Controlling methicillin-resistant Staphylococcus aureus: Quantifying the effects of interventions and rapid diagnostic testing

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Edited by Simon A. Levin, Princeton University, Princeton, NJ, and approved January 29, 2006 (received for review November 21, 2005)

Control of nosocomial transmission of methicillin-resistant Staphylococcus aureus (MRSA) has been unsuccessful in most countries. Yet, some countries have maintained low endemic levels by implementing nationwide MRSA-specific infection control measures, such as “search & destroy” (S&D). These strategies, however, are not based on well designed studies, and their use in countries with high levels of endemicity is controversial. We present a stochastic three-hospital model and an analytical one-hospital model to quantify the effectiveness of different infection control measures and to predict the effects of rapid diagnostic testing (RDT) on isolation needs. Isolation of MRSA carriers identified by clinical cultures is insufficient to control MRSA. However, combined with proactive search (of high-risk patients on admission and/or contacts of index patients), it will maintain prevalence levels <1%. Concerted implementation of S&D in countries with high nosocomial endemicity reduces nosocomial prevalence to <1% within 6 years. Stepwise implementation of control measures can reduce isolation capacities needed. RDT can markedly enhance isolation and screening efficacy; and (iv) MRSA-prevalence levels can be reduced to <1% in high-endemic settings by S&D or a stepwise approach to interventions. RDT can markedly enhance feasibility.

Conflict of interest statement: No conflicts declared.

Abbreviations: HCW, healthcare worker; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus; S&D, search & destroy; RDT, rapid diagnostic testing.

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PNAS

5620–5625 | PNAS | April 4, 2006 | vol. 103 | no. 14

www.pnas.org/cgi/doi/10.1073/pnas.0510077103
to an extramural population, with a possibility of interward transfer ($P = 0.02$ per patient per day) (Fig. 1a).

Length of stay does not depend on colonization status and is exponentially distributed with a mean of 3 and 7 days for ICU and regular wards, respectively. Five percent of admissions are from other hospitals, and all patients are discharged to their own extramural population. A high-risk population (10% of total catchment population), characterized by a higher hospitalization rate (1 per year vs. 0.1 per year), constitutes, on average, half of the hospital population. All deaths are immediately replaced by noncolonized individuals, who enter the extramural population in the same community and the same group (high-risk group or non-high-risk group), thereby ensuring a constant population size. During hospitalization, 2.9% of the hospitalized patients die. The death rate within ICUs is higher as compared with regular wards (ratio 3:1). In the extramural population, life expectancy, given that the patient is not hospitalized, is exponentially distributed. The overall life expectancy (including death during hospitalization) is 20 and 78 years for the high-risk and non-high-risk population, respectively.

Two types of HCWs (HCW1 and HCW2) are incorporated. HCW1 interact with patients in a single ward. Staff:patient ratios are 1:1 in ICU and 5:18 in general wards, respectively. Five percent of admissions are from other hospitals, and all patients are discharged to their own extramural population. A high-risk population (10% of total catchment population), characterized by a higher hospitalization rate (1 per year vs. 0.1 per year), constitutes, on average, half of the hospital population. All deaths are immediately replaced by noncolonized individuals, who enter the extramural population in the same community and the same group (high-risk group or non-high-risk group), thereby ensuring a constant population size. During hospitalization, 2.9% of the hospitalized patients die. The death rate within ICUs is higher as compared with regular wards (ratio 3:1). In the extramural population, life expectancy, given that the patient is not hospitalized, is exponentially distributed. The overall life expectancy (including death during hospitalization) is 20 and 78 years for the high-risk and non-high-risk population, respectively.

The model was investigated with Monte Carlo simulations. All analyses are based on 1,000 simulations for a 30-year time period after a burn-in period of 10 years to guarantee the correct distribution over the high-risk and the non-high-risk group.

**Dynamics of MRSA**

Nosocomial acquisition of MRSA occurs through patient-to-patient transmission (i.e., cross-transmission via transiently colonized HCWs) or through transmission of MRSA from persistently colonized HCWs (Fig. 1b), with cross-transmission occurring eight times more frequently than transmission from a persistently colonized HCW in high-endemicity settings. Transmission occurs according to the mass action principle, with mass action being 20 times higher for transmission within a single unit (for both transmission possibilities) as compared with the global mass action term for the hospital at large (e.g., see ref. 15). As compared with regular wards, transmission risk is higher in ICUs (ratio 3:1) because of higher patient susceptibility, more intense patient–HCW contacts, and higher antibiotic use, which may give resistant bacteria an advantage in colonizing patients compared with nonresistant bacteria.

Once treated in isolation, transmission and acquisition (in case of false alarm) are equally prevented with efficacy $\pi$. Hospitals can “infect” each other by transfer of MRSA-colonized patients. To mimic the Dutch situation, 0.0038 of admissions come from endemic settings (i.e., foreign hospitals), with 4.7% being colonized with MRSA (11). The ultimate average nosocomial endemic MRSA prevalence without interventions is set at 15%. This prevalence is based on determination of endemic prevalences (16–19) as well as on proportions of MRSA (40% to 50%) among staphylococcal bloodstream infections (EARSS and NNIS data), with 30% of the hospital population carrying $S. aureus$.

In the extramural setting, colonization will disappear at a fixed rate, with an average duration of colonization, in absence of readmission, of 370 days (20). Patient-to-patient transmission of hospital-related MRSA strains in the extramural setting is considered of minor importance (21) and, therefore, is neglected.

The value of the transmission parameters was determined by fitting the endemic curve to observed curves in the U.S. and the U.K., leading to nosocomial prevalence levels of 15%. The relative importance of the individual transmission routes, as described here, however, was maintained. The compartmental model structure and the depletion of susceptibles within a unit complicate definition and calculation of $R_c$, defined as the average number of secondary cases resulting from one primary case when other patients are susceptible during a single hospital admission of the primary case (22). Hence, we obtained several values for $R_c$, depending on the initial ward and the superspreader status of the patient.

**Interventions**

The per patient probability per day to detect MRSA colonization (or infection) by way of clinical microbiological cultures is 0.03, which is based on the average time between admission and detection of unexpected colonization (M.J.M.B. and M.C.J.B., unpublished data). Measures of S&D include the following [guidelines from the Dutch Workingparty Infection Prevention at www.wip.nl/UK/free_content/Richtlijnen/MRSA(1).pdf]:

I. Identified MRSA carriers are treated in single rooms with barrier precautions (i.e., isolation).

II. High-risk patients (previously identified MRSA carriers or those transferred from endemic settings) are screened for MRSA colonization upon admission and precautionarily isolated, with 0.88 efficacy; i.e., 12% are not isolated (based on ref. 23). Isolation instructions are only withdrawn upon negative results of conventional microbiological cultures.

III. All patients in a single ward will be screened for MRSA colonization in case of an unexpected finding of MRSA colonization (i.e., in a patient not treated in isolation).

IV. In addition to measure III, all HCWs in the affected ward will be screened for MRSA colonization, and colonized HCWs will be furloughed from working until decontamination has been achieved.

V. Wards will be closed for new admissions when there is evidence of MRSA transmission among patients (1 MRSA carrier) and will remain closed until isolation capacity is sufficient for all carriers.

VI. MRSA colonization is eradicated at the end of hospitalization with an efficacy of 0.25 (24, 25).

Hand disinfection is not specifically mentioned as an intervention, because adherence should be high, regardless of colonization status of patients. Yet, the effects of increased adherence to hand hygiene in general can be analyzed by reducing the likelihood of transmission with the same factor for all transmission routes.

**RDT**

Conventional microbiological cultures are assumed to be 100% reliable but require quite some time (up to 5 days; ref. 11). RDT will determine colonization status within a few hours and will reduce unnecessary precautionary isolation days of high-risk patients screened on admission. It will also lead to a faster detection of spread among contact patients and HCWs, however, possibly at the
The isolation of identified carriers as a single control measure (measure I, with 100% efficacy) will not be sufficient to maintain endemic levels <1%, although endemic levels will rise slowly (to 1.5% in 30 years). The addition of either screening and precautionary isolation of high-risk patients (measure II) or screening of contact patients in case of the identification of an unexpected index patient (measure III) will be sufficient to maintain low endemicity (Fig. 3a). Additional measures such as screening of HCWs in case of the identification of an unexpected index patient (measure IV), temporary closing of wards (measure V), and eradication of carriage (measure VI) offer little extra benefit. Stealth dynamics and stochastic control failure, as described by Cooper et al. (22), are equally relevant in our simulations but are not described in detail here. In addition, the efficacy of intervention measures depends critically on interventions taken by other hospitals, also confirming previous findings (27, 28).

Results

Low-Endemicity Settings. Starting from low MRSA-prevalence levels and without any infection control measure, average nosocomial endemic MRSA prevalence will increase in all simulations from almost absent (<1%) to saturation (15%) within a period of ~10 years (Fig. 2). This rise may be delayed considerably because of stochastic effects (up to 10 years). Therefore, the mean prevalence in 1,000 simulations rises more slowly to saturation than the prevalence in a typical individual simulation (Fig. 2a). The extramural prevalence remains <2%, in line with longitudinal epidemiological observations in both the U.S. and U.K. (26). Ultimately, MRSA prevalence will be 9% within the high-risk population and 18% in the extramural and intramural populations, respectively.

Effect of Individual Components of S&D. The isolation of identified carriers as a single control measure (measure I, with 100% efficacy)
is very small does isolating patients with a history of MRSA upon admission become less effective, whereas the screening of contact patients becomes more effective. A higher relative influence of persistently colonized HCWs on the spread of MRSA has no major consequences when duration of persistent colonization (1 year) is shorter than the time scale of a decrease in the prevalence levels within hospitals (several years), although the effect of screening of HCWs in the affected wards (measure IV) will increase.

**RDT.** The average number of patients in isolation per day in the University Medical Center Utrecht from 1999 to 2004 was 1.88, which coincides well with the prediction of the simulation model (2.0). If RDT would perform as well as conventional culture techniques (sensitivity = 1; specificity = 1), the number of isolation days needed for the full S&D policy in a low-endemicity setting would be reduced by >90%. Obviously, even with less-optimal test characteristics, RDT will reduce the number of isolation days in the short term, because it may take years to establish high-endemic levels, even without infection control measures.

RDT will reduce unnecessary precautionary isolation days of high-risk patients. However, with suboptimal test characteristics, RDT may fail to identify some of the MRSA carriers among contact patients (because of false-negative RDT results) and may identify noncarriers as MRSA carriers (because of false-positive RDT results). Both effects will balance for certain test characteristics, and these lines are depicted. The upper line represents the scenario in which conventional cultures are used as back-up; the lower line is the scenario without back-up cultures. Above the lines, the use of RDT will increase the number of isolation days needed. Below the lines, reduction of isolation days will dominate and the net effect will thus be fewer isolation days. (Fig. 5). Above the lines, the use of RDT will increase the number of isolation days needed. Below the lines, reduction of isolation days will dominate and the net effect will thus be fewer isolation days. (Fig. 5). Above the lines, the use of RDT will increase the number of isolation days needed. Below the lines, reduction of isolation days will dominate and the net effect will thus be fewer isolation days. (Fig. 5).

Control Strategies for High-Endemiaity Settings. In a high-endemicity setting, any intervention (measures I–VI) will reduce endemic prevalence, although average time to reach a certain threshold level will differ considerably (Fig. 5b). Typically, a two-phase reduction is seen. During the first phase (first weeks), endemic levels will rapidly decrease as a result of lower transmission of MRSA because of interventions. After the initial phase, endemic levels will further decrease because of the feedback-loop dynamics with the community, which are as follows: reduced nosocomial spread leads to a lower extramural prevalence, lower fractions of patients colonized on admission, and lower endemic levels in the hospital.

The isolation of MRSA patients identified by clinical cultures as the only intervention can reduce endemic prevalence to 5% within 15 years. Yet, the efficacy of isolation will be crucial (Fig. 6a). With isolation efficacy of 50%, ultimate prevalence levels will remain >10%. Addition of other preventive measures will markedly enhance MRSA control. Screening of contact patients (with precautionary isolation) of an index case (measures I + III) is more effective than screening of high-risk patients on admission (measures I + II), because it will take, on average, 8 and 15 years, respectively, to reach endemic levels <1% (Fig. 6b). Again, we assumed 100% isolation efficacy. The application of the full S&D policy (measures I–VI) will reduce endemic prevalence levels to <1% within 6 years. Precautionary isolation will require a large isolation capacity in high-endemicity settings (Fig. 6d and, therefore, may not be feasible. Instead, several MRSA patients could be cohorted in designated rooms, although this measure will probably reduce the efficacy of isolation. Hence, we propose two alternative approaches for high-endemicity settings, namely cohorting multiple patients and gradual implementation of intervention measures. (Screening of HCWs, eradication of colonization, and closing of wards added little to ultimate prevalence levels and, therefore, are not shown.) In the first approach, the initial efficacy of isolation is set at 50% and only after 5 years is the efficacy increased to 80%, e.g., by switching from cohorting of multiple MRSA patients in single rooms to isolating individual patients in single beds. In this scenario, combinations of measures I + II, I + III, and I + II + III will reduce prevalence levels to levels <2% within 30, 31, and 18 years, respectively (Fig. 6b). Regimens, including screening of contacts (measure III), require the highest isolation capacity (Fig. 6e) but will lead to a faster decline in prevalence levels as compared with measures I + II. The total number of isolation days per hospital required over 30 years is 132,000, 102,000 and 112,000 for measures I + II, I + III, and I + II + III, respectively.

In the second approach, only measure I is used with an efficacy of 80% during the first 5 years. After 5 years, the policy is extended to measures I + II, I + III, or I + II + III (efficacy of isolation remains at 80%). Naturally, only the combined approach of three measures will reduce prevalence levels to <1% (Fig. 6c). This policy
would reduce the required isolation capacity at the start of interventions from 6% of hospital beds in approach 1 to 3% in approach 2. After 5 years, 3% of hospital beds would be needed for isolation with both approaches (Fig. 6f). The total number of isolation days per hospital over 30 years with this approach would be 109,000, 82,000, and 84,000 for measures I + II, I + III, and I + II + III, respectively.

RDT in High-Endemivity Settings. The effects of RDT were determined for the two stepwise approaches introduced in the Control Strategies for High-Endemivity Settings. The screening of high-risk patients and contact patients is based on RDT with sensitivity of 90% and specificity of either 90% or 100%. RDT with a specificity of 100% reduces peak isolation capacity by 20% (Fig. 5c) and reduces prevalence levels faster than when infection control is based on conventional cultures (Fig. 5b). A specificity of 90%, however, would increase the number of isolation beds needed, as compared with the strategy without RDT. The use of RDT in combination with conventional microbiological culture methods offers little additional benefit.

Discussion

The results of our simulation model do the following:

(i) strongly suggest causality between S&D and the low prevalence of MRSA in hospitals and community;
(ii) indicate that isolating MRSA carriers identified by clinical cultures as a single infection control measure, although useful, is unlikely to be sufficient to eliminate or prevent endemicity;
(iii) suggest that a combined approach of screening high-risk patients upon admission plus the screening of contact patients when an index patient is identified is responsible for the success of S&D; and
(iv) suggest that with full S&D, or one with a stepwise approach toward this policy, high nosocomial endemicity levels can be reduced to levels <1% within 6–12 years.

Furthermore, RDT is likely to reduce isolation needs considerably in low-endemivity settings and will enhance the decline in prevalence levels in high endemicity settings, although without reducing isolation needs on the short term.

Our findings strongly support the use of S&D to control nosocomial spread of MRSA and indicate that elimination of MRSA in high-endemivity settings is likely achievable with targeted approaches (29). Successful elimination can be enhanced by a concerted approach of healthcare organizations, and feasibility of these measures can be improved by using RDT. In our model, we sought to mimic hospital and population structures as reliably as possible, by using empirical data from a single medical center where possible. Naturally, model construction will always involve simplifications, but valuable information on trends and dynamics can be gained. Because nationwide prospective trials to evaluate these measures will never be performed, mathematical modeling, taking intramural and extramural dynamics and stochastic effects into account, offers the best approach.

Two other mathematical models have been used to investigate transmission dynamics of MRSA with and without infection control measures and with integration of intramural and extramural transmission dynamics, although with important differences in modeling approaches (22, 28, 29). Unique in our approach is the compartmental structure of hospitals, which reflects reality more closely and allows modeling of specific intervention measures. Smith et al. (28), Pan et al. (29), and Cooper et al. (22) used models in which hospitals were reflected as a single unit with transmission occurring according to the mass-action principle. The representation of individual wards already affects transmission dynamics, which mimics clinical observations that outbreaks predominantly occur within single wards. Other unique aspects of our approach are that persistent carrierge among HCWs and heterogeneity in infectivity of patients have been taken into account and that a simplified one-hospital model was used to quantify effectiveness of each of the components of S&D. The latter also allowed sensitivity analyses of other critical variables. Further differences include the way in which intervention strategies are evaluated.

Smith et al. (28) and Pan et al. (29) used a deterministic model with a single unspecified intervention strategy that affects the transmission rate (e.g., improved hand hygiene), whereas Cooper et al. (22) considered isolation of patients as identified by clinical cultures as the only intervention measure. Screening on admission of high-risk patients was evaluated in a simulation model of a single ward without feedback loop and with a constant fraction of patients colonized on admission, thereby neglecting interaction between intramural and extramural dynamics (30).

Cooper et al. (22) concluded from their model that prompt and effective isolation of MRSA carriers (identified as such by clinical cultures) can contribute to control by reducing transmission, but its efficacy would be limited by shortage of isolation capacity (22). Our predictions about this single intervention are even less optimistic. Although this measure will maintain low MRSA levels in low-endemivity settings for some time, it is unlikely to eliminate MRSA in high-endemivity settings (although substantial reduction can be obtained). Indeed, the only randomized trial on this intervention in such a setting failed to control transmission of MRSA (17).

Two important differences in parameter values between Cooper’s model (22) and ours must be discussed. First, we have used a lower detection rate of MRSA through clinical isolates (0.03 vs. 0.1; ref. 22), motivated by data from our own hospital. A higher detection rate, for instance through surveillance cultures, would dramatically enhance efficacy of control measures (Fig. 4d). The second difference is that we did not assume that MRSA colonization prolongs the length of stay. The additional length of stay attributable to MRSA bacteremia in studies adequately controlling for duration of exposure, have ranged from 0 to 2 days (33). Yet, the majority of colonized patients will not develop systemic infections, and colonization in itself is unlikely to prolong the length of stay.

Increased adherence to hand hygiene practices clearly would effect transmission of MRSA, because it would reduce the general transmission parameter and, thereby, prevalence levels (see Fig. 9) and critical basic reproduction ratios (Fig. 4b). Because unchanged hand disinfection practices were assumed in all analyses of our study, our findings must be considered as conservative estimates of efficacy that could be enhanced by simultaneous enforcement of better hand hygiene.

Decolonization of MRSA carriers within hospitals is only successful occasionally ($P = 0.25$; refs. 24 and 25). In essence, decolonization after discharge and screening of previously colonized patients upon readmission have similar effects, because both measures prevent colonized patients to transmit when readmitted. Therefore, as part of S&D, more effective decolonization after hospital discharge would only have moderate effects on transmission dynamics, even though the number of isolation days needed could be reduced considerably. Naturally, more successful eradication of MRSA carriage during hospital stay would dramatically contribute to the efficacy of control measures.

Although we have tried to stay with our model as close to real MRSA dynamics as possible, it should be explicitly stated that our findings represent average behavior of 1,000 simulations, with large variations attributable to stochastic processes. The latter is especially important for low-endemivity settings, because interventions may fail to control MRSA. Moreover, we had to make “guessimates” for some parameters (Table 1) such as the fraction of superspreaders (0.01) and their increased capacity to spread MRSA (10 times), the intrahospital transfer rate (0.02 per patient per day),
Table 1. Parameters in the models

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Source</th>
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</thead>
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<tr>
<td>Fraction superspreaders</td>
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<tr>
<td>Relative infectivity of superspreaders</td>
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<td>10 A</td>
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<tr>
<td>Interverward transfer (per patient/day)</td>
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<td>0.02 A</td>
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<td>Average LOS in ICU</td>
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<td>Average LOS in regular ward</td>
<td></td>
<td>7 days</td>
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<tr>
<td>Average LOS in simplified model</td>
<td></td>
<td>d 8 days</td>
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<tr>
<td>Admission from other hospitals</td>
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<tr>
<td>High-risk patients</td>
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<tr>
<td>Rel. admission rate of high-risk patients</td>
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<tr>
<td>Staff:patient ratio in ICU</td>
<td></td>
<td>1:1</td>
<td>U</td>
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<tr>
<td>Staff:patient ratio in regular ward</td>
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<td>5:18 U</td>
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<tr>
<td>Ratio of cross-transmission to HCW transmission</td>
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<td>Mass action term unit vs. hospital</td>
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<td>[11]</td>
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<td>Extramural acquisition from different populations</td>
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<tr>
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U, parameters estimated from data from University Medical Center Utrecht; A, parameters based on assumptions and, therefore, subjected to a sensitivity analysis; LOS, length of stay.

We thank Hajo Grundmann, Richard Wenzel, Robert Weinstein, Jan Kluytmans, and Ben Cooper for stimulating discussions. Financial support was provided by Nederlandse Organisatie voor Wetenschappelijk Onderzoek Grants ZonMW 2100.0051 and CLS 635.100.002.