results?

The annual incidence ratio represents the ratio of the number of new infection in the year pre-intervention (\(T_0\)) to the number of new cases in the first year post-intervention (\(T-1\)). As mentioned in the method section, \(Y_{in}\) represents the
actual number of observed infections of strain i in population n, which is proportional to the cumulative number of acquisitions in each population in these two time periods.

We have now changed the methods section 'measuring the impact of hospital infection control' to the following:

“Annual incidence rate ratios (IRR) were calculated using simulated data for one year pre- and post-intervention (T\textsubscript{0} and T\textsubscript{1} respectively) after first running the model to equilibrium. To aid comparison with reported infection data, we assumed the number of new infections (Y\textsubscript{in}) with and without a hospital link was proportional to the cumulative number of acquisitions (I\textsubscript{in}) in the hospital and community, respectively, in each of the two time periods:

Equation 5

Confidence intervals were calculated using 1000 Monte Carlo replicates on the assumption that the actual number of observed infections of each strain (Y\textsubscript{in}) followed a negative binomial distribution where Var(Y\textsubscript{in}) = μ + μ\textsuperscript{2}/k, with k (the dispersion parameter) = μ/( - 1), with = 5, and assuming 1 in 10 carriage episodes acquired in hospital resulted in a reported infection. This was 1 in 50 for community-acquired episodes. Hence we allowed for differences in reporting rates in both settings as well as heterogeneity in case-mix affecting the likelihood of developing an infection. Then the IRR\textsubscript{in} corresponded to the ratio of the number of new observed infections of strain i in population n in the year pre-intervention to the number in the first year post-intervention:”

Equation 6

8. Interpretation of results about the dynamic after hospital infection control. To make the interpretation of Figure 3 more convincing, it would be important to disentangle what processes come from the community- to-community transmission, the hospital- to-community (ie community importations) transmission, the hospital- to-hospital transmission and the community-to-hospital (ie hospital importations) transmission. Could the authors present, in addition to Figure3, the incident cases coming from these different processes?

We fully agree that it is helpful to show where the transmission events are actually occurring and this is what we are depicting in the top row of figure 3 - i.e. community-to-community transmission (dashed line) and hospital-to-hospital transmission (dotted line). The model assumes that community-to-hospital and hospital-to-community transmission events do not occur (we do not depict importation events of colonized patients to the hospital as these simply scale with community prevalence and would provide no new information). We apologies that the caption to figure 3 did not make this clear and we have now revised it:

“Trends in the incidence of new acquisitions (symptomatic and asymptomatic) and carriage prevalence for resistant and sensitive bacterial strains following a 10% stepwise
improvement in hand hygiene compliance after one year from a baseline of 40%. Incidence trends are depicted as transmission events following from community-to-community transmission (dashed line) and hospital-to-hospital transmission (dotted line). As prevalence in the hospital represents only a small fraction of the overall prevalence (in hospital and community populations combined), the latter is almost identical to the community prevalence for both the resistant and sensitive bacterial strains."

9. The modelled hospital population is 1000 patients and 100 HCWs. The proposed model is deterministic. How would stochasticity impact the results?

See the response to comment 1 reviewer #1

Minor comments

1. Does R0 define the number of secondary cases of infection or colonisation? As transmission occurs through colonization my choice would go for that one but in the main text and Table 2 legend, the authors mention "infection". In addition, as R0 is actually defined in a setting with already 40% hand hygiene at baseline, this is actually not the strict basic reproductive number of the bacteria. I therefore suggest naming it reproductive number (R) which seems more correct to me.

In our model and the manuscript through out, R0 is considered the expected number of secondary cases in the hospital and community resulting from one colonised individual in a fully uncolonized and susceptible population at baseline hand hygiene rates of 40%, accounting for the possibility of readmissions while still colonized. The text in Table 2 has now been altered to reflect colonisation instead of infection. Moreover, we have altered R0 has now been changed to R_n (the net reproduction number) across the manuscript.

2. Table1. hCWR and hCWS notations do not match with notations in the model depicted in fig1. Could the authors check they use the same notations?

Many thanks for this sharp observation. We have now updated figure 1, which now matches our notation in Table 1.

References


Competing Interests: We declare no competing interest

Comments on this article

Version 1

Reader Comment 16 May 2017

David Eyre, University of Oxford, UK

This article comments directly on the findings of reference 4, “Effects of control interventions on Clostridium difficile infection in England: an observational study” (available at http://dx.doi.org/10.1016/S1473-3099(16)30514-X). As the authors of reference 4, we have responded to the content of this article and an associated letter to The Lancet Infectious Diseases (http://dx.doi.org/10.1016/S1473-3099(17)30186-X). Our response published by The Lancet Infectious Diseases can be found at http://dx.doi.org/10.1016/S1473-3099(17)30185-8.

Competing Interests: I have no competing interests to declare.

Reader Comment 25 Mar 2017

Tim Lawes,

Dear Authors,

I read your article with interest. The outcomes of your modelling study are congruent with our empirical observations of the relative effects of changing antibiotic use and infection prevention and control measures on MRSA molecular epidemiology in an area of NE Scotland [Lawes et al Turning the tide or riding the waves? Impacts of antibiotic stewardship and infection control on MRSA strain dynamics in a...

From multivariable non-linear time-series models applied to a large hospital population we established that (i) reductions in bed-occupancy (ii) shorter average length-of-stay, and (iii) hand-hygiene contributed to declines in hospital-epidemic strains (in particular CC22, CC30) but not in CC5/Other strains which appeared to spread from community to the hospital and show much less multi-drug resistance. In addition, we found that levels of MRSA admission screening and importation pressure above which changes in hospital prevalence density were seen (thresholds) were much higher for CC5/Other strains than CC22 and CC30. This may have important implications for admission screening policies which are now targeted (based upon risk-factors such as prior hospitalisation) since they may miss MRSA colonisation by community strains in patients without typical risk-factors.

Overall we concluded that even those infection control measures expected to have general effects can have strain-specific impacts due to differences in the temporal and spatial distribution of clonal complexes. Moreover it is likely that our interventions shape molecular epidemiology in populations. An important implication for policy is that need to proceed with caution when translating results from interventions in one region or time-period - infection prevention and control colleagues will need to continually adjust to changing epidemiology if the successes in control of MRSA and C.difficile are to continue

Yours sincerely,
Dr. Tim Lawes
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*Competing Interests:* I have no competing interests to declare.