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Antibiotic Reduction Campaigns Do Not Necessarily Decrease Bacterial Resistance: the Example of Methicillin-Resistant *Staphylococcus aureus*

Lidia Kardaś-Słoma,[a,b] Pierre-Yves Boëlle,[b,c,d] Lulla Opatowski,[e,f,g,h] Didier Guillemot,[e,f,h,i] Laura Temime[a]

Laboratoire Modélisation et Surveillance des Risques pour la Sécurité Sanitaire, Conservatoire National des Arts et Métiers, Paris, France[a]; Université Pierre et Marie Curie—Paris 6, Paris, France[b]; INSERM, UMR-S707, Paris, France[c]; Hôpital Saint-Antoine, Assistance Publique—Hôpitaux de Paris, Paris, France[d]; Institut Pasteur, Unité de Pharmacoépidémiologie et Maladies Infectieuses, Paris, France[e]; INSERM U 657, Paris, France[f]; Department of Infectious Disease Epidemiology, MRC Centre for Outbreak Analysis and Modelling, Imperial College London, London, United Kingdom[g]; Université de Versailles—Saint-Quentin, Versailles, France[h]; Hôpital Raymond-Poincaré, Assistance Publique—Hôpitaux de Paris, Garches, France[i]

Interventions designed to reduce antibiotic consumption are under way worldwide. While overall reductions are often achieved, their impact on the selection of antibiotic-resistant selection cannot be assessed accurately from currently available data. We developed a mathematical model of methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA) transmission inside and outside the hospital. A systematic simulation study was then conducted with two objectives: to assess the impact of antibiotic class-specific changes during an antibiotic reduction period and to investigate the interactions between antibiotic prescription changes in the hospital and the community. The model reproduced the overall reduction in MRSA frequency in French intensive-care units (ICUs) with antibiotic consumption in France from 2002 to 2003 as an input. However, the change in MRSA frequency depended on which antibiotic classes changed the most, with the same overall 10% reduction in antibiotic use over 1 year leading to anywhere between a 69% decrease and a 52% increase in MRSA frequency in ICUs and anywhere between a 37% decrease and a 46% increase in the community. Furthermore, some combinations of antibiotic prescription changes in the hospital and the community could act in a synergistic or antagonistic way with regard to overall MRSA selection. This study shows that class-specific changes in antibiotic use, rather than overall reductions, need to be considered in order to properly anticipate the impact of an antibiotic reduction campaign. It also highlights the fact that optimal gains will be obtained by coordinating interventions in hospitals and in the community, since the effect of an intervention in a given setting may be strongly affected by exogenous factors.

Antibiotic use—and misuse—is the main driver for the selection of antibiotic-resistant bacteria in hospital environments and in the community. This has led many countries to implement interventions designed to reduce overall antibiotic consumption (1–4), following which successful decreases in antibiotic use have been reported (3, 5). For instance, a national campaign to reduce unnecessary antibiotic use and control antimicrobial resistance was decided on in France in November 2001, and antibiotic consumption was indeed reduced by 10% in both hospitals and the general community between 2002 and 2003 (6).

However, the impact on resistance of such a reduction in antibiotic use is difficult to assess. For instance, while several studies have reported successful decreases in methicillin-resistant *Staphylococcus aureus* (MRSA) infections in hospitals following restrictions on the use of an antibiotic class (2, 7, 8), most of them did not take into account other interventions that may have contributed to the decrease in resistance, such as infection control measures (1, 3, 9).

Furthermore, a decrease in the use of one class of antibiotics may be offset by a concomitant increase in the use of another class (10). In French hospitals, for example, while the use of beta-lactamase-sensitive penicillins (J01CE code of the ATC classification system) decreased by 68% between 2002 and 2003, the use of fluoroquinolones increased by 9% over the same period (6). Such changes in prescription patterns may lead to the selection of more-antibiotic-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) (11).

In the case of MRSA, the situation is further complicated by the cocirculation of hospital-associated (HA-MRSA) and community-associated (CA-MRSA) groups, with distinct antibiotic susceptibility profiles. These resistant bacteria have become prevalent in both hospital and community settings (12) but may respond differently to changes in antibiotic prescriptions.

In this study, we examined the impact of an overall reduction in antibiotic use on the selection of MRSA in both hospital and community environments. Using a coupled mathematical model of *S. aureus* transmission in hospital and community settings, we investigate how changes in the relative distribution of prescribed antibiotics classes influence this impact, and we explore the interplay of the two settings. We illustrate our findings using French data on antibiotic use and resistance frequency after the launch of the November 2001 antibiotic reduction campaign.

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Address correspondence to Laura Temime, laura.temime@cnam.fr.
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MATERIALS AND METHODS

Modeling *S. aureus* transmission. We modeled the transmission of *S. aureus* in two interacting settings: a 20-bed intensive-care unit (ICU)-type hospital ward (hospital setting) and the general population of a city based on Paris, France (community setting). Hospital patients were admitted from and discharged to the community. In order to fully reproduce the transmission dynamics of *S. aureus*, we simulated the three main cocirculating phenotypic groups in these two settings: methicillin-sensitive *S. aureus* (MSSA), community-associated methicillin-resistant *S. aureus* (CA-MRSA), and hospital-associated methicillin-resistant *S. aureus* (HA-MRSA) (13). Here, we defined these groups on the basis of differences in their antibiotic susceptibility profiles rather than on the basis of other epidemiological characteristics of CA-MRSA and HA-MRSA (14, 15).

For the hospital setting, we used a previously described agent-based computerized model (NosoSim [11, 16]) of a hypothetical ICU to simulate the spread of *S. aureus* among patients and health care workers (HCWs). For the community, we developed a compartmental mathematical model of *S. aureus* transmission. For this study, the community and NosoSim models were coupled (see Fig. S1 and S2, Tables S1 and S2, and the equations in Text S2 in the supplemental material).

Hospital model. NosoSim models a specific hospital setting, consisting here of a 20-bed ICU, where the actions of each patient and HCW are reproduced, and pathogen colonization and transmission through direct contact between humans are simulated. The probability of *S. aureus* transmission from a colonized HCW to a patient or from a colonized patient to an HCW was calculated as the product of the per-minute transmission rate multiplied by the duration of contact. We designated the per-minute transmission rate p_M for MSSA, p_C for CA-MRSA, and p_H for HA-MRSA.

During a simulation, characteristics of HCWs (e.g., colonization status) and patients (e.g., colonization status, exposure to antibiotics) changed according to contacts between HCWs and patients and according to patient admission or discharge.

Figure S2 in the supplemental material provides a schematic representation of the modeled ward. The main parameters of the NosoSim model are presented in Table S1 in the supplemental material, and the model is described in more detail in references 11 and 16.

Community model. In the community model, individuals were grouped into four compartments according to their colonization status: MSSA (M), CA-MRSA (C), or HA-MRSA (H) carriers and uncolonized individuals (U). Colonized individuals could be decolonized following either antibiotic exposure or spontaneous clearance, which occurred at rate γ per day. Uncolonized individuals became colonized with MSSA, CA-MRSA, and HA-MRSA at rates β_M/N_C, β_C/N_C, and β_H/N_C, respectively, where N_C represented the community population size of the city of Paris, France. The main parameters of this model are presented in Table S2, and model equations are provided in Text S2, in the supplemental material.

(i) Model coupling. The community model was coupled to NosoSim through hospital admissions and discharges. Each day, the total number of individuals discharged from the hospital into each community compartment was computed from NosoSim predictions. Conversely, the frequency of colonization with MSSA, CA-MRSA, and HA-MRSA at hospital admission was updated each day from predictions of the community model, adjusted to take into account a 5-times-higher readmission rate of HA-MRSA carriers (17). The length of hospital stay was drawn from a gamma distribution. At the end of the hospital stay, patients were discharged to the community according to their colonization status and were immediately replaced with new admissions from the community.

More details on model coupling are provided in Text S2 in the supplemental material.

(ii) Model calibration. The coupled model was calibrated to reproduce the French situation from 2002 in both the hospital and community settings.

To calibrate the community model, we formally computed the coexistent equilibrium with three phenotypic groups (see Text S2 in the supplemental material) and deduced the transmission rates of MSSA, CA-MRSA, and HA-MRSA (β_M, β_C, and β_H, respectively), which allowed us to reproduce the baseline prevalence of carriage observed in the general French population: 22.5% MSSA carriers, 0.13% CA-MRSA carriers, and 1% HA-MRSA carriers (18, 19). The computed transmission parameters were as follows: β_M, 0.0161 per day; β_C, 0.0146 per day; β_H, 0.0144 per day.

We then coupled the calibrated community model with NosoSim, and we calibrated NosoSim transmission rates p_M and p_H using Monte Carlo methods in order to reproduce the observed 39% methicillin resistance among *Staphylococcus aureus* isolates in French ICUs in 2002 (20), assuming that the ratio of p_C to p_M was the same as that of β_C to β_M in the community, that is, 91%. The calibrated transmission rates per minute of contact were as follows: p_M, 0.0086; p_C, 0.0078; p_H, 0.0058.

Modeling antibiotic exposure. In both the community and hospital models, we described antibiotic use through a global rate of exposure and its breakdown into antibiotic classes. Individuals could be exposed to one or several antibiotics, and treatment was assumed to occur independently of the staphylococcal colonization status. Furthermore, antibiotic exposure of a colonized patient cleared carriage of sensitive strains but had no impact on resistant strains.

We assumed that 60% of patients in the ICU (21) and 3% of individuals in the general community (3) were exposed to antibiotics at baseline. We also assumed that the distribution of prescribed antibiotics in these two settings was similar to that observed in France in 2002 (6) (Table 1). Antibiotics were classified into four groups, according to their activity on each staphylococcal phenotypic group (11) (Table 2): group A (e.g., ampicillin), to which all *S. aureus* strains were resistant; group B (e.g., methicillin), to which MSSA strains were susceptible and all MRSA strains were resistant; group C (e.g., clindamycin), to which MSSA and CA-MRSA strains were susceptible but HA-MRSA strains were resistant; and group D (e.g., vancomycin), to which all *S. aureus* strains were susceptible.

Data on antibiotic use in France: impact of the 2002 antibiotic reduction campaign. In the early 2000s, France faced growing problems with multiresistant bacteria and was identified as the country with the highest antibiotic consumption in Europe and one of the highest antimicrobial users worldwide—even though antibiotics were prescription drugs only. Thus, in November 2001, the French government decided on a nationwide campaign, aimed at both the general public and health care professionals, to promote better-targeted antibiotic use (3). The public

TABLE 1 Hospital and ambulatory antibiotic prescriptions in 2002 and 2003 in France[a]

Setting	Group	Prevalence of antibiotic exposure (%)		Relative change (%)	Antibiotic prescription rate, per 1,000 days		Relative change (%)
		2002	2003		2002	2003	
Hospital	Total	60	54	−10			
	A	14.49	12.53	−13.5			
	B	28.25	23.97	−15.1			
	C	9.91	10.13	+2.2			
	D	7.36	7.37	+0.2			
General community	Total				3.3	2.97	−10
	A				0.98	0.83	−14.8
	B				1.10	0.97	−12.4
	C				0.20	0.20	−0.3
	D				1.02	0.97	−4.7

[a] See reference 6. Total antibiotic use in hospitals was 419.6 and 377.6 defined daily doses per 1,000 patient days in 2002 and 2003, respectively. Total antibiotic use in the community was 32.0 and 28.9 defined daily doses per 1,000 inhabitants per day in 2002 and 2003, respectively. In both settings, total antibiotic use decreased 10% from 2002 to 2003.

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TABLE 2 Classification of prescribed antibiotics into groups A, B, C, and D according to the susceptibility of MSSA, CA-MRSA, and HA-MRSA[a]

Staphylococcal group	Susceptibility to the following antibiotic group[b]:			
	Group A	Group B	Group C	Group D
MSSA	−	+	+	+
CA-MRSA	−	−	+	+
HA-MRSA	−	−	−	+

[a] See reference 11.

[b] A plus sign indicates that the antibiotic group is effective against a particular staphylococcal phenotypic group, while a minus sign indicates antibiotic resistance. Examples of antibiotics belonging to the different groups are ampicillin for group A, methicillin for group B, clindamycin for group C, and vancomycin for group D. A detailed list of the antibiotic classes belonging to each of the 4 groups is available in reference 11.

campaign, started in 2002 and entitled "Antibiotics Are Not Automatic," was built with the primary aim of decreasing antibiotic prescriptions, particularly during the viral respiratory infection (VRI) epidemic season and among children, for whom >40% of the prescriptions are written. More information on the campaign is available in Text S1 in the supplemental material.

As a consequence, the number of ambulatory prescriptions decreased by 10% from 2002 to 2003, and again by 6% from 2003 to 2004. The number of hospital prescriptions also decreased by 10% between 2002 and 2003 (6). From 2004 to 2009, a slight increasing trend in prescription rates was noticed again in all settings.

In this study, we focused on the 2002-to-2003 period, during which the impact of the antibiotic reduction campaign was most apparent. The corresponding data, detailing the distribution of prescribed antibiotics, are shown in Table 1.

Modeling a reduction in antibiotic use. We investigated the impact of a 10% reduction in overall antibiotic use in both community and hospital settings over a period of 1 year on MRSA dissemination, starting from the French 2002 situation.

In order to assess the impact of changes in the distribution of prescribed antibiotics, we explored a wide array of hypothetical prescription patterns for the year 2003. The usage frequencies investigated for each antibiotic group (τ_A, τ_B, τ_C, and τ_D) ranged from 0 to 100% of overall antibiotic consumption, which was fixed at 10% less than its 2002 level. The values explored were 0, 20, 40, 60, 80, and 100%, leading to 56 antibiotic prescription scenarios (e.g., $\tau_A = 0\%$, $\tau_B = 20\%$, $\tau_C = 60\%$, and $\tau_D = 20\%$).

Analysis of model simulations. At the end of the simulated period, we calculated the frequencies of MSSA and MRSA carriers among all *S. aureus* carriers (MSSA and MRSA rates) in both the ICU and the general community. This outcome was determined as the average over 1,000 simulation replicates, in order to hold stochastic components of the model constant at their average values.

Formal computations. In order to better understand the relative part played by antibiotic use in hospitals and the community, we formally analyzed a simplified mathematical model of MRSA selection in these two coupled settings. This analysis is presented in Text S3 in the supplemental material.

RESULTS

Model validation: comparison with observed French data. The model-predicted reductions in MRSA frequency in hospital and community settings were compared to data from the European Antimicrobial Resistance Surveillance System (EARSS) for MRSA frequency in France between 2002 and 2003 (20).

Using the changes in antibiotic use reported in France over the 2002-to-2003 period (i.e., a 10% reduction overall in hospitals and the community; a detailed breakdown is reported in Table 1), the model predicted that the frequency of MRSA among *S. aureus* carriers in hospitals decreased from 39% to 36% (95% confidence interval [95% CI], 34.8%, 36.4%; a 7.7% reduction). As shown in Fig. 1, this is consistent with the data reported to the EARSS network for clinical MRSA rates in French ICUs over the same period: a decrease from 39% to 34% (95% confidence interval, 28.3% to 37.8%; a 12.8% reduction) in 2003.

Over the 2002-to-2003 period, the model-predicted MRSA frequency increased by 0.03% (95% confidence interval, 0.02%, 0.04%) in the community, while the predicted overall carriage of *S. aureus* increased by 6.22% (95% confidence interval, 5.62%, 6.81%) and 0.8028% (95% confidence interval, 0.8027%, 0.8030%), respectively, in hospitals and in the community.

Impact of changes in the distribution of antibiotic prescriptions. Figure 2 depicts the range of predicted MRSA frequencies in French ICUs and in the general community in 2003 following an overall 10% reduction in antibiotic use over 1 year, combined with each of the 56 investigated distributions of prescribed antibiotics. Although the overall decrease in antibiotic use was the same, the final MRSA frequency ranged from 12.4% to 59.5% in ICUs and from 3.4% to 7.4% in the community.

In order to study the impact of each group of antibiotics (A, B, C, or D, expressed as a fraction of total antibiotic exposure in 2003) on the frequency of MRSA in hospitals and in the community, we computed Kendall partial rank correlation coefficients (PRCCs) (Table 3).

PRCCs showed that when the consumption of antibiotics from group A (to which all *S. aureus* strains were resistant) or group D (effective on all *S. aureus* strains) increased, the frequency of MRSA decreased in both community and hospital settings (PRCCs for groups A and D were negative). The most important increase in MRSA frequency was observed when most prescribed antibiotics belonged to group B (effective on MSSA only) or C (effective on MSSA and CA-MRSA) (PRCCs for groups B and C were positive).

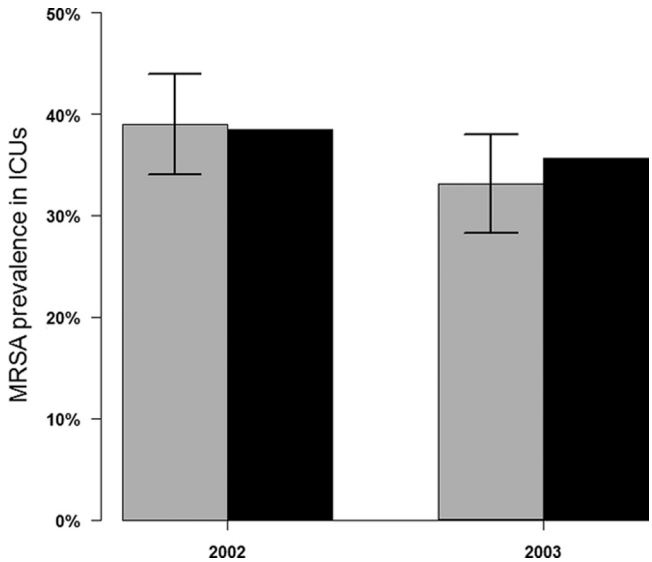

FIG 1 Validation of model predictions. Shown are the percentages of MRSA strains among *S. aureus* strains in French ICUs between 2002 and 2003. Data from the EARSS network (shaded bars) (error bars, 95% CI) are compared with model predictions (filled bars).

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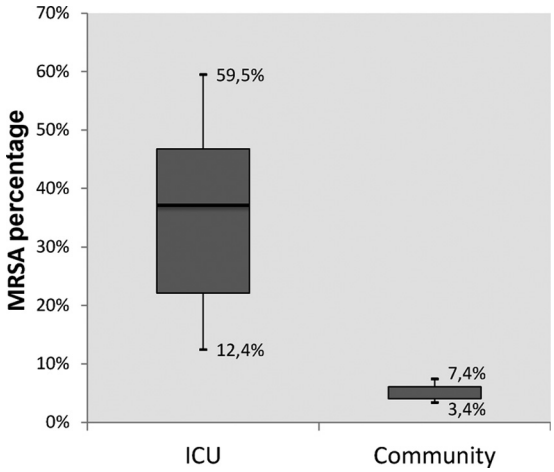

FIG 2 Impact of changes in the distribution of prescribed antibiotics on the effect of the antibiotic reduction campaign. Shown are box plots of predicted MRSA frequencies in French ICUs (left) and the general population (right) in 2003, starting from the observed frequency of MRSA strains in ICUs in 2002 (bold black line). A 10% reduction in antibiotic use over this 1-year period is combined with the investigated array of hypothetical changes in the distribution of prescribed antibiotics. Minimum and maximum predicted frequencies are shown, together with the 25th and 75th percentiles.

These results are explainable by competition phenomena (22): when most prescribed antibiotics belong to group A or D, none of the three phenotypic groups investigated has a selective advantage over the others, since all three are either resistant to most prescribed antibiotics or susceptible to most prescribed antibiotics. Hence, the epidemicity of each group drives its transmission dynamics, leading to increased circulation of MSSA and decreased circulation of MRSA (which is less easily transmitted).

In contrast, when most prescribed antibiotics belong to group B or C, antibiotic exposure provides MRSA with a selective advantage, since MSSA is then susceptible to most prescribed antibiotics, but either HA-MRSA (in the case of group C) or all MRSA strains are resistant to these antibiotics. Hence, the circulation of MRSA is enhanced.

In addition, overall staphylococcal carriage increased when most prescribed antibiotics belonged to group A and decreased when most prescribed antibiotics belonged to group D (see Table S3 in the supplemental material). Examination of the extreme scenarios where all prescribed antibiotics in 2003 belonged to a single group (A, B, C, or D) underlined the impact of group A antibiotics on the prevalence of MSSA carriage (see Fig. S3 in the supplemental material).

Interplay of hospital and community settings. We simulated the impact of observed changes in French hospitals between 2002 and 2003 (10% reduction in antibiotic use combined with observed changes in the distribution of prescribed antibiotics [Table 1]) while assuming that no change had occurred in the general community. The predicted frequency of MRSA in hospitals decreased by 9% over a year (95% confidence interval, −10.6%, −7.5%), a larger reduction than that obtained when changes in the general community were taken into account (Fig. 3a and b).

On the other hand, simulation of changes observed in the general community but not those observed in hospitals led to a much lower, 0.7% reduction in hospital MRSA frequency (95% confidence interval, −2.4%, +0.9%) (Fig. 3c).

In order to better understand the coupled dynamics of hospital and community settings, we analyzed a simplified mathematical model of the selection of MRSA in both settings under antibiotic exposure (see Text S3 and Fig. S5 in the supplemental material). The results illustrate that changes in antibiotic exposure in one setting may impact MRSA selection in the other setting, either amplifying the effect already observed, if antibiotic prescription patterns have a similar impact on MRSA selection, or countering this effect. This is illustrated by the French data, where changes in hospitals from 2002 to 2003 included a significant decrease in prescriptions of group B antibiotics in hospitals, selecting for less MRSA, but this effect was limited both by the increase in group C antibiotics and by the decrease in group A and D antibiotics in the community, which selected for more MRSA.

DISCUSSION

In this study, we investigated the impact of an overall reduction in antibiotic consumption on the selection of methicillin-resistant *S. aureus*, using a mathematical model of transmission in the community and the hospital and multiple antibiotic exposure. Our results underlined the importance of changes in the distribution of prescribed antibiotics occurring simultaneously with antibiotic use reduction. Model predictions reproduced the MRSA frequency in ICUs observed in France during the national campaign initiated in 2001 for reducing antibiotic use, while suggesting that uncoordinated changes in ambulatory and hospital prescriptions actually limited the impact of this antibiotic reduction campaign.

Model validation. Starting from the 2002 situation, our model was able to reproduce French data on MRSA frequency in ICUs in 2003. No further reduction in hospital antibiotic prescriptions was observed in the following years, leading us to focus on the first year.

As is often the case with surveillance data, the MRSA frequency reported by the EARSS network is based on invasive isolates only, while our model describes carriage. However, there is no large difference in France between the percentage of resistant strains among all samples collected in hospitals (invasive or noninvasive) and that reported by EARSS: for instance, in 2002, EARSS reported 33% MRSA strains in French hospitals, while a recently published study reported 32.2% MRSA strains among all clinical strains (23).

Data in the community are much sparser, so no external validation of the model-based predictions is possible. Longitudinal

TABLE 3 Impact of antibiotic use prescription patterns on the frequency of MRSA among all staphylococcal strains carried

Antibiotic group	$PRCC_{MRSA}$[a]	
	ICU	Community
A	−0.65	−0.69
B	0.71	0.79
C	0.60	0.63
D	−0.77	−0.77

[a] Partial rank correlation coefficients (PRCCs) between assumed 2003 exposures to antibiotic groups A, B, C, and D (expressed as fractions of total antibiotic exposure) and predicted MRSA frequencies, in ICUs and in the community. Positive PRCCs indicate that when the rate of consumption of antibiotics from a particular group increases, the frequency of MRSA among staphylococcal strains increases. Negative PRCCs indicate that when the rate of consumption of antibiotics from a particular group increases, the frequency of MRSA decreases. The results are significant at the 0.001 probability level.

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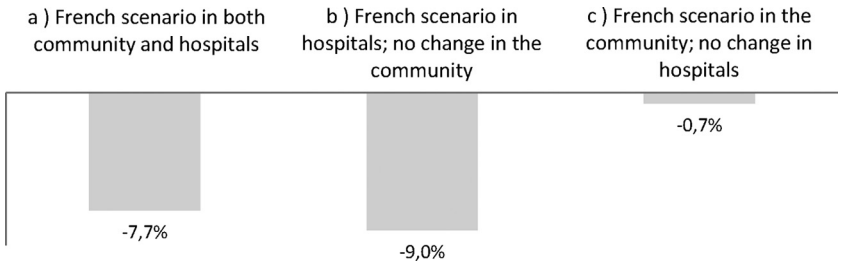

FIG 3 Predicted decreases in MRSA frequency in French ICUs between 2002 and 2003 in three different scenarios. (a) Observed French scenario: 10% reduction in antibiotic use in hospitals and the community according to the observed class-specific pattern of prescribed antibiotics (Table 1). (b) Ten percent reduction in hospital antibiotic use combined with observed changes in the distribution of prescribed antibiotics in hospitals, but no change in antibiotic consumption in the general community. (c) Ten percent reduction in ambulatory antibiotic use combined with observed changes in the distribution of prescribed antibiotics in the general community, but no change in antibiotic consumption in hospitals.

surveillance of staphylococcal carriage and resistance, in particular in the years following an antibiotic reduction campaign, should be undertaken to allow assessment of interventions.

Modeling approach. Mathematical models have been widely used to improve our understanding of the epidemiology of antibiotic resistance, as well as to evaluate various control strategies in hospital and community environments (24, 25). In this paper, we used an agent-based model for modeling the spread of *S. aureus* in a hospital setting. This approach allows the modeling of stochastic events and heterogeneous individual behaviors in a small hospital environment, although increasing the number of behavioral details leads to high computational intensity.

In order to model the interaction between the hospital and community environments without increasing the already high computational demands of the model, we coupled the NosoSim hospital model (11, 16) with a compartmental deterministic model of *S. aureus* transmission in a community. In contrast with the agent-based approach, this simple model assumes compartment homogeneity and deterministic interactions between individuals and is well suited for modeling transmission dynamics in large populations.

One limitation of our modeling approach concerns the scale of the modeled populations. Within the hospital, we modeled a single ICU-type 20-bed ward. Although this choice was justified by several studies suggesting that ICUs act as incubators for MRSA and other antibiotic-resistant pathogens within hospitals, in future studies it would be interesting to extend the model to a whole hospital, taking into account transfers between wards and ward-specific data. However, for this purpose, ward-specific data on antibiotic use and MRSA frequency would have to be available.

In addition, the community population we modeled was approximately the size of the city of Paris, France. The relative sizes of the coupled community and hospital wards may obviously impact model predictions. With respect to previously published models coupling hospital and community settings (17, 26), our model tended to minimize the impact of the hospital setting on the general community. However, the theoretical model developed in the supplemental material shows that the influence of changes in antibiotic exposure in one setting on antibiotic resistance in the other still holds, even if we consider populations of different sizes (see Text S3 in the supplemental material).

Modeling *S. aureus* colonization. Recent epidemiological studies show that the three main staphylococcal phenotypic groups cocirculating worldwide are MSSA, CA-MRSA, and HA-MRSA, with a high prevalence of HA-MRSA in hospitals and a rising prevalence of CA-MRSA in the community—as well as in hospitals, most notably in the United States, but also in other countries (13). In order to reproduce the coupled dynamics of *S. aureus* colonization between hospitals and the general population, we included all three phenotypic groups in our model.

This called for two hypotheses. First, carriage studies suggest that MSSA and MRSA compete for human colonization, although simultaneous carriage may be observed (27). In the hospital model, simultaneous carriage was allowed, although the probability of acquisition of another *S. aureus* strain was reduced by 50% in already-colonized individuals to reflect competition between strains (27). However, in order to simplify the community model, we did not allow for any simultaneous carriage in that setting.

Second, model parameters included transmission rates for all three phenotypic groups. Epidemiological data suggest that CA-MRSA, like MSSA, is more transmissible than HA-MRSA (28), but to date, no study has estimated CA-MRSA transmissibility. Here, we chose to assume that the ratio between the transmissibility of CA-MRSA and that of MSSA was the same in hospitals and the general population, and we calibrated all three transmission rates in order to reproduce the observed carriage prevalence in both settings.

Antibiotic use. We reviewed the systemic antimicrobials prescribed in hospitals and the community in France from 2002 to 2003. The susceptibility of MSSA, CA-MRSA, and HA-MRSA to each of these antimicrobials was assessed. Variations in the susceptibility of CA-MRSA and HA-MRSA, e.g., to macrolides or fluoroquinolones in the case of CA-MRSA, have been reported (11). Here, we based our classification on the best-case scenario for antibiotic efficacy, meaning that CA-MRSA and HA-MRSA were assumed to be susceptible to antibiotics for which such variations have been reported. Other assumptions might change our quantitative predictions of MRSA frequency but not the importance of antibiotic class-specific changes for predicting the impact of an antibiotic reduction intervention.

Age distribution. Several studies suggest that there are differences in the age distributions of CA- and HA-MRSA infections. CA-MRSA infections tend to occur in younger patients, while HA-MRSA are more frequently isolated from older individuals who are exposed to the health care setting (14). Little is known about the age distribution of CA-MRSA and HA-MRSA carriers, but carriage of HA-MRSA is not limited to older patients. Recently, a study of children attending child care centers in North

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Carolina and Virginia detected 47% CA-MRSA and 53% HA-MRSA among all MRSA strains identified (29).

All in all, most of the differences observed between the age distributions of CA-MRSA and HA-MRSA carriers appear to be related to the risk of recent hospitalization, which is higher for older individuals. Our model takes this into account by assuming a 5-times-higher hospital admission rate for HA-MRSA carriers.

Furthermore, the level of reduction in antibiotic use during a campaign may differ significantly between age groups, both in terms of volume and in terms of the distribution of reductions among antibiotic classes. In this study, we used French data on antibiotic use between 2002 and 2003, following the 2001 antibiotic reduction campaign. While these data included detailed information on the consumption of each antibiotic class in both hospital and community settings, it was not age specific, although reports from France suggested that the reduction in antibiotic use occurred mostly in young children (3).

Such age differences may have impacted our predictions. However, we do not feel that this compromises our results; to the contrary, we would argue that our main message is strengthened by these potential differences. Indeed, our model, which is not structured by age, already predicts that the impacts of an antibiotic reduction campaign on MRSA selection may differ wildly according to scenarios of class-specific changes in antibiotic use. Taking age into account would lead to a wider range of scenarios and hence to even more variability in the predicted MRSA prevalence. This could be investigated in further studies using an age-structured model of staphylococcal carriage and transmission, provided concomitant age-specific and antibiotic class-specific antibiotic use data become available.

Conclusions. In conclusion, this study strongly suggests that although reducing the number of antibiotic prescriptions may impact the dissemination of MRSA among *S. aureus* strains, it is not by itself sufficient to control antibiotic resistance if special attention is not paid to the distribution of prescribed antibiotics. Actions taken in different settings (e.g., hospitals and the general community) should also be coordinated. This underlines the importance of surveillance data on both antibiotic class-specific changes in antibiotic use and antibiotic resistance in the years following an antibiotic reduction campaign.

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REFERENCES

1. **Barbosa TM, Levy SB.** 2000. The impact of antibiotic use on resistance development and persistence. Drug Resist. Updat. **3:**303–311.
2. **Charbonneau P, Parienti JJ, Thibon P, Ramakers M, Daubin C, du Cheyron D, Lebouvier G, Le Coutour X, Leclercq R.** 2006. Fluoroquinolone use and methicillin-resistant *Staphylococcus aureus* isolation rates in hospitalized patients: a quasi experimental study. Clin. Infect. Dis. **42:**778–784.
3. **Sabuncu E, David J, Bernede-Bauduin C, Pepin S, Leroy M, Boelle PY, Watier L, Guillemot D.** 2009. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002–2007. PLoS Med. **6:**e1000084. doi:10.1371/journal.pmed.1000084.
4. **Tacconelli E, De Angelis G, Cataldo MA, Pozzi E, Cauda R.** 2008. Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. J. Antimicrob. Chemother. **61:**26–38.
5. **Huttner B, Goossens H, Verheij T, Harbarth S.** 2010. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. Lancet Infect. Dis. **10:**17–31.
6. **Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS).** June 2011, posting date. Dix ans d'évolution des consommations d'antibiotiques en France. http://ansm.sante.fr/var/ansm_site/storage/original/application/263354f238b8f7061cdb52319655ca07.pdf.
7. **Madaras-Kelly KJ, Remington RE, Lewis PG, Stevens DL.** 2006. Evaluation of an intervention designed to decrease the rate of nosocomial methicillin-resistant *Staphylococcus aureus* infection by encouraging decreased fluoroquinolone use. Infect. Control Hosp. Epidemiol. **27:**155–169.
8. **Parienti JJ, Cattoir V, Thibon P, Lebouvier G, Verdon R, Daubin C, du Cheyron D, Leclercq R, Charbonneau P.** 2011. Hospital-wide modification of fluoroquinolone policy and meticillin-resistant *Staphylococcus aureus* rates: a 10-year interrupted time-series analysis. J. Hosp. Infect. **78:**118–122.
9. **Harbarth S, Samore MH.** 2008. Interventions to control MRSA: high time for time-series analysis? J. Antimicrob. Chemother. **62:**431–433.
10. **Burke JP.** 1998. Antibiotic resistance–squeezing the balloon? JAMA **280:**1270–1271.
11. **Kardas-Sloma L, Boelle PY, Opatowski L, Brun-Buisson C, Guillemot D, Temime L.** 2011. Impact of antibiotic exposure patterns on selection of community-associated methicillin-resistant *Staphylococcus aureus* in hospital settings. Antimicrob. Agents Chemother. **55:**4888–4895.
12. **Kajita E, Okano JT, Bodine EN, Layne SP, Blower S.** 2007. Modelling an outbreak of an emerging pathogen. Nat. Rev. Microbiol. **5:**700–709.
13. **Stefani S, Chung DR, Lindsay JA, Friedrich AW, Kearns AM, Westh H, Mackenzie FM.** 2012. Meticillin-resistant *Staphylococcus aureus* (MRSA): global epidemiology and harmonisation of typing methods. Int. J. Antimicrob. Agents **39:**273–282.
14. **David MZ, Daum RS.** 2010. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. Clin. Microbiol. Rev. **23:**616–687.
15. **Mera RM, Suaya JA, Amrine-Madsen H, Hogea CS, Miller LA, Lu EP, Sahm DF, O'Hara P, Acosta CJ.** 2011. Increasing role of *Staphylococcus aureus* and community-acquired methicillin-resistant *Staphylococcus aureus* infections in the United States: a 10-year trend of replacement and expansion. Microb. Drug Resist. **17:**321–328.
16. **Temime L, Kardas-Sloma L, Opatowski L, Brun-Buisson C, Boëlle P-Y, Guillemot D.** 2010. NosoSim: an agent-based model of nosocomial pathogens circulation in hospitals. Procedia Comput. Sci. **1:**2245–2252.
17. **Cooper BS, Medley GF, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Duckworth G, Lai R, Ebrahim S.** 2004. Methicillin-resistant *Staphylococcus aureus* in hospitals and the community: stealth dynamics and control catastrophes. Proc. Natl. Acad. Sci. U. S. A. **101:**10223–10228.
18. **Ficca G, Chauvel M, de Mouy D.** 2006. Prevalence of community-acquired methicillin-resistant *Staphylococcus aureus*. Med. Mal. Infect. **36:**207–212. (In French.)
19. **Thibaut S, Caillon J, Lepelletier D, Lombrail P, Potel G, Ballereau F.** 2010. Who are the carriers of MRSA in the community? A prospective study in the Pays de la Loire region of France. Clin. Microbiol. Infect. **16:**915–920.
20. **European Antimicrobial Resistance Surveillance System (EARSS).** August 2003, posting date. Annual report 2002. EARSS, Bilthoven, Netherlands. http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Documents/2002_EARSS_Annual_Report.pdf.
21. **Patry I, Leroy J, Henon T, Talon D, Hoen B, Bertrand X.** 2008. Evaluation of antibiotic prescription in a French university hospital. Med. Mal. Infect. **38:**378–382. (In French.)
22. **Muto CA, Jernigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, Farr BM.** 2003. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and enterococcus. Infect. Control Hosp. Epidemiol. **24:**362–386.
23. **Jarlier V, Trystram D, Brun-Buisson C, Fournier S, Carbonne A, Marty L, Andremont A, Arlet G, Buu-Hoi A, Carlet J, Decre D, Gottot S, Gutmann L, Joly-Guillou ML, Legrand P, Nicolas-Chanoine MH, Soussy CJ, Wolf M, Lucet JC, Aggoune M, Brucker G, Regnier B.** 2010. Curbing methicillin-resistant *Staphylococcus aureus* in 38 French hospitals through a 15-year institutional control program. Arch. Intern. Med. **170:**552–559.

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24. **Opatowski L, Guillemot D, Boelle PY, Temime L.** 2011. Contribution of mathematical modeling to the fight against bacterial antibiotic resistance. Curr. Opin. Infect. Dis. **24:**279–287.
25. **Donker T, Wallinga J, Grundmann H.** 2010. Patient referral patterns and the spread of hospital-acquired infections through national health care networks. PLoS Comput. Biol. **6:**e1000715. doi:10.1371/journal.pcbi.1000715.
26. **Smith DL, Dushoff J, Perencevich EN, Harris AD, Levin SA.** 2004. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: resistance is a regional problem. Proc. Natl. Acad. Sci. U. S. A. **101:**3709–3714.
27. **Huang SS, Datta R, Rifas-Shiman S, Kleinman K, Placzek H, Lankiewicz JD, Platt R.** 2011. Colonization with antibiotic-susceptible strains protects against methicillin-resistant *Staphylococcus aureus* but not vancomycin-resistant enterococci acquisition: a nested case-control study. Crit. Care **15:**R210. doi:10.1186/cc10445.
28. **DeLeo FR, Otto M, Kreiswirth BN, Chambers HF.** 2010. Community-associated meticillin-resistant *Staphylococcus aureus*. Lancet **375:**1557–1568.
29. **Miller MB, Weber DJ, Goodrich JS, Popowitch EB, Poe MD, Nyugen V, Shope TR, Foster DT, Miller JR, Kotch J.** 2011. Prevalence and risk factor analysis for methicillin-resistant *Staphylococcus aureus* nasal colonization in children attending child care centers. J. Clin. Microbiol. **49:**1041–1047.

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