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. This follows from 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 in reducing resistant strains.
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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 Clean-Your-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 preexisting trends\(^2\),\(^3\). A remarkably similar pattern has recently been reported for *Clostridium difficile* infection (CDI) in England\(^4\). 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\(^3\),\(^4\). 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\(^5\). 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 asymptptomatically over long periods, we account for movements of colonized individuals between the hospital and community\(^6\). We explicitly model a hospital hand hygiene intervention 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).

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**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).
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\textsuperscript{6,7}. 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\textsuperscript{8}. Individuals were assumed 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). The model allowed for the possibility of assortative mixing within populations 2 and 3. 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\textsuperscript{9}.

Model equations are given below. Variables are defined in Table 1 and parameter definitions and values in Table 2.

<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 colonized with the resistant (hospital-adapted) strain who have a short expected time to hospital admission</td>
</tr>
<tr>
<td>$R_3$</td>
<td>Resistant population 3: number of individuals in community setting colonized with the resistant (hospital-adapted) strain who have a long expected time to hospital admission</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 patients in hospital setting colonized with the sensitive (community-adapted) strain who have a short expected time to hospital admission</td>
</tr>
<tr>
<td>$S_3$</td>
<td>Sensitive population 3: number of patients in hospital setting colonized with the sensitive (community-adapted) strain who have a long expected time to hospital admission</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 $R_0$ a value of 1.5 for the resistant strain and a value of 1.4 for the sensitive strain. Here, $R_0$ 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, with a baseline hand hygiene rate of 40% and accounting for the possibility of readmissions while still colonized.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_1$</td>
<td>Number of hospitalised patients</td>
<td>1000</td>
</tr>
<tr>
<td>$N_{hcw}$</td>
<td>Number of healthcare workers (HCW)</td>
<td>100</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>
</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>
</tr>
<tr>
<td>$\tau$</td>
<td>Hospital patient removal rate (reciprocal of mean hospital stay)</td>
<td>$10d^{-1}$</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</td>
<td>$hN_2/N_1$</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>
</tr>
<tr>
<td>$h$</td>
<td>Admission rate to hospital of people in the general population</td>
<td>See methods</td>
</tr>
<tr>
<td>$r$</td>
<td>Admission rate to hospital of recently discharged people</td>
<td>See methods</td>
</tr>
<tr>
<td>$c$</td>
<td>Mean number of HCW contacts per patient day</td>
<td>10</td>
</tr>
<tr>
<td>$\gamma_{R_1}, \gamma_{R_2}, \gamma_{R_3}$</td>
<td>Carriage clearance rate of the resistant (hospital-adapted) strain in the hospital/community (reciprocal of mean carriage duration)</td>
<td>400$d^{-1}$</td>
</tr>
<tr>
<td>$\gamma_{S_1}, \gamma_{S_2}, \gamma_{S_3}$</td>
<td>As above for the sensitive (community-adapted) strain</td>
<td>$40d^{-1}, 400d^{-1}, 400d^{-1}$</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>
</tr>
<tr>
<td>$\beta_{S_1}$</td>
<td>As above for the sensitive strain*</td>
<td>$0.100 (0.040, 0.216)$</td>
</tr>
<tr>
<td>$\beta_{R_2}, \beta_{R_3}$</td>
<td>Transmission parameters for the resistant strain in the community populations*</td>
<td>$0.00212 (0.00013, 0.00335)$</td>
</tr>
<tr>
<td>$\beta_{S_2}, \beta_{S_3}$</td>
<td>As above for the sensitive strain*</td>
<td>$0.00320 (0.00236, 0.00330)$</td>
</tr>
<tr>
<td>$\lambda_{R_1}, \lambda_{R_2}, \lambda_{R_3}$</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>
</tr>
<tr>
<td>$\lambda_{S_1}, \lambda_{S_2}, \lambda_{S_3}$</td>
<td>As above for the sensitive strain</td>
<td>See methods</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Baseline hand hygiene compliance (probability of successful hand decontamination following patient contact)</td>
<td>40%</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Hand hygiene rate</td>
<td>See methods</td>
</tr>
<tr>
<td>$\omega_{R_1}$</td>
<td>Bacterial interference: risk ratio for acquiring the resistant strain if carrying the sensitive strain relative to a non-carrier</td>
<td>0</td>
</tr>
<tr>
<td>$\omega_{S_1}$</td>
<td>As above for the sensitive strain</td>
<td>0</td>
</tr>
<tr>
<td>$f_{\bar{1}}$</td>
<td>Fraction of $N_1$ individuals that mixes with $N_1$ (where 1 assumes homogeneous mixing)</td>
<td>$N_1/N_1$</td>
</tr>
<tr>
<td>$f_{\bar{2}}$</td>
<td>Fraction of $N_1$ individuals that mixes with $N_1$ (where 1 assumes homogeneous mixing)</td>
<td>1</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%</td>
</tr>
<tr>
<td>-</td>
<td>As above for the community-adapted strain</td>
<td>2.5</td>
</tr>
</tbody>
</table>
Equations

\[
\frac{dU}{dt} = rU - hU - \lambda_1 U_1 - \lambda_2 U_2 + \gamma_1 R_1 + \gamma_2 S_1 \tag{1}
\]

\[
\frac{dU}{dt} = -rU_2 - vU_2 + \lambda_1 U_1 - \lambda_2 U_2 + \gamma_1 R_2 + \gamma_2 S_2 \tag{2}
\]

\[
\frac{dU}{dt} = -hU_1 + vU_1 - \lambda_1 U_1 - \lambda_2 U_2 + \gamma_1 R_1 + \gamma_2 S_2 \tag{3}
\]

\[
\frac{dR}{dt} = rR_2 + hR_2 - \lambda_1 R_1 - \lambda_2 R_2 + \omega_R \lambda_1 S_1 - \omega_R \lambda_2 S_2 \tag{4}
\]

\[
\frac{dR}{dt} = -rR_2 - vR_2 + \lambda_1 R_1 + \lambda_2 R_2 + \omega_R \lambda_1 S_1 - \omega_R \lambda_2 S_2 \tag{5}
\]

\[
\frac{dS}{dt} = rS_1 + \nu S_1 - \lambda_1 S_1 + \lambda_1 U_1 - \lambda_2 U_2 + \omega_\lambda \lambda_1 S_1 - \omega_\lambda \lambda_2 S_2 \tag{6}
\]

\[
\frac{dS}{dt} = -rS_1 - \nu S_1 + \lambda_1 S_1 + \lambda_2 S_2 + \omega_\lambda \lambda_1 R_1 - \omega_\lambda \lambda_2 S_2 \tag{7}
\]

\[
\frac{dS}{dt} = -hS_1 + vS_1 - \lambda_1 S_1 + \lambda_1 U_1 + \omega_\lambda \lambda_1 S_1 - \omega_\lambda \lambda_2 S_2 \tag{8}
\]

\[
\frac{dS}{dt} = -hS_1 + vS_1 - \lambda_1 S_2 - \lambda_2 U_2 + \omega_\lambda \lambda_1 S_2 - \omega_\lambda \lambda_2 S_2 \tag{9}
\]

\[
\frac{dhcw_k}{dt} = \beta_{S_1} (N_{hcw} - hcw) \frac{N_{hcw}}{N_2} - \eta hcw \tag{10}
\]

\[
\frac{dhcw_s}{dt} = \beta_{S_1} (N_{hcw} - hcw) \frac{N_{hcw}}{N_2} - \eta hcw \tag{11}
\]

\[
\lambda_1 = \beta_1 hcw_k / N_{hcw}
\]

\[
\lambda_2 = \beta_2 R_1 / N_2 + \beta_2 R_1 f_2 / N_2
\]

\[
\lambda_3 = \beta_3 U_1 / N_2 + \beta_3 R_1 f_3 / N_3
\]

\[
\lambda_4 = \beta_4 S_1 / N_2 + \beta_4 f_4 / N_3
\]

\[
\lambda_5 = \beta_5 S_2 / N_2 + \beta_5 S_2 f_5 / N_2
\]

\[
\lambda_6 = \beta_6 S_3 / N_2 + \beta_6 S_3 f_6 / N_2
\]

\[
\eta = HcN_1 / (N_{hcw}(1 - H))
\]

\[
N_1 = U_1 + R_1 + S_1
\]

\[
N_2 = U_2 + R_2 + S_2
\]

\[
N_3 = U_3 + R_3 + S_3
\]

The basic reproduction numbers for both resistant and sensitive pathogens (1.5 and 1.4, respectively) were calculated as the dominant eigenvalues of the next generation matrix \( \mathcal{R} \). Here, \( \mathcal{R} \) 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\(^1\). Model code is available online at https://zenodo.org/record/345136#.WLmdTVWTcv2.

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 healthcare 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 after first running the model to equilibrium. These correspond to the ratio of the number of new infections in the year pre-intervention to the number in the first year post-intervention. To aid comparison with reported infection data\(^1\), we assumed the number of new infections with and without a hospital link was proportional to the cumulative number of acquisitions in the hospital and community, respectively, in each of the two time periods. Confidence intervals were calculated using 1000 Monte Carlo replicates on the assumption that the actual number of observed infections of each strain \( (Y) \) followed a negative binomial distribution with \( \text{Var}(Y) = \mu + \mu^2/\kappa \); with \( \kappa \) (the dispersion parameter) = \( \mu(\theta - 1) \) where \( \theta = 5 \), and assuming 1 in 10 carriage episodes resulted in an infection.

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 basic 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 increases in
sensitive infections linked to community acquisitions ($\text{IRR} = 1.10 \ [1.03–1.17]$, 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$^4$ (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.

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*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).
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%. 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 material). 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 (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 while keeping the basic reproduction number 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 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.
Figure 4. Annual incidence rate ratios associated with an infection control intervention under different levels of adaptation of sensitive and resistant strains to hospital and community settings. In all simulations, basic reproduction number for resistant and sensitive strains were held constant at 1.5 and 1.4, respectively. White spaces represent scenarios where no co-existence occurred. An IRR = 1 corresponds to no change.

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 nonspecific 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\(^1\). Similar associations have been reported elsewhere (e.g. \(^14\)).

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\(^15,16\). These suggest that both antibiotic stewardship and infection control measures contributed importantly 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 and the degree of bacterial interference between the two strains can easily be altered. In addition, by capturing dynamic transmission in both hospital- and community-populations (something commonly ignored in mathematical models of nosocomial pathogens\(^9,20\)), 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\(^6\), and competition for ecological niches has been reported for C. difficile (e.g. \(^18,19\)), 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. 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://zenodo.org/record/345136#_WLmdTVWLTcv20

Archived source code as at the time of publication: https://zenodo.org/record/345136#_WLmdTVWLTcv20\(^20\)

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**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**

The authors declared they have no competing interests.

**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.*

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\(^1\) BSC was also supported by The Medical Research Council and Department for International Development (grant number MR/K006924/1).

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\(^9\) BSC was also supported by The Medical Research Council and Department for International Development (grant number MR/K006924/1).

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\(^16\) BSC was also supported by The Medical Research Council and Department for International Development (grant number MR/K006924/1).

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\(^20\) BSC was also supported by The Medical Research Council and Department for International Development (grant number MR/K006924/1).
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 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 in hand hygiene compliance from a baseline of 40%.

Click here to access the data

References

Open Peer Review

Current Referee Status:  

Chris Robertson  
Department of Mathematics and Statistics, University of Strathclyde, Glasgow, G1 1XH, UK

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

Referee Report 27 April 2017
doi:10.21956/wellcomeopenres.11901.r21315

? Lulla Opatowski
Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases Unit (B2PHI), UMR1181, Université Versailles Saint Quentin, Institut Pasteur, Inserm, University of Paris-Saclay, Paris, France

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?

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 fig 1. 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.

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

I have read this submission. I 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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**Discuss 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
Royal Aberdeen Children’s Hospital
Aberdeen
Scotland, UK

**Competing Interests:** I have no competing interests to declare.