



## Linking antimicrobial prescribing to antimicrobial resistance in the ICU: Before and after an antimicrobial stewardship program

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### ABSTRACT

Antimicrobials are an effective treatment for many types of infections, but their overuse promotes the spread of resistant microorganisms that defy conventional treatments and complicate patient care. In 2009, an antimicrobial stewardship program was implemented at Mount Sinai Hospital (MSH, Toronto, Canada). Components of this program were to alter the fraction of patients prescribed antimicrobials, to shorten the average duration of treatment, and to alter the types of antimicrobials prescribed. These components were incorporated into a mathematical model that was compared to data reporting the number of patients colonized with *Pseudomonas aeruginosa* and the number of patients colonized with antimicrobial-resistant *P. aeruginosa* first isolates before and after the antimicrobial stewardship program. Our analysis shows that the reported decrease in the number of patients colonized was due to treating fewer patients, while the reported decrease in the number of patients colonized with resistant *P. aeruginosa* was due to the combined effect of treating fewer patients and altering the types of antimicrobials prescribed. We also find that shortening the average duration of treatment was unlikely to have produced any noticeable effects and that further reducing the fraction of patients prescribed antimicrobials would most substantially reduce *P. aeruginosa* antimicrobial resistance in the future. The analytical framework that we derive considers the effect of colonization pressure on infection spread and can be used to interpret clinical antimicrobial resistance data to assess different aspects of antimicrobial stewardship within the ecological context of the intensive care unit.

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### Introduction

The introduction of antimicrobial agents for the treatment of serious bacterial infections is one of the major biomedical advances of the last century. However, gains in health and life-years associated with antimicrobials have been progressively eroded in recent decades by the ongoing emergence of antimicrobial-resistant organisms (ARO), with an increasing fraction of serious infections caused by multidrug-resistant organisms (Cardo et al., 2004; Paterson et al., 2005; Jones et al., 2009, 2010). This problem has become particularly severe in the healthcare setting in general, and in the intensive care unit (ICU) environment in particular, where several factors combine to give resistant pathogens

a strong competitive advantage (Weber et al., 1999; Vincent, 2003). Key among these is the selective advantage conferred upon ARO in patients who are heavily exposed to antimicrobial agents (Weber et al., 1999; Oosdijk et al., 2009). In addition, the use (both necessary and unnecessary) of broad-spectrum antimicrobials in vulnerable patient populations increases these patients' susceptibility to colonization and invasive infection with pathogens (Bonten et al., 1999; Safdar and Maki, 2002; Thuong et al., 2003; Boyer et al., 2011).

Non-lactose fermenting gram-negative microbes, such as *Pseudomonas aeruginosa* have been particularly adept at acquiring resistance to multiple antimicrobial classes. Mechanisms of resistance commonly encountered in *P. aeruginosa* include efflux pumps, production of enzymes that inactivate antimicrobials, mutation of antimicrobial target sites, and reduced permeability to antimicrobials (Sun et al., 2011). The propensity for antimicrobial resistance displayed by *P. aeruginosa* is particularly concerning given the high level of virulence of this microbe, especially in patients with indwelling devices, on mechanical ventilation (Thuong et al., 2003), or with anatomical or immune differences due to such illnesses as cystic fibrosis, burns or HIV infection (Gustafsson and Martínez,

**Abbreviations:** ARO, antimicrobial-resistant organisms; ICU, intensive care unit; MSH, Mount Sinai Hospital.

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2005). Efforts to reduce the prevalence of resistance in *P. aeruginosa* and other pathogens often focus on strategies that alter the selective pressure created via antimicrobial exposure. These strategies include antimicrobial cycling or mixing (Sandiumenge et al., 2006) and aggressive ‘stewardship’ of antimicrobial resources that limit the duration and intensity of antimicrobial exposure (Shlaes et al., 1997; Dellit et al., 2007). Furthermore, frequently multiple interventions are implemented simultaneously making it difficult to assess the effect due to any one intervention (Dellit et al., 2007).

To describe the effects of different aspects of an antimicrobial stewardship program, we derive a mathematical model that relates antimicrobial prescribing to the prevalence of antimicrobial resistance. The model is compared to data from the Mount Sinai Hospital (MSH) ICU reporting the prevalence of antimicrobial resistance before and after the implementation of an antimicrobial stewardship program in February 2009. We consider each of three different aspects of the antimicrobial stewardship program and characterize the contribution of each to the reported declines in the number of patients colonized with *P. aeruginosa* and the prevalence of antimicrobial resistance among first isolates. Finally, we identify which of three different aspects of antimicrobial stewardship would most substantially reduce the prevalence of antimicrobial resistance in the future.

## Methods

During each six-month period from October 2005 to October 2011, the number of patients colonized and the number of first *P. aeruginosa* isolates resistant to different antipseudomonal antimicrobials was recorded (‘first isolate’ refers to the earliest recovered sample given that the same patient may be sampled multiple times). We express these recorded quantities in terms of their contributing epidemiological processes. The rate of change in the number of patients colonized,  $C$ , is the sum of the rate that patients are admitted colonized, and the rate that patients become colonized in the ICU,

$$\dot{C} = m\mu N + \beta(X^T + X^A)(S + R). \quad (1)$$

Here, patients are admitted to the ICU per bed at a rate  $\mu$  and discharged at the same rate to maintain a fixed number,  $N$ , of patients in the ICU at all times. The fraction of patients that are admitted colonized is  $m$ . Uncolonized patients that are receiving,  $X^T$ , or have received antimicrobials,  $X^A$ , are susceptible to *P. aeruginosa* colonization, and the transmission of *P. aeruginosa* occurs at a rate  $\beta(S + R)$  per patient susceptible to colonization. The number of patients colonized or infected with antimicrobial-susceptible and antimicrobial-resistant *P. aeruginosa* ( $S$  and  $R$ , respectively) contributes to the total colonization pressure,  $S + R$ . Each of  $X^T$ ,  $X^A$ ,  $S$  and  $R$  are dynamic variables that are interdependent and influenced by the ecology of the ICU as fully described in the mathematical model (Eqs. (A.1)–(A.14)).

To relate Eq. (1) to the MSH clinical data, the number of patients that were colonized while in the ICU during a six-month period is  $C = \int_0^{365/2} \dot{C} dt$ . This integral is approximated as,

$$C \approx \frac{365}{2} (m\mu N + \beta(\hat{X}^T + \hat{X}^A)(\hat{S} + \hat{R})), \quad (2)$$

where  $\hat{X}^T$ ,  $\hat{X}^A$ ,  $\hat{S}$ , and  $\hat{R}$  denote the equilibrium values of each dynamic variable and where the validity of this approximation is discussed in Appendix A. For patients who carry resistant *P. aeruginosa*, the clinical data distinguishes between *P. aeruginosa* clones that are resistant to ceftazidime ( $i=1$ ), ciprofloxacin ( $i=2$ ), and meropenem ( $i=3$ ) and clones resistant to two antimicrobials are denoted by the  $ij$  subscript. For simplicity, we model only resistance to these three antimicrobials as the *P. aeruginosa*

**Table 1**

List of assumptions.

- 
- (i) Antimicrobial treatment does not eradicate *P. aeruginosa* colonization
  - (ii) The transmission rate is the same for all patients (whether colonized, infected, or receiving treatment) and does not depend on the *P. aeruginosa* clone’s susceptibility to antimicrobials
  - (iii) Superinfection does not occur
  - (iv) *P. aeruginosa* transmission occurs via healthcare workers and healthcare workers acquire *P. aeruginosa* contamination in the ICU
  - (v) All infected patients are prescribed an antimicrobial that the infecting *P. aeruginosa* clone is susceptible to. When receiving an antimicrobial, resistance emerges at a constant rate which is the same for both colonized and infected patients
  - (vi) The treatment status of patients remains unchanged when they become colonized
  - (vii) The rate of ending treatment for all colonized (and infected) patients is the same regardless of whether the patient was treated when uncolonized (or colonized)
  - (viii) Cefazidime, ciprofloxacin and meropenem are never prescribed in combination
  - (ix) The rate of discharge is independent of the patient’s status (i.e., if the patient is uncolonized, colonized or infected)
- 

isolates from MSH were highly susceptible to tobramycin and piperacillin-tazobactam (with median susceptibilities of 89% and 93%). Resistance to all three antimicrobials was not considered for simplicity and because triple-resistant mutants are less common. Let  $\mathcal{R}_i$ ,  $\mathcal{R}_{i\text{x}}$  and  $\mathcal{R}_{ij}$  be the number of patients with first isolates resistant to the antimicrobial  $i$ , the antimicrobial  $i$  only, and the antimicrobials  $i$  and  $j$  recorded over the six-month period. Then,

$$\mathcal{R}_i \approx \mathcal{R}_{i\text{x}} + \sum_j \mathcal{R}_{ij}, \quad (3)$$

where,

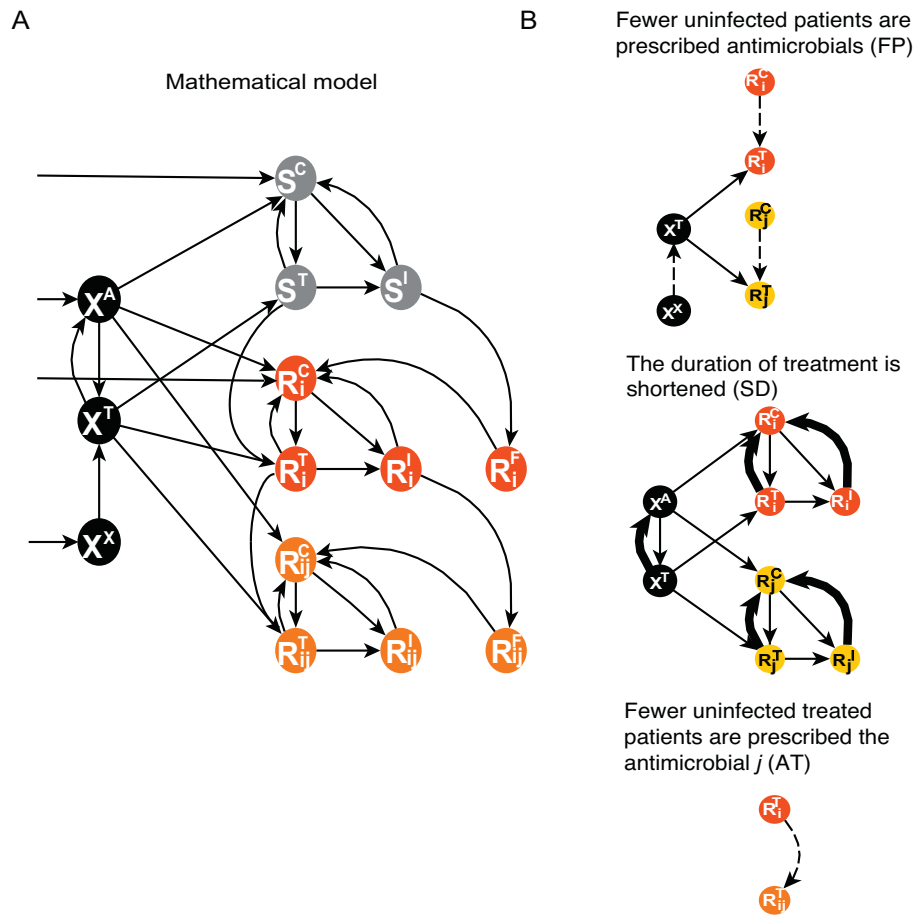
$$\mathcal{R}_{i\text{x}} \approx \frac{365}{2} (r_i m \mu N + \beta(\hat{X}^T + \hat{X}^A) \hat{R}_i), \quad (4)$$

$$\mathcal{R}_{ij} \approx \frac{365}{2} \beta(\hat{X}^T + \hat{X}^A) \hat{R}_{ij}. \quad (5)$$

For simplicity, Eq. (5) assumes that no patients are admitted colonized with *P. aeruginosa* clones that are resistant to more than one antimicrobial.

The effect of antimicrobial stewardship on patient colonization and resistance occurs through the affect of stewardship on the values of  $\hat{X}^T$ ,  $\hat{X}^A$ ,  $\hat{S}$  and  $\hat{R}$ . These relationships are shown in Fig. 1 and described in Appendix A (Eqs. (A.1)–(A.14)). The assumptions of the model formulation (Eqs. (A.1)–(A.14)) are listed in Table 1 and these assumptions were made either to simply or to accurately reflect the ecology of *P. aeruginosa* spread.

The changes in antimicrobial prescribing arising from the antimicrobial stewardship program can be summarized as having three effects that are described by the model parameters  $\tau_0$ ,  $\tau_1$  and the  $\omega_i$ s (Fig. 1B). In practice, the antimicrobial stewardship program at MSH consisted of a collaborative daily review of all patients during which members of the antimicrobial stewardship program team advised the ICU team on antimicrobial use, primarily on the basis of antimicrobial efficacy and drug safety (i.e., toxicity), but where subsequent considerations included using therapies targeted to known pathogens (rather than unnecessarily broad-spectrum or antipseudomonal antimicrobials), reducing costs, and reducing the duration of treatment from 11–12 days to 8 days. In terms of the mathematical model (Eqs. (A.1)–(A.14)), one effect of the antimicrobial stewardship program is to have altered the fraction of uninfected patients that were prescribed antimicrobials (FP). This fraction is approximated as  $\tau_0/(\tau_0 + \mu)$  (see Appendix A) and the reference to ‘uninfected patients’ in the context of the model means ‘without a *P. aeruginosa* infection’. A second effect is that



**Fig. 1.** The number of ICU patients that are uncolonized, colonized, infected or have experienced a treatment failure and the susceptibility of *P. aeruginosa* clones to antimicrobials depends on patient admission, colonization, infection, antimicrobial treatments and the emergence of resistance. The mathematical model (Eqs. (A.1)–(A.14)) is depicted in (A) (patient discharge is not shown). Different aspects of the antimicrobial stewardship program would decrease (dashed line) or increase (thick line) the rate that patients transition from one state to another as shown in (B).

after the implementation of the antimicrobial stewardship program, the duration of antimicrobial treatment,  $1/\tau_1$ , was shortened (SD). Finally, the third effect is that the antimicrobial stewardship program may have facilitated a shift to using alternative types of antimicrobials (AT). This change is represented in the mathematical model (Eqs. (A.1)–(A.14)) as a change in the probability of prescribing ceftazidime, ciprofloxacin, and meropenem to uninfected patients ( $\omega_1, \omega_2$  and  $\omega_3$ ).

The predictions of the mathematical model,  $\mathcal{C}$ ,  $\mathcal{R}_1$ ,  $\mathcal{R}_2$ , and  $\mathcal{R}_3$  (Eqs. (2) and (3)) can be compared to the analogous quantities reported in the MSH data,  $\bar{C}^+$ ,  $\bar{C}^-$ ,  $\bar{R}_i^+$  and  $\bar{R}_i^-$ , where the superscripts denote before (+) and after (–) the implementation of the antimicrobial stewardship program and where the bar denotes that a mean was taken over several six-month periods. The superscripts reflect that for MSH these mean values, after the antimicrobial stewardship program, were less than before such that  $\bar{C}^- < \bar{C}^+$  and  $\bar{R}_i^- < \bar{R}_i^+$  for all  $i$ .

*Variability in the data*

The number of patients colonized, and the number of patients colonized with resistant *P. aeruginosa*, for each six-month period reported in the data is highly variable. Such variability is likely due to chance events and given this stochasticity the parameters in the mathematical model should be interpreted as means (i.e., the mean transmission rate is  $\beta$  and chance events that are not explicitly modelled may produce variability around this mean). Furthermore,

the ordinary differential equation model that we derive treats the number of patients in each state as a continuous variable rather than treating the number of patients in each state as a discrete quantity that takes on integer values between zero and  $N$ . A potential inaccuracy may arise given that under the continuous variable formulation the colonization pressure,  $S + R$ , is never equal to zero (given a positive initial condition), while in a real ICU, at some point in time it may happen that no patients are colonized or infected. To justify the formulation of the mathematical model with continuous state variables, we note that *P. aeruginosa* can persist on equipment and in the environment, and so, in practice, even when no patients are colonized there is still a small risk that patients in the ICU will become colonized.

*Parameter estimation*

The mathematical model was parameterized using data reported in the published literature, from expert knowledge, and by comparing the predictions of the mathematical model for different parameter values with the data from MSH (Table 2). Parameters that were unknown but specific to MSH were estimated from expert opinion, while general parameters were estimated from the published literature (these calculations are provided in Appendix A). The remaining parameters  $r_i$ ,  $m$ , and  $\beta$ , and the unknown parameters related to the effect of antimicrobial stewardship,  $\tau_0$  and  $\omega_i$ , were estimated from the MSH data (Fig. 2).

**Table 2**  
Parameter estimates.

Parameter	Definition	Estimate	Est. method
$\mu$	Rate of admission and discharge per bed	0.17 day <sup>-1</sup>	MSHd
$N$	Number of beds in the ICU	16	MSHd
$a$	Fraction of admitted patients with prior exposure to antimicrobials	0.6	MSHe
$m$	Fraction of patients admitted colonized	[0, 0.0188]	See Methods
$r_1$	Fraction of patients admitted colonized with ceftazidime-resistant isolates	0.07	see Methods
$r_2$	Fraction of patients admitted colonized with ciprofloxacin-resistant isolates	0.25	see Methods
$r_3$	Fraction of patients admitted colonized with meropenem-resistant isolates	0.07	see Methods
$\beta$	Transmission rate	[0.0095, 0.0175] day <sup>-1</sup> patient <sup>-1</sup>	see Methods
$\sigma$	Rate that colonized patients become infected	0.14 day <sup>-1</sup>	Boyer et al. (2011)
$\tau_0$	Rate of beginning an antimicrobial treatment	day <sup>-1</sup> ; less after the ASP	see Result 1
$\tau_1$	Rate of ending an antimicrobial treatment	0.087 day <sup>-1</sup> (before ASP)	MSHe
		0.125 day <sup>-1</sup> (after ASP)	MSHe
$\tau_2$	Rate of ending antimicrobial treatment given a treatment failure	0.067 day <sup>-1</sup>	MSHe
$\epsilon_1$	Rate of emergence of ceftazidime resistance	0.025 day <sup>-1</sup>	Juan et al. (2005)
$\epsilon_2$	Rate of emergence of ciprofloxacin resistance	0.033 day <sup>-1</sup>	Juan et al. (2005)
$\epsilon_3$	Rate of emergence of meropenem resistance	0.024 day <sup>-1</sup>	Juan et al. (2005)
$\omega_1$	Fraction of colonized patients prescribed ceftazidime	Less after the ASP	see Result 3
$\omega_2$	Fraction of colonized patients prescribed ciprofloxacin	Less after the ASP	see Result 3
$\omega_3$	Fraction of colonized patients prescribed meropenem	Less after the ASP	see Result 3
$\alpha_1$	Probability of prescribing ceftazidime to a patient with a <i>P. aeruginosa</i> infection	0.4	MSHe
$\alpha_2$	Probability of prescribing ciprofloxacin to a patient with a <i>P. aeruginosa</i> infection	0.1	MSHe
$\alpha_3$	Probability of prescribing meropenem to a patient with a <i>P. aeruginosa</i> infection	0.1	MSHe
$\alpha_4$	Probability of prescribing piperacillin-tazobactam to a patient with a <i>P. aeruginosa</i> infection	0.4	MSHe

MSHd, a parameter estimate specific to the MSH ICU estimated from data; MSHe, a parameter specific to MSH and estimated from expert opinion; ASP, antimicrobial stewardship program.

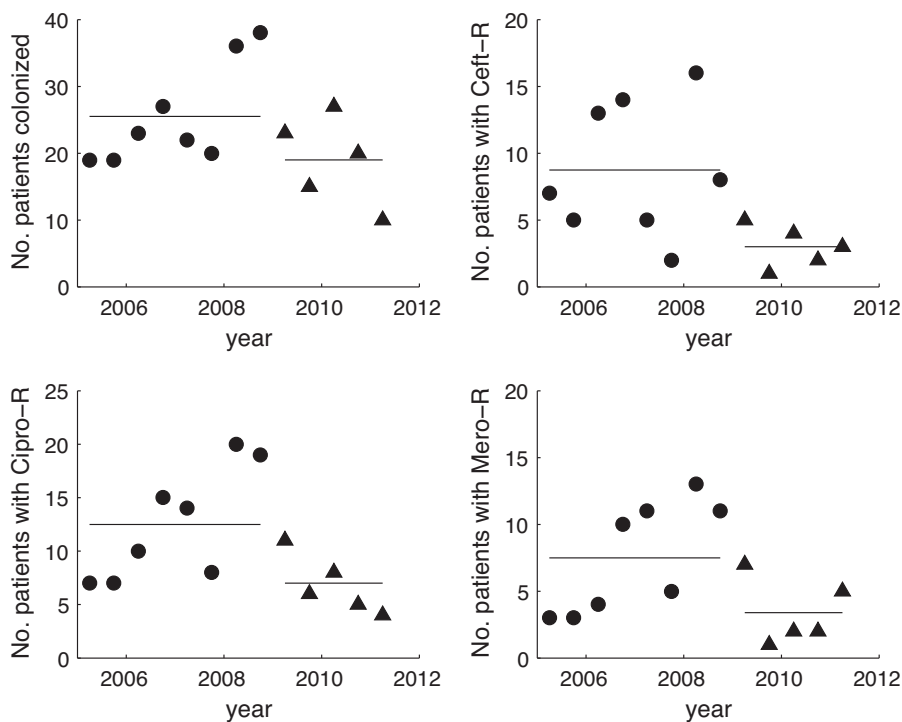
#### Method for estimating $r_1$ , $r_2$ and $r_3$

The model predicted fraction of first isolates that are resistant,  $\mathcal{R}_i/C$ , is greater than or equal to the fraction of resistant isolates amongst patients admitted colonized,  $r_i$ , because the mathematical model assumes that in the ICU susceptible clones of *P. aeruginosa* may become resistant, but not that resistant clones may become susceptible. The minimum prevalence of resistance in the MSH data is 0.07 for ceftazidime, 0.25 for ciprofloxacin and 0.07 for meropenem. If  $r_1$ ,  $r_2$  and  $r_3$  exceed these values then the

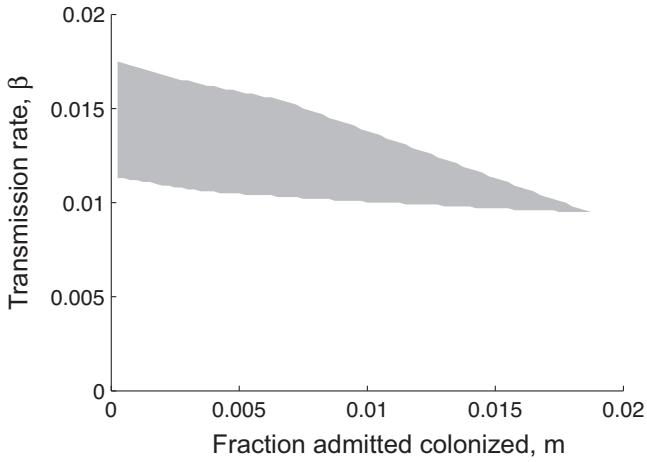
parameterized model cannot achieve these minima no matter how an antimicrobial stewardship program is implemented. Therefore,  $r_1$ ,  $r_2$  and  $r_3$  were estimated as 0.07, 0.25 and 0.07.

#### Method for estimating $m$ and $\beta$

Given that  $m$  is the fraction of patients admitted colonized and  $\beta$  is the transmission rate, if either of these values are too large then the model predicted number of patients colonized will greatly exceed the corresponding reported values. These parameters,  $m$



**Fig. 2.** The number of patients colonized and colonized with first isolates resistant to ceftazidime (Ceft-R), ciprofloxacin (Cipro-R) and meropenem (Mero-R) during a six-month period before (circles) and after (triangles) the implementation of the antimicrobial stewardship program. The horizontal lines show the mean values before and after the stewardship program was enacted.



**Fig. 3.** Combinations of  $\beta$  and  $m$  parameter values (grey shading) such that the conditions described in Eq. (6) are met. From the MSH data the mean number of patients colonized and colonized with resistant first isolates are  $C^+ = 25.5$ ,  $R_1^+ = 8.75$ ,  $R_2^+ = 12.5$ ,  $R_3^+ = 7.5$  (before the antimicrobial stewardship program) and  $C^- = 19$ ,  $R_1^- = 3$ ,  $R_2^- = 7$ ,  $R_3^- = 3.4$  (after the antimicrobial stewardship program). The lower bound on the model predictions was estimated by setting  $\tau_0 = \omega_1 = \omega_2 = \omega_3 = 0$  and the upper bound was estimated by setting  $\tau_0 = 5$  and  $\omega_1 = \omega_2 = \omega_3 = 1/3$ . All other values were estimated as described in Table 2. These results demonstrate that the estimated value of  $m$  must be between 0 and 0.0188, that the estimated value of  $\beta$  must be between 0.0095 and 0.0175.

and  $\beta$ , also determine the model predicted number of patients colonized with resistant *P. aeruginosa*, and if  $m$  is too large relative to  $\beta$ , the predicted number of patients colonized with resistant *P. aeruginosa* will be too few. We have not yet estimated the unknown parameters related to antimicrobial stewardship ( $\tau_0$  and  $\omega_i$ ), however, for any  $m$  and  $\beta$ , the minimum and maximum model predictions are determined by considering the two possible extremes in antimicrobial stewardship. We identify feasible combinations of  $\beta$  and  $m$  by requiring that the range of the model predictions includes the mean values reported in the MSH data, both before and after the antimicrobial stewardship program.

Formally, let  $C^-$  and  $R_i^-$  denote the minimum model predictions where these are determined by setting  $\tau_0 = 0$ , and let  $C^+$  and  $R_i^+$  denote the maximum model predictions where these are determined by letting  $\tau_0 \rightarrow \infty$  and by setting  $\omega_1 = \omega_2 = \omega_3 = 1/3$  (this assumes that the maximum fractions of treated patients prescribed each antimicrobial are equal; see also assumption (viii) in Table 1). Then, feasible combinations of  $\beta$  and  $m$  must satisfy the conditions,

$$C^- \leq \bar{C}^- < \bar{C}^+ \leq C^+ \quad \text{and,} \tag{6}$$

$$R_i^- \leq \bar{R}_i^- < \bar{R}_i^+ \leq R_i^+ \quad \text{for all } i.$$

Using this estimation method, we determine that the feasible parameter estimates are the combinations of  $m$  and  $\beta$  shown in Fig. 3. The results shown in Fig. 3 imply that necessary (but not sufficient) conditions are  $0.0095 \leq \beta \leq 0.0175$  and  $0 \leq m \leq 0.0188$  (Table 2).

**Results**

Having derived an appropriate model and estimated all the model parameters except those related to antimicrobial stewardship, we now analyze the mathematical model to understand how changes in antimicrobial stewardship translate into changes in the predicted number of patients colonized and colonized with resistant *P. aeruginosa*. Our analysis produces three main results.

1. *Fewer patients were treated after the implementation of the antimicrobial stewardship program* To show that fewer patients (FP)

were prescribed antimicrobials after the implementation of the antimicrobial stewardship program, consider the expression for  $C$ , the model predicted number of patients colonized during a six-month period (Eq. (2)). The dependence of this quantity on antimicrobial stewardship is via the possible dependence of the number of patients susceptible to colonization,  $\hat{X}^T + \hat{X}^A$ , and the colonization pressure,  $\hat{S} + \hat{R}$ , at equilibrium, on the parameters related to antimicrobial stewardship,  $\tau_0$ ,  $\tau_1$  and  $\omega_i$ . By adding Eqs. (A.2) and (A.3) and Eqs. (A.4)–(A.14) and setting the results equal to zero, we have the following system of equations,

$$a(1 - m)\mu N - \beta(\hat{X}^T + \hat{X}^A)(\hat{S} + \hat{R}) + \tau_0 \hat{X}^\times - \mu(\hat{X}^T + \hat{X}^A) = 0, \tag{7}$$

$$m\mu N + \beta(\hat{X}^A + \hat{X}^T)(\hat{S} + \hat{R}) - \mu(\hat{S} + \hat{R}) = 0, \tag{8}$$

and in setting Eq. (A.1) equal to zero, we have that,

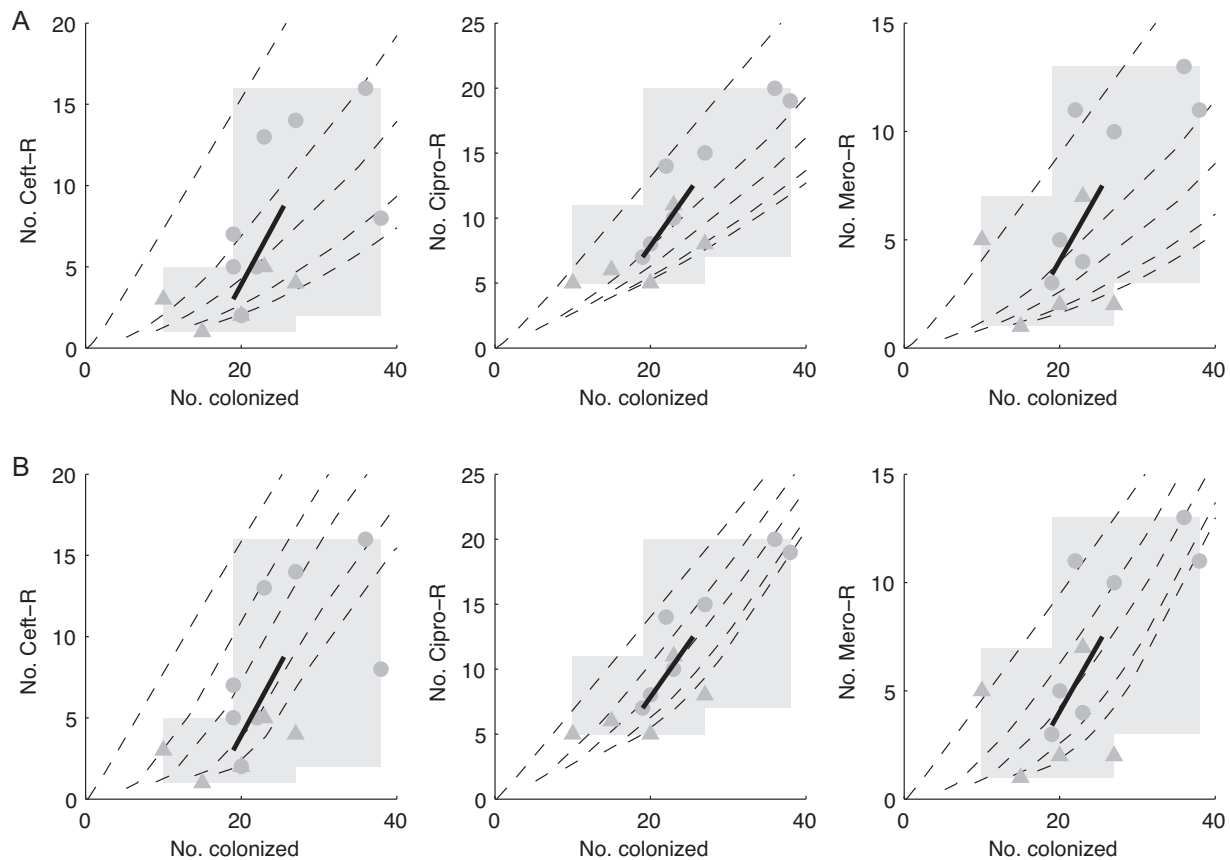
$$\hat{X}^\times = \frac{(1 - a)(1 - m)\mu N}{\tau_0 + \mu}. \tag{9}$$

Eqs. (7) and (8) are a system of two equations that can be solved for  $\hat{X}^T + \hat{X}^A$  and  $\hat{S} + \hat{R}$ , where doing so, reveals that the only parameter related to antimicrobial stewardship appearing in these expressions is  $\tau_0$ , the parameter characterizing the fraction of uninfected patients prescribed antimicrobials. Importantly, the other parameters related to antimicrobial stewardship, the types of antimicrobials prescribed to uninfected patients that are treated,  $\omega_i$ , and the average duration of treatment,  $1/\tau_1$ , do not appear in Eqs. (7)–(9).

The result that only treating fewer patients (FP), by way of decreasing  $\tau_0$ , can reduce the number of patients colonized arises as a consequence of the model assumptions (i) and (ii) (Table 1). Both these assumptions were made because these accurately reflect the best current understanding of *P. aeruginosa* ecology in the ICU. Assumption (i) states that upon ending treatment, patients or the patient’s immediate environment remains colonized, and as a consequence, the rate of ending treatment,  $\tau_1$ , does not affect colonization pressure,  $S + R$ . Assumption (ii) states that all *P. aeruginosa* clones are equally transmissible. If this were not the case,  $C$ , (Eq. (2)) would depend on the number of patients colonized with clones of different antimicrobial susceptibilities, and not simply the sum,  $S + R$ . Even under assumption (ii), the number of patients carrying *P. aeruginosa* clones susceptible to all three antimicrobials,  $S$ , and resistant to at least one antimicrobial,  $R$ , depends on  $\tau_1$  and  $\omega_i$ , however, notably, their sum,  $S + R$ , does not. Therefore, since the data at MSH reports that fewer patients were colonized after the implementation of the antimicrobial stewardship program than were before ( $19 = \bar{C}^- < \bar{C}^+ = 25.5$ ) we conclude that fewer patients (FP) were treated after the antimicrobial stewardship program was implemented.

2. *Shortening the duration of treatment had a negligible effect* Given the parameter values estimated in Table 2, reducing the duration of treatment (SD) from 11–12 to 8 days had almost no effect on *P. aeruginosa* resistance. To understand why, consider that the chance of resistance to ciprofloxacin emerging is 27.5% for an 11.5 day treatment versus 21% for an 8 day treatment. However, the chance of resistance emerging before discharge from the ICU is reduced only from 11% to 10%; and the chance of resistance to ceftazidime and meropenem emerging before discharge is reduced by even less (see Appendix A for more details). This suggests, firstly, that for ICUs with longer average durations of stay, reducing the duration of antimicrobial treatment might have a more noticeable effect, and secondly, that the effects due to reducing the duration of antimicrobial treatment may not be noticeable in the ICU, but noticeable at the level of the entire hospital (with the proviso that patients in other wards are generally less susceptible to *P. aeruginosa* colonization). Finally, we





**Fig. 4.** Comparison of the data before (circles) and after (triangles) the antimicrobial stewardship program with the model predictions (dashed lines) under the assumptions that after the implementation of the antimicrobial stewardship program: (A) fewer patients were treated (FP only); and (B) fewer patients were treated and alternative types of treatments were used (FP and AT both). The solid black line connects the mean values before and after the antimicrobial stewardship program for the MSH data. In (A), the slope of the dashed curves (model predictions) is never as steep as the slope of the solid black line (data), whereas in (B) the slopes of these curves show better agreement. For (A), the dashed curves were generated by allowing  $\tau_0$  to range between 0 and 1 with  $\omega_i = 0.2$  for all  $i$ . For (B),  $\omega_i$  changes along with  $\tau_0$  (specifically,  $\omega_i(\tau_0) = 0.003 \exp(30\tau_0) / (0.3 + 0.001(\exp(30\tau_0) - 1))$ ). The grey shaded areas show the range in the reported number of patients colonized and the number of patients colonized with resistant first isolates before and after the antimicrobial stewardship program at MSH. The different dashed lines show  $m = 0.001, 0.0025, 0.005, 0.01$  and  $0.015$ , where the corresponding  $\beta$  values were the mean of the lower and upper bounds of the grey region of Fig. 3 for each  $m$ .

note that assumptions (v) and (ix) (Table 1) are necessary for this conclusion to hold.

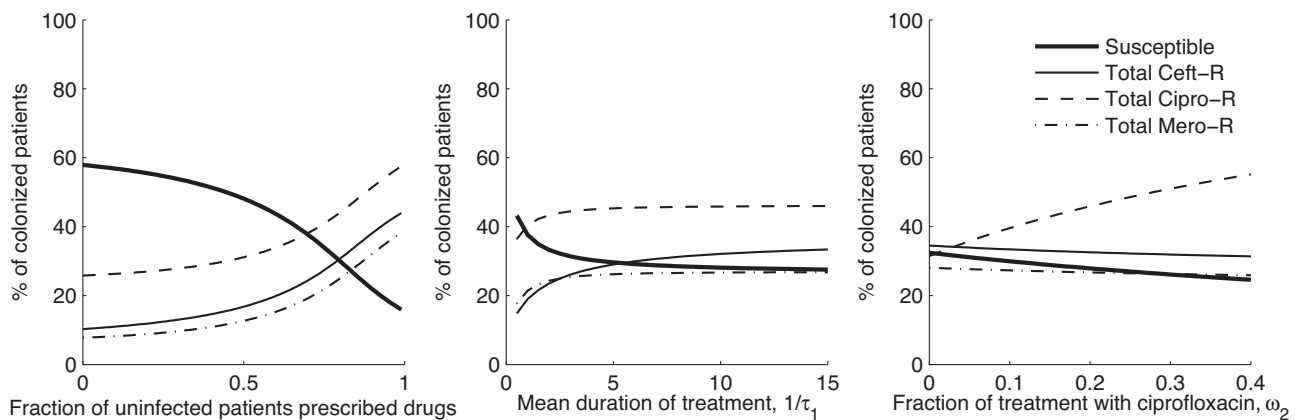
3. *Fewer antipseudomonal antimicrobials were prescribed after the implementation of the antimicrobial stewardship program* Prescribing antimicrobials to fewer patients (FP) not only leads to a decrease in the number of patients colonized, it also produces a decrease in the number of patients colonized with resistant first isolates. We numerically solved the system of Eqs. (A.1)–(A.14) to evaluate Eqs. (2) and (3) for a range of different  $\tau_0$  values. Fig. 4A shows that no matter which values of  $m$  and  $\beta$  are chosen, if only fewer patients are prescribed antimicrobials after the implementation of the antimicrobial stewardship program, then the model predicts more patients colonized with resistant *P. aeruginosa* than was reported in the MSH data. For the numerical results shown in Fig. 4A, the types of treatment (AT) are unchanged ( $\omega_i = 0.2$  for all  $i$ ) as the shift to treating fewer patients occurs. Alternatively in Fig. 4B, the dual effect of antimicrobial stewardship is to treat fewer patients and to use antipseudomonal antimicrobials less often (FP and AT) and Fig. 4B shows a better agreement between the model predictions and the data from MSH. To summarize, given the decrease in the mean number of patients colonized after the antimicrobial stewardship program, the decrease in the number of patients colonized with resistant first isolates reported at MSH is too large to be explained by treating fewer patients alone (FP only).

#### Aspects of an antimicrobial stewardship program which would most substantially decrease resistance

In addition to identifying the aspects of the antimicrobial stewardship program most responsible for the changes reported at MSH, we identify which aspect of antimicrobial stewardship would contribute most substantially to decreasing the prevalence of resistance if any one intervention could be implemented. We numerically solved Eqs. (A.1)–(A.14) for reasonable parameter values and determined that the most substantial reductions in the number of patients colonized with resistant first isolates would be achieved when the fraction of patients prescribed antimicrobials (FP) is initially close to one and is decreased (Fig. 5).

#### Discussion

The past decade has seen an increasing emphasis on patient safety in clinical care settings (Kohn et al., 2000). The recognition of the substantial costs and adverse health outcomes associated with hospital-acquired infections and preventable medical errors has led to restructuring of fee schedules by the US Centers for Medicare/Medicaid Service and has spawned antimicrobial stewardship programs and other innovative efforts by clinicians seeking to minimize such outcomes (Centers for Medicare/Medicaid Services, HHS, 2011). We utilized primary data from an antimicrobial stewardship program at a major North American teaching hospital to build



**Fig. 5.** The change in *P. aeruginosa* resistance given a change in one of the components of the antimicrobial stewardship program. The three components of the antimicrobial stewardship program are reducing the fraction of uninfected patients prescribed antimicrobials (FP), shortening the duration of antimicrobial treatment (SD), and altering the type of antimicrobials prescribed to treated patients (AT). Parameters used were  $\beta = 0.0112 \text{ day}^{-1} \text{ patient}^{-1}$ ,  $m = 0.0019$ ,  $\tau_1 = 0.087 \text{ day}^{-1}$ ,  $\tau_0 = 0.8$ ,  $\omega_1 = 0.05$ ,  $\omega_2 = 0.2$  and  $\omega_3 = 0.2$  (except for the panels where these parameters were varied) and otherwise as given by Table 2.

and parameterize a mathematical model of the transmission of *P. aeruginosa* in an intensive care setting. Our analysis showed that the best explanation for the reported decrease in the prevalence of resistance was the reduced use of antimicrobials in uninfected patients (FP) and the reduced use of antipseudomonal antimicrobial agents (AT). It is, of course, possible that the use of other agents (e.g. sulfas, ceftriaxone, and penicillins other than antipseudomonal penicillins) has enhanced resistance to these other agents but in the intensive care context the preservation of susceptibility in *P. aeruginosa* is likely to have been a more important achievement.

Our model makes assumptions about both antimicrobial utilization and the ecology of the ICU. We are unable to evaluate the possibility that contemporaneous changes in infection control practices occurring as part of a ‘culture of safety’ might have caused the reported declines in resistant *P. aeruginosa* infections, for example via improved hand hygiene or improved compliance with contact precautions in those caring for patients with ARO. While we cannot rule out this possibility, we have no reason to believe that such dramatic improvements in infection control occurred at this time, whereas we know that measures to improve antimicrobial stewardship were undertaken.

Other model assumptions were made to promote either biological realism or model simplicity but we do not believe that these assumptions strongly influence our conclusions. We assumed that antimicrobial use did not eradicate *P. aeruginosa* colonization, which is concordant with the available literature suggesting that long-term decolonization of individuals with carriage of gram-negative ARO is difficult, though recovery of microbes has been transiently suppressed with selective digestive decontamination (for example, Saidel-Odes et al. (2012)). However, even if antimicrobials do eradicate colonization, this would occur towards the end of a patient’s stay and would contribute minimally to reducing the risk of healthcare worker contamination.

While novel in its evaluation of an antimicrobial stewardship program, our model follows numerous other studies that have employed mathematical models to gain similar insights into the epidemiology of antimicrobial resistance (Bonhoeffer et al., 1997; Austin et al., 1999; Lipsitch et al., 2000; Smith et al., 2004; Bootsma et al., 2006; Boldin et al., 2007; D’Agata et al., 2009). The ability of such models to explicitly consider the non-independence of infections that constitutes a key attribute of communicable diseases and provides an important and distinct advantage in the exploration of data when compared, for example, to the interrupted time series analyses that have been typically employed in the evaluation of stewardship programs (Ansari et al., 2003; Peto et al.,

2008; Yong et al., 2010). Mathematical models can thus provide a platform that allows synthesis of available data on stewardship programs and exploration of mechanistic aspects of the programs most likely to have resulted in the observed changes in the risk of infection with resistant pathogens. To the best of our knowledge, the application of mathematical modeling tools to the evaluation of antimicrobial stewardship programs has been extremely limited to date.

## Conclusions

A relatively simple model that incorporated several different attributes of the stewardship program (i.e., diminished administration of antimicrobials to uninfected individuals; limited duration of therapy; reduced use of antipseudomonal antimicrobials) was successful in reproducing observed declines in the mean risk of colonization or infection with resistant *P. aeruginosa* before and after the implementation of an antimicrobial stewardship program. Using this approach we were able to determine the effects of the different elements of the antimicrobial stewardship program and to identify reduced prescribing of antimicrobials (FP) as the attribute of an antimicrobial stewardship program that would most substantially reduce antimicrobial resistance in *P. aeruginosa* in the future.

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## Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.epidem.2012.12.001>.

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