Mathematical studies on nosocomial spread of antibiotic-resistant bacteria

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Ph.D. Thesis Utrecht University, December 2017
ISBN 978-90-393-6907-4

Mathematical studies on nosocomial spread of antibiotic-resistant bacteria

Wiskundige studies over verspreiding van antibioticaresistente bacteriën in ziekenhuizen

(met een samenvatting in het Nederlands)

Математические исследования нозокомиального распространения антибиотикорезистентных бактерий

(с резюме на русском языке)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 5 december 2017 des middags te 12.45 uur

door

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geboren op 14 maart 1976

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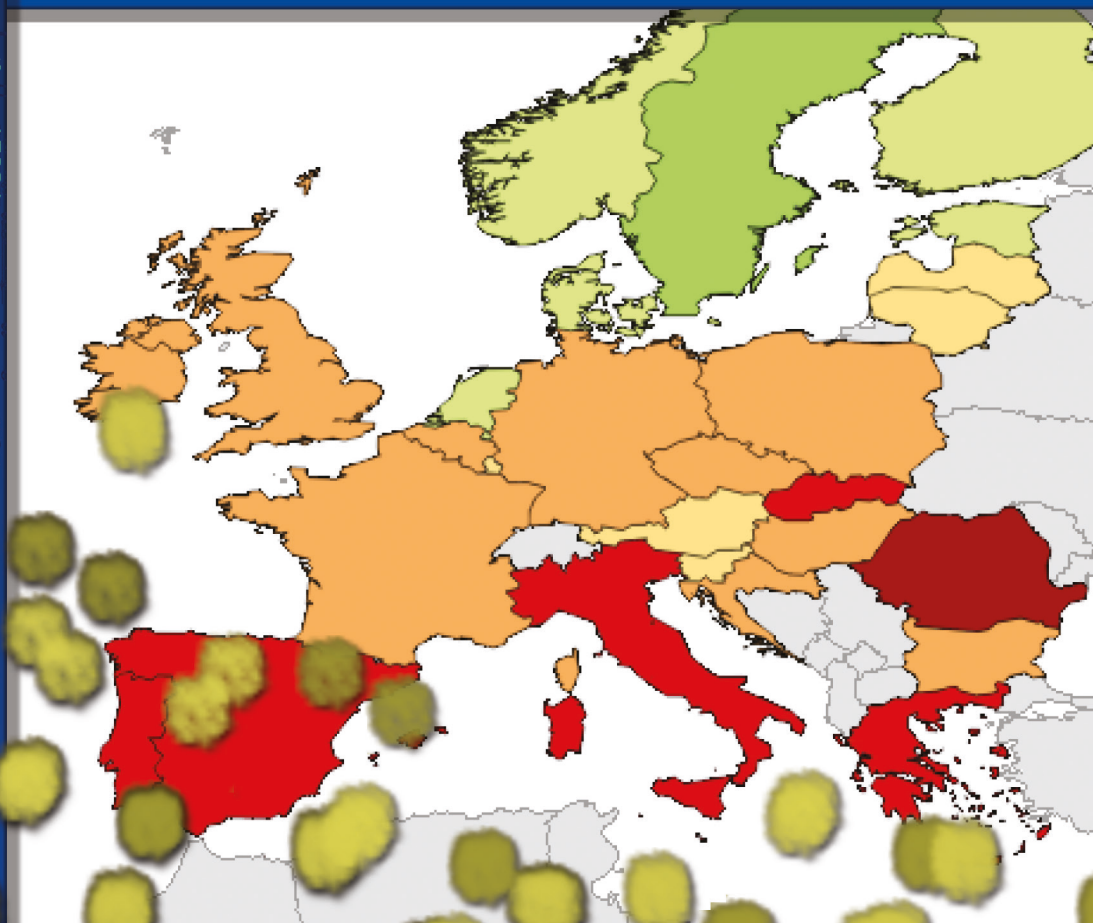
The research described in this thesis was supported by a European Union FP6 grant: LSHP-CT-2007-037941

Contents:

Chapter 1

General introduction



1.1. Antibiotic resistant nosocomial infections.

Nosocomial infections are a common menace in hospitals around the world. The situation is most-problematic in low and middle income countries [1]. However, the problem is serious as well for many high-income countries. For instance, in the United States alone approximately 721,800 hospital-associated infections occurred in 2011, which caused or contributed to 75,000 deaths [2].

Let us repeat the simple estimations as they were done in the book "Prevention and Control of Nosocomial Infections" [3]. The population of the world consists of approximately 7.5 billion people [4]. The assumption, made in the book, that 5% of the world population is hospitalized each year is very conservative. This corresponds to 375 million hospitalized patients annually. It was estimated, that 4-6% of patients acquire at least one nosocomial infection during his/her hospitalization [2]. Therefore, 15 million nosocomial infections occur annually. With a death rate due to infection of 10% [5], we obtain an estimate of 1.5 million deaths per year due to nosocomial infections. This conservatively estimated number is very impressive.

The real numbers, though, are probably higher. In Europe 2,5 million new cases of nosocomial infections occur each year, which are associated with 501 disability-adjusted life years (DALYs) per 100,000 total population, where 2 million years of life lost (YLL) contribute to 75% of DALYs [6].

Infections often occur in Intensive Care Units (ICUs) due to frequently performed medical interventions - surgery, catheter use, immunomodulation, etc., that all increase the risk of infections. These infections are often caused by antimicrobial-resistant bacteria (ARB). ARB can lead, for instance, to severe pneumonia, bloodstream infections and surgical wound infections. Infections caused by ARB have an even larger effect on patients' health, morbidity, mortality and length of stay in hospital compared to infections caused by bacterial strains that are sensitive to the antimicrobials. ARB usually implies that bacteria are not susceptible to the first-line antibiotics, but still are susceptible to so-called second-line antibiotics. As health care costs are strongly correlated with morbidity and the length of hospital stay, infections with ARB are also associated with additional health care costs in comparison to infections caused by antibiotic sensitive bacteria [7–11]. There are two important reasons for this association. First, patient may start on inappropriate antimicrobial therapy, i.e., the bacteria causing the infection are resistant, or less susceptible, to the initial antimicrobial therapy. This may delay effective treatment. Second, infections with ARB may require more expensive and/or more toxic antimicrobial agents. As a side-effect of the emergence of ARB, physicians may decide to start treatment with second-line and more broad-spectrum antimicrobial therapy, which increases selection pressure for resistance and escalates the problem even further [12,13].

Therefore, proper control and reduction of infections, and ARB infections in particular, are major challenges of contemporary health care. Attempts to reduce the

incidence of nosocomial infections have been performed in hospitals worldwide. Some interventions were reported to be successful [14,15], others failed to obtain a positive effect for similar interventions [16].

One of the difficulties to control the incidence of infections in hospital settings is the ability of bacteria to colonize patients asymptomatically. Asymptomatically colonized patients can contribute to spread of bacteria. As their colonization status often remains unknown, transmission prevention measures are often not installed for asymptomatic carriers. For many important nosocomial pathogens, asymptomatic carriage occurs frequently. For instance, only 8-30% [17–19] of the carriers of methicillin-resistant Staphylococcus aureus and around 12% [19] of the carriers of Escherichia coli or Klebisella pneumoniae will develop overt infections. These three bacteria are also the main focus of this thesis, in which we try to determine factors which drive the spread of these bacteria in hospital settings. Knowledge of these factors is crucial to develop effective control strategies.

1.1.1. MRSA

Staphylococcus aureus is a Gram-positive bacterium, which can asymptomatically colonize the nose, the respiratory tract and the skin. In some cases asymptomatic colonization with *S. aureus* can develop into infections like bacteremia, pneumonia and surgical wound infections.

Almost all *S. aureus* strains were susceptible to penicillin in the beginning of the 1940s. Already by 1960 the majority (95%) of hospital strains had become resistant against penicillin. Around the same time, the first methicillin-resistant isolates were found in a British study, only one year after the development of methicillin [20]. The first hospital outbreak of methicillin-resistant *S. aureus* (MRSA) was registered in the United States at the Boston City Hospital, Massachusetts in 1968. Since then, a steady increase in infections with MRSA have been observed worldwide [21]. Nowadays 3.3% - 5.4% patients are colonized with MRSA at admission to European ICUs [19]. In the USA, this number is reported to be higher - 13.6% in a study that includes 153 hospitals in the period October 2007 – September 2010 [14]. Importantly, MRSA seems not to replace methicillin-susceptible *S. aureus* (MSSA) strains, but it adds to the burden of *S. aureus* infections [22].

To determine the point prevalence of carriage of MRSA among patients at a certain moment in time, one needs to screen all patients for MRSA to detect asymptomatic carriage as well. As this is not done routinely in most hospital settings, certainly not at a hospital-wide level, one often uses the prevalence of methicillin-resistance among available *S. aureus* isolates to infer the level of methicillin-resistance among *S. aureus* in a population. However, this statistic, even if available at multiple moments in time, does not tell whether the prevalence of *S. aureus* irrespective of methicillin-resistance, increases or decreases over time. If one knows the total number of *S. aureus* as well, the level of increase or decrease could be calculated, but it runs into the problem that both the frequency of and reasons for testing may have changed over time.

Table 1. Percentage of methicillin-resistance among invasive *S. aureus* isolates in European countries in 2014 [23].

Portugal	47.4%	Australia	11.8%
Greece	37.1%	United Kingdom	11.3%
Italy	33.6%	Denmark	2.5%
Slovakia	28%	Finland	2.5%
Hungary	23.1%	The Netherlands	1%
France	17.4%		

The documented proportion of MRSA among *S. aureus* isolates obtained during hospital admission varies considerably between countries. To illustrate this, I refer to the data of the European Centre for Disease Prevention and Control that was registered in some countries in 2014 (Table 1).

According to the European Centre for Disease Prevention and Control (ECDC) MRSA is responsible for 5% of all healthcare-associated infections [24].

The difference in the proportion of MRSA among *S. aureus* isolates between countries can be explained by multiple factors. One factor is the amount of intramural and extramural antimicrobial consumption. Another important factor is the policy of a country concerning control measures. Thus, In the Netherlands, the so-called "search-and-destroy" policy is used and this is thought to be an important factor in explaining the very low MRSA rates in the Netherlands (<1% of invasive *S. aureus* isolates is methicillin-resistant). The corner stone of this policy is that hospitalized carriers of MRSA are treated in isolation. The policy consists of active screening for MRSA at admission and pre-emptive isolation of all patients of "risk categories", isolation of MRSA positive patients and decolonization treatment of patients infected or colonized with MRSA [10].

While in some countries the rate of *S. aureus* infections is declining, in other countries, it has remained relatively stable over the last years [25,26]. Despite attempts to control MRSA and even a decrease of MRSA incidence in some countries during the last years, many countries still have high-endemicity MRSA-levels. The effects of interventions aimed to decrease infections with and the spread of MRSA in hospital settings, such as screening of all patients at hospital or ICU admission followed by contact precautions for patients with positive screening and/or decolonization with mupirocin twice daily for 5 days combined with 4% chlorhexidine body washing, are controversial [27,28]: some studies reported quite significant reductions in MRSA infections [14,29,30], up to 70% in ICU wards, while others reported absence of any effects of interventions [16,31,32].

1.1.2. *Klebsiella*

Klebsiella is a Gram-negative bacterium of the Enterobacteriaceae family; *Klebsiella pneumonia* and *Klebsiella oxytoca* are most prevalent in hospitals [34].

Klebsiella species can be found in the gastrointestinal tract as part of the normal flora, and occasionally at other body sites (such as nose and mouth) of humans. *Klebsiella* species are opportunistic pathogens able to cause respiratory and urinary tract infections, bloodstream infections, septicemia, meningitis, diarrhea, and soft tissue infections, especially in immunocompromised hosts.

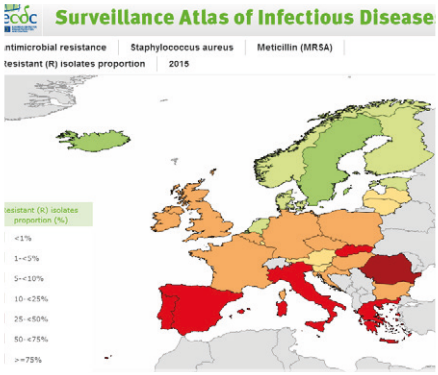


Fig.1. Proportion of Methicillin Resistant *Staphylococcus aureus* (MRSA) Isolates in Participating Countries in 2015: generated by The Surveillance Atlas of Infectious Diseases from national data uploaded annually by the national data manager to The European Surveillance System (TESSy) at ECDC [33]

Since the 1980s multi-drug-resistant *K. pneumoniae* has become an important hospital-acquired bacterial pathogen, because of its ability to produce extended-spectrum beta-lactamases (ESBLs) and carbapenemases, facilitating resistance to almost all beta-lactam antibiotics. The plasmid-mediated nature of ESBLs enables transfer of the resistance genes between *Enterobacteriaceae* of the same species as well as of different species. This complicates the control of the spread of ESBL-positive *Klebsiella* species, as interventions should not only target carriers of ESBL-positive *Klebsiella* species, but carriers of all ESBL-positive *Enterobacteriaceae*.

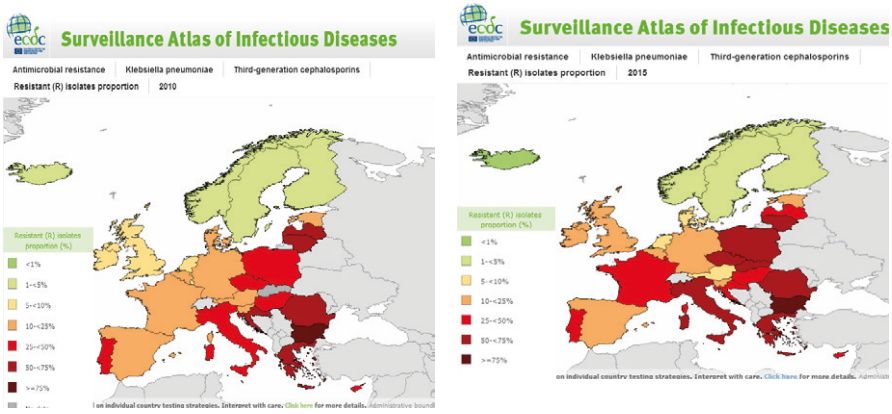


Fig.2. Increasing resistance of the *Klebsiella pneumonie* to 3rd generation cephalosporinis between 2010 and 2015 years. Generated by The Surveillance Atlas of Infectious Diseases from national data uploaded annually by the national data manager to The European Surveillance System (TESSy) at ECDC [33].

Klebsiella spp. are responsible for 8.9%, 7.8% and 10.8% of all bloodstream infections, urinary tract infections and ICU-acquired pneumonia, respectively, in ICUs in Europe, with considerable variation between countries [35].

Infections with *Klebsiella* species have been associated with an increased length of stay in hospital and an absolute increase in mortality [11,34,36,37]. These increases are primarily due to ESBL-producing *Klebsiella* strains, partially because of inappropriate treatment or delay in effective antimicrobial therapy. [38].

On average 25.6% of the *Klebsiella pneumoniae* isolates in Europe are resistant to 3rd-generation cephalosporins and 8 of 27 European countries have reported a significant increase while no country had a significant decrease in the period 2006-2013 [35], see also Figure 2. In the USA, a similar trend was observed. The proportion of *Klebsiella* isolates which are ESBL-positive varies between 3% and 35%, also with an increasing trend during the last decades [39].

1.1.3. *E. coli*

Escherichia coli is a Gram-negative bacterium of the *Enterobacteriaceae* family, which can be found in the lower intestines of most humans. While some strains of *E. coli* are part of the normal gut flora, pathogenic strains of *E. coli* are the cause of 7.6% of all ICU-acquired bloodstream infections in Europe, 26.2% of all ICU-acquired urinary tract infections and 10% of all ICU-acquired pneumonias [35].

In 2010 and 2015, on average, 8.5% [40] and 13.1% [41], respectively, of the *E. coli* isolates in Europe were resistant to 3rd-generation cephalosporins (G3CREC) [35], see also Fig. 3, often as a result of presence of ESBL genes.

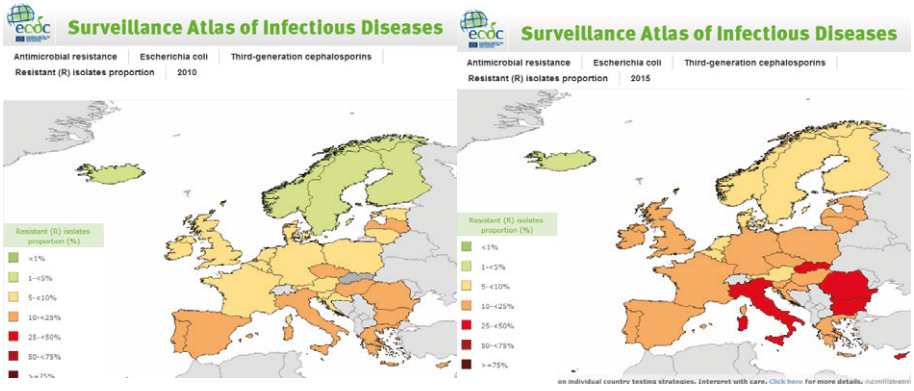


Fig.3. Increasing resistance of the *E.coli* to 3rd-generation cephalosporinis between 2010 and 2015 years. Generated by The Surveillance Atlas of Infectious Diseases from national data uploaded annually by the national data manager to The European Surveillance System (TESSy) at ECDC [33].

In the USA the percentage ESBL-producing *E.coli* among *E. coli* isolates is reported to vary between 5% and 20% and has an increasing trend during the last decades as well [39].

Bloodstream infections with third-generation cephalosporin-resistant *Enterobacteriaceae*, compared to susceptible strains, increase the absolute hazard of death by 63% [11]. Also extramurally, the prevalence of ESBL producing *Enterobacteriaceae* has increased worldwide, up to 15% of the general population carries ESBL-producing bacteria [42]. The extramural epidemiology of ESBLs, though, has not been fully understood but acquisition during travel, nosocomial transmission and within-household transmission are all important acquisition routes [43].

1.2. Why are mathematical and simulation models needed?

...

-OK, I've created a model of a spherical horse moving through vacuum, but to make a more realistic approach I need 5 more years...

(scientific humor)

Although mathematical models always represent a simplification of real phenomena, with all its imperfections, limitations and assumptions, it is a very powerful tool to discover regularities and patterns in a process. This tool becomes especially useful and sometimes irreplaceable when experiments are complicated by ethical, economical or other prohibitive circumstances. When classical experiments cannot be done, mathematical models or simulations can almost always be performed.

Real-world studies are also constrained by time. Clinical studies often last for years and sometimes even decades, and the number of interventions that can be tested is limited by the availability of suitable subjects. Mathematical models can give predictions of multiple scenarios in a relatively short time. In contrast to a clinical trial, stochastic simulation models can be run many times to obtain proper statistics about the level of uncertainty in the outcome.

Moreover, subjecting virtual patients to an intervention in a mathematical model is not limited by any ethical or practical boundaries. This allows for the investigation of extreme scenarios or the maximal effect of certain interventions, e.g., isolation of patients with 100% efficacy. In real-world settings, these extreme conditions are very hard to meet, but knowledge on the possible gains by improving the efficacy of interventions is useful.

Importantly, the predictions of mathematical models depend heavily on the plausibility of the model structure, the simplifying assumptions and availability of

parameter estimates. However, lack of reasonable estimates of some parameters can also be the incentive to run mathematical models. As models can be run with many different parameter values, identification of those parameters with the largest impact on the model outcome can be of interest for subsequent experimental evaluation. For instance, in Chapter 3 we identified that the proportion of health care workers being permanently colonized with MRSA and the relative importance of permanently colonized and transiently colonized health care workers to be two unknown key parameters for the transmission dynamics of MRSA and, hence, for decision making.

Hence, classical epidemiological approaches and mathematical modeling can and should complement each other. Despite all limitations and imperfections, mathematical models are widely used to understand dynamics of infections and transmission. Models can help to indentify key factors in this process, to explore scenarios under varying conditions, to compare effectiveness of different measures or to highlight the direction of future investigations [44].

1.3. Compartmental modeling.

Classical models of infectious diseases divide the host population into a few compartments: e.g., susceptible, infectious and removed (usually reflecting the immune population). To model nosocomial infections, the S-I (susceptible - infectious) model with demography is frequently used [44–46]. In this model, individuals are either susceptible or colonized, without development of immunity. This implies also that we do not differentiate between colonization and infection. Patients may be colonized on admission or acquire colonization during hospital stay. Patients who are colonized are assumed to remain colonized till their discharge or death. This approximation is appropriate for bacteria with a long average period of colonization compared to the length of stay in hospital and when decolonization treatment is absent. An example of a bacterium that fits these assumptions is MRSA. The average duration of colonization is one year [47], while the average length of stay in hospitals is only a few days. When these assumptions cannot be met (for example when active decolonization treatment is successfully performed for some patients), the model should allow for transitions from the "I" compartment to the "S" compartment, and we obtain so-called S-I-S models.

In this thesis most models assume that the force of infection (the probability per unit of time to acquire colonization) for an uncolonized patients is given by $\alpha+\beta\ (C(t))/(N(t))$, where C(t) is the number of colonized patients in the unit/ward at time t, N(t) is total number of patients in the unit at the moment t, α represents the endogenous route, which does not depend on number of colonized patients, and β represents the chance to get colonized due to cross-transmission.

One of the main difficulties for modeling is the lack of good estimates of parameter values. This often precludes inclusion of more detailed modeling structures.

Moreover, there is always the question of balance: the model should not be too complicated, but should describe reality good enough to answer the research question. The structure of hospitals and transfers of patients between units, between hospitals in case of multi-hospital model, admission, discharge and screening protocols are based on experimental evidence or undergo to sensitivity analysis and differ between the models in this thesis.

1.4. Strategies to control the spread of infectious diseases in hospitals, their effects and costs.

A newly detected carrier of a pathogen in a hospital may have acquired the pathogen within the hospital but he/she may also have been colonized before hospital admission. Acquisition may have occurred due to transmission of the pathogen from another human or the environment, and for some ARB, a non-resistant strain from the patient's own microbiota may become resistant due to de-novo mutations. Once a colonized patient carries these bacteria, irrespective of the source, there is a risk that these bacteria are transmitted to susceptible patients. This risk may depend on many factors such as: contact frequencies with, for example, health care workers, hand hygiene, the bacterial load of the colonized patient, and, hence, the antimicrobial use, which influences the load of many bacterial species.

Different measures exist to prevent nosocomial infectious diseases. Some intervention aim to prevent infections in already colonized patients, an example is the use of intravascular lines coated with antibiotics or antiseptics. Other interventions try to eradicate the pathogen or try to reduce the bacterial load: examples are selective decontamination with antibiotics, chlorhexidin body washing and the use of mupirocin nasal ointment to eradicate nasal colonization with MRSA. Reducing the bacterial load may reduce the rate of transition from asymptomatic colonization to infection, but it may as well reduce the risk of transmission. A problem with these strategies is that the decolonization process usually takes several days. Other interventions aim to prevent the nosocomial spread of pathogens. Spread may occur due to direct patient-to-patient contact, via environmental contamination or via health care workers, whose hands may become temporary contaminated after contact with a colonized patient. Interventions to prevent spread are environmental cleaning and good hand hygiene by health care workers, which are both part of standard care practices. Other transmission prevention measures aim to reduce the frequency of contacts with risk of transmission. Examples are cohorting of patients and health care workers and isolation of known carriers or patients at high-risk of being a carrier. All these interventions can be very effective in theory, but in practice the effect frequently is suboptimal, for instance because the compliance to infection prevention measures will never be perfect.

Diagnostics are needed to determine whether a patient is a carrier or not. There are many diagnostic tools that can be applied in different ways: both the moment

of screening (admission screening, screening at fixed time intervals or screening in case of clinical signs) and the population that is screened (universal screening, screening of high-risk patients or screening of ICU admission only) can vary. The efficacy of detecting depends on these factors but also on the diagnostics used, e.g., conventional microbiologic techniques, or DNA-based techniques. These diagnostics differ in turnaround time, in sensitivity, specificity and in costs. Importantly, screening is only helpful in prevention of transmission if there is subsequent action in case of a positive result. However, even with universal admission screening followed by isolation of carriers, which should prevent subsequent transmission completely, there still is a window of opportunity for spread between the moment of testing and the start of isolation. This turnaround time is at least a few hours for rapid diagnostic tests and at least 2 days for conventional tests [48,49]. Pre-emptive isolation till the test results become available could solve this, if the hospital would have enough recourses to implement this policy. On the other hand, it is well known from epidemic theory that not all transmission events have to be prevented to control an outbreak, as long as the amount of transmission remains below a certain threshold.

All these strategies do not only lead to different effects but also to different costs. **In Chapter 2** we look at the costs and effects of different strategies to control MRSA. Universal screening of all patients at hospital admission followed by contact precaution/isolation or/and decolonization would be most effective, but costly and labour-intensive. On the other hand, screening only patients, who were earlier detected as carriers and patients who were hospitalized within the last year, would detect a large part of the colonized patients at relatively low costs. Screening of all patients admitted to the ICU would detect colonization in the most vulnerable population, in which the cost of an infection is highest.

Health care workers may also become colonized with MRSA for a prolonged period of time, for instance in the nose. These health care workers may spread the bacterium to patients, and this cannot be prevented by compliance to the hand hygiene protocol. **In Chapter 3** we quantified the effects of detection followed by decolonization/removing such health care workers on the prevalence of MRSA among hospitalized patients. This strategy is compared to strategies, in which patients, not health care workers, are screened.

The primary goal of interventions is to reduce the number of infections as these lead to increased morbidity, increased length of stay, additional costs and increased mortality. Therefore, it is important to understand how interventions can result in a lower frequency of infections. This is especially important if clinical studies investigate the effects of a bundle of interventions instead of a single intervention. Assigning effects to the wrong part of the bundle may lead to inappropriate recommendations to change infection prevention policies. **In Chapter 4** we re-analyze data from a large study [14]. The study demonstrated an amazing reduction in the number of infections with MRSA after implementation of a bundle of interventions. The conclusions, however, about the effect of the different components were not supported by the data. More specifically, in Chap-

ter 4 we mathematically prove that the reduction in infections with MRSA in this study cannot be explained by a reduction of transmissions of the bacteria in the hospitals and ICUs among patients, and that, therefore, transmission prevention measures cannot be the main driving force behind the reduction in infections with MRSA.

Transmission capacities of bacteria are key-parameters of the transmission process and the effectiveness of control strategies sensitively depends on the values of these parameters. **In Chapter 5** we use data from a multicenter study in 13 European ICUs prospective surveillance and a mathematical model to estimate transmission capacities of *Escherichia coli* and other non-*E. coli Enterobacteriacea* (mostly *Klebsiella*), where non-*E.coli* appears to be 3.7 times more transmissible than *E.coli.* The single admission reproduction numbers (RA) of non-*E. coli Enterobacteriacea* and of *E. coli* are both estimated to be lower than one (0.17 (95% credibility interval 0.094-0.29) and 0.047 (0.018-0.098) respectively).

1.5. List of publications

The content of this thesis relate to following publications:

(1) Chapter 2 is adapted with minor changes from :

Gurieva T, Bootsma MCJ, Bonten MJM (2013) Cost and Effects of Different Admission Screening Strategies to Control the Spread of Methicillin-resistant *Staphylococcus aureus. PLoS Comput Biol. 2013;9(2):e1002874.*

(2) Chapter 3 is adapted with minor changes from

Gurieva T, Bootsma MCJ, Bonten MJM (2012) Decolonization of patients and health care workers to control nosocomial spread of methicillin-resistant *Staphylococcus aureus*: a simulation study. BMC Infect Dis. 2012 Nov 14;12:302

(3) Chapter 4 is adapted with minor changes from

Gurieva T, Bootsma MCJ, Bonten MJM (2012) The Successful Veterans Affairs Initiative to Prevent Methicillin-Resistant Staphylococcus aureus Infections Revisited. Clin Infect Dis.

(4) Chapter 5 is adapted with minor changes from

Gurieva T, Dautzenberg MJD, Gniadkowski M, Derde LPG, Bonten MJM, Bootsma MCJ. (2017) The transmissibility of antibiotic-resistant Enterobacteriaceae in Intensive Care Units. Clin Infect Dis.. 2017 Sep 15

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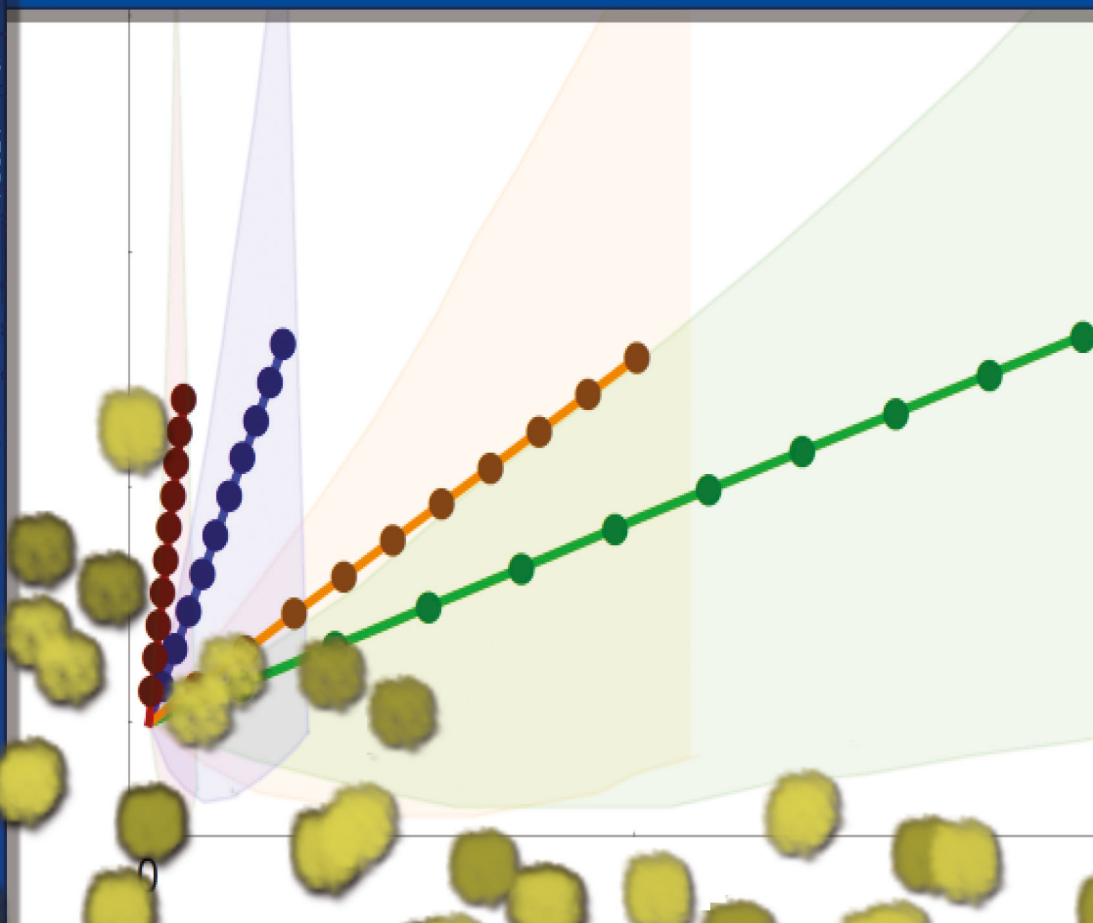
Chapter 2

Cost and effects of different admission screening strategies to control the spread of methicillin-resistant *Staphylococcus aureus*

Gurieva T, Bootsma MCJ, Bonten MJM.
PLoS Comput. Biol. 2013; 9:e1002874.



Abstract

Nosocomial infection rates due to antibiotic-resistant bacteriae, e.g., methicillin-resistant *Staphylococcus aureus* (MRSA) remain high in most countries. Screening for MRSA carriage followed by barrier precautions for documented carriers (so-called screen and isolate (S&I)) has been successful in some, but not all settings. Moreover, different strategies have been proposed, but comparative studies determining their relative effects and costs are not available. We, therefore, used a mathematical model to evaluate the effect and costs of different S&I strategies and to identify the critical parameters for this outcome. The dynamic stochastic simulation model consists of 3 hospitals with general wards and intensive care units (ICUs) and incorporates readmission of carriers of MRSA. Patient flow between ICUs and wards was based on real observations. Baseline prevalence of MRSA was set at 20% in ICUs and hospital-wide at 5%; ranges of costs and infection rates were based on published data. Four S&I strategies were compared to a do-nothing scenario: S&I of previously documented carriers ("flagged" patients); S&I of flagged patients and ICU admissions; S&I of flagged and group of "frequent" patients; S&I of all hospital admissions (universal screening). Evaluated levels of efficacy of S&I were 10%, 25%, 50% and 100%. Our model predicts that S&I of flagged and S&I of flagged and ICU patients are the most cost-saving strategies with fastest return of investment. For low isolation efficacy universal screening and S&I of flagged and "frequent" patients may never become cost-saving. Universal screening is predicted to prevent hardly more infections than S&I of flagged and "frequent" patients, albeit at higher costs. Whether an intervention becomes cost-saving within 10 years critically depends on costs.

Author Summary

Within hospitals antibiotic-resistance of bacteria is common and it complicates treatment of bacterial infections. Screening of patients on admission for carriage of methicillin-resistant *Staphylococcus aureus* (MRSA) allows for strategies where carriers are treated with barrier precautions, e.g., isolation in single-bedrooms. At least theoretically, this should prevent spread of these bacteria. Several screen-and-isolate studies have been performed. However, the outcome was not unequivocal, possibly because clinical trials to determine the optimal screening strategy would necessitate long periods of follow-up due to stochasticity. In the absence of direct evidence we have used mathematical modelling to quantify the theoretical effectiveness and expenses of different screen-and-isolate strategies in hospitals with a high prevalence of antibiotic-resistant bacteria. We find that a strategy to screen patients who were previously known as carriers, possibly combined with screening of ICU-patients is the most cost-saving strategy for the best estimate of isolation efficacy of 25%. With a high efficacy of isolation all strategies are expected to become cost-saving compared to the do-nothing scenarioper infection in ICU, costs of screening and isolation efficacy.

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) may cause severe infections in hospitalized patients, such as bloodstream infections, surgical wound infections and pneumonia. These infections are associated with increased mortality rates, longer length of hospital stay and higher health care costs compared to methicillin-sensitive strains [1]. Typically, such infections are most prevalent in intensive care units (ICUs) [2]. Patient to patient transmission via – temporarily – contaminated hands of health care workers is considered an important mode of spread [3]. Therefore, prevention of nosocomial spread has been focused on reducing transmission opportunities through isolation measures and enhanced adherence to basic infection control practices, such as hand hygiene [4]. Nevertheless, despite multiple guidelines recommending these practices, infection rates due to MRSA remain high in most countries [5,6].

It has become increasingly clear that rapid identification of carriage of MRSA, followed by implementation of barrier precautions for carriers, could be a powerful tool in controlling nosocomial spread [7-10]. However, screening all patients admitted to the hospital (universal screening) imposes a huge (financial) burden on a hospital system, and its benefits have not been unequivocally demonstrated [11-13]. Other screening strategies may, therefore, be more cost-beneficial, such as screening of ICU admissions only, screening of certain high-risk patients or screening of patients who were detected as MRSA-carriers at previous admissions. The optimal screening strategy may differ between settings, but evidence for the most cost-effective strategy in each setting is lacking. As a result, screening strategies vary substantially between hospitals, even within countries. Experimental trials to determine the optimal screening strategy for each of those settings would necessitate long periods of follow-up and huge financial investments. For such complex problems in the absence of direct evidence, mathematical modelling might offer the best alternative to quantify theoretical effectiveness and expenses of different screening strategies in different settings [14].

Here we have performed multiple scenario analyses of a mathematical model to compare the effects and costs of different "screen and isolate" (S&I) strategies, with special emphasis of such a strategy in ICU populations.

Methods

Simulation model

We have used an extended version of a previously described dynamic stochastic simulation model that contains three hospitals of 693 beds, each with an extramural population of 220,000 subjects [9]. Upon hospitalization, patients are usually admitted to "their own" hospital, but sometimes to one of the other hospitals (ratio 38 to 1). Each hospital comprises two types of wards: 36 18-bed normal

wards with five health care workers (HCWs) per ward and five 9-bed Intensive Care Units (ICUs) with nine HCWs per ICU and 80 HCW per hospital with non-restricted patient contacts. After 8-hours, each shift of HCWs is replaced and HCWs are confined to a single ward during each shift. Upon hospitalization patients can be admitted to both types of wards. One of the most important changes of the model [9] is a change in the length of stay and mortality of patients in the different wards. In ICUs, 70% of the patients stay, on average, 1.5 days, with an ICU mortality of 2% per stay. After ICU discharge, these patients stay, on average, seven days in non-ICU wards, before hospital discharge. The remaining 30% of ICU-patients stay, on average, 10 days in ICU and have an ICU-mortality of 25% per stay. The ICU survivors remain hospitalized for, on average, 15 days in non-ICU wards. Patients without ICU admission stay on average 7 days. These parameters are based on patient data from a multi-center ICU study in the Netherlands [15]. Apart from transfer from ICUs to other wards, patients can be transferred between non-ICU wards, from non-ICU wards to ICUs, between ICUs, and between hospitals, all with different rates. Most important model parameters are shown in Table 1.

Individuals are also subdivided into “frequent” patients and “occasional” patients, distinguished by hospitalization rates of once per year (frequent) and once per ten years (occasional) (average sizes in the population being 20,000 belonging to the ”frequent” group and 200,000 to the ”occasional” group). Patients from either group can be admitted to both non-ICU and ICU wards and the mortality rate during hospitalization is the same for both groups. As a result, on average, 50% of the hospital population consists of “frequent” patients. In this study we use the ”frequent” group as a high-risk population for MRSA carriage, and one of the possible screening strategies includes screening of “frequent” patients. All patients are either carrier of MRSA or uncolonized and susceptible for colonization and 1% of the colonized patients is 10 times more infectious (so-called superspreaders).

Table 1: Model parameters.

Parameter	Default value	Source
Average length of stay* in ICU (70% of admissions) (days)	1.5	[15]
Average length of stay* in ICU (30% of admissions) (days)	10	[15]
Average length of stay* in general wards after ICU-discharge for ICU-survivors (70%) (days)	7	[15]
Average length of stay* in general wards after ICU-discharge for ICU-survivors (30%) (days)	15	[15]
Average length* of stay for patients without ICU admission (days)	7	UMC**
ICU-mortality of short stay ICU-admissions (70% of admissions), %	2	[15]
ICU-mortality of long stay admissions to ICU (30% of admissions), %	25	[15]
Non-ICU mortality, %	2	[15]
Staff : patient ratio in ICU	1:1	UMC**
Staff : patient ratio in non-ICU ward	5:18	UMC**
Staff : patient ratio of HCWs not restricted to a ward	01:08.70	UMC**
Duration of colonization in extramural population (days)	370	[40, 41]
Transmission risk ICU: transmission risk in non-ICU wards	3:1	Assumption
Specificity of rapid diagnostic test, %	96	[21,22]
Sensitivity of rapid diagnostic test, %	93	[21,22]
Turnaround time of conventional microbiological test	1 day	[21,22]
Specificity of conventional microbiological test, %	100	Gold standard
Sensitivity of conventional microbiological test, %	100	Gold standard
Turnaround time of conventional microbiological test	4 days	[21,22]
Daily MRSA detection rate by clinical cultures in non-ICU wards	0.03	UMC**
Daily MRSA detection rate by clinical cultures in ICU	0.3	UMC**
Cost of RDT+ conventional test at admission (range), €	20 (2-102)	[31]
Incremental costs of an isolation day (range), €	20 (2-102)	[31]
Costs of an infection in an ICU (range), k€	30 (1-40)	[30]
Costs of an infection in a non-ICU ward (range), k€	1 (0.5-2.5)	[30]
Daily infection risk for a colonized patients in ICU (range), %	0.7 (0.14-1.4)	[27,28]
Compliance of admission screening, %	88	UMC**

* The length of stay is geometrically distributed.
**UMC parameters are estimated from data from the University Medical Center Utrecht, the Netherlands.

Infection control interventions are not based on the true colonization status, but on the available documentation of the colonization status only. Patients either (1) have documented carriage, (2) are not suspected of MRSA colonization (but could still be colonized), or (3) are suspected of colonization, e.g., after documented carriage during previous hospitalization or because of risk factors for MRSA carriage. Throughout this paper the latter patient category will be labelled as "flagged" patients. Importantly, we assume that the pathogen predominantly spreads in hospitals through cross-transmission and that there is hardly any spread in the community. Transmission occurs primarily between patients and HCW in the same ward, but occurs also, at a much lower rate, between wards. Transmission parameters are chosen such that the per admission reproduction number RA [16] is around 1.1 and 0.3 for ICU and non-ICU wards respectively, which corresponds in our do-nothing scenario to an endemic prevalence of 5% hospital-wide and of 20% in ICUs. Although most estimates of the prevalence of MRSA in ICUs and hospital wards are slightly lower than our values [17], in some ICUs MRSA-prevalence of 20% is not uncommon even with isolation measures [18].

MRSA blood stream infections may impact LOS, as was shown, by de Kraker et al. [1] and Wolkewitz et al. [19]. However, the attributable mortality and LOS due to MRSA colonization is limited [20]. As most patients colonized with MRSA do not have overt infections, the transmission dynamics of MRSA will be dominated by these patients. We, therefore, have chosen not to explicitly incorporate the additional LOS in patients with overt infections in the model, but to incorporate these additional LOS in the costs associated with an MRSA infection.

Results are based on 1,000 independent runs of the stochastic simulation model for a period of 10 years after implementation of interventions.

Screening for carriage

The microbiological screening method is, in all simulations, a rapid diagnostic test with turnaround time of 1 day and sensitivity and specificity of 93% and 96%, respectively [21, 22]. This is supplemented with conventional microbiological cultures with a turnaround time of 4 days and an assumed sensitivity and specificity of 100%. The conventional culture results are used as backup to correct false-negative and false-positive results of the rapid diagnostic test. MRSA carriers that are not detected by screening (due to absence of screening, false-negative results or acquisition of MRSA after screening) can be identified as carrier when conventional microbiological cultures, i.e., with a turnaround time of 4 days, are performed for clinical reasons at a rate of 0.03 and 0.3 per patient day for non-ICU wards and ICUs, respectively. The main reason for taking clinical cultures is the presence of fever.

We consider four different S&I strategies that are compared to a do-nothing scenario without any active screening at admission. In all four S&I strategies pa-

tients identified as MRSA-carrier will be "flagged" as such. The flagged status will be removed when such a patient has a negative conventional culture. The following S&I strategies are considered:

- S&I of flagged patients at hospital admission
- S&I of all patients at ICU admission and flagged patients at hospital admission
- S&I of "frequent" patients and flagged patients at hospital admission
- S&I of all patients at hospital admission (universal screening).

In all scenarios we assume that 12% of the admission screenings that should be performed according to the strategy are missed. In each scenario patients documented as carrier will be treated in isolation, which reduces the likelihood of transmission by 100% (perfect isolation), 50%, 25% or 10%, with 25% as default value [18, 23]. Screening of flagged patients, e.g., patients with a history of MRSA colonization [24, 25] and screening of ICU patients both are strategies that are used in hospitals across the world [12, 18].

Screening of "frequent" patients is not a strategy that is currently applied. Yet, since previous hospitalization is associated with MRSA colonization [26], we have chosen this strategy as an intermediate between screening flagged patients only and universal screening.

Although no limits to isolation capacity are assumed, we keep track of the number of patients in isolation to determine the volume of isolation capacity needed. The daily probability to develop an infection for a colonized patient is set at 0.7% and 0.2% in ICU and non-ICU wards, respectively, with sensitivity analysis ranges of (0.14%-1.4%) and (0.1%-0.3%) respectively. This implies that on average 3% and 1.4% of all patients in ICU and non-ICU wards will develop an infection in the do-nothing scenario (Table 1) [27, 28].

Estimates of expenses

We estimated the costs of the different S&I strategies for a hospital using a 3% inflation rate per year. The analysis was performed from a hospital perspective and costs are reported in Euros using the price level of 2010. The default incremental costs from a hospital perspective of these infections (including a costs of prolonged due to MRSA-infection length of stay) were €30,000 in ICU and €1,000 in non-ICU wards, with ranges for sensitivity analysis of (€1,000-€40,000) and (€500-€2,500) respectively [29, 30]. The costs of a screening test performed at admission ranged from €2 to €102 with €20 as default value [31]. The incremental costs of treating a patient one day in isolation varied from €2 to €102 with €20 as default value [31].

For every S&I strategy and set of costs we determined (see supplementary Text S1) the time till the mean daily costs with the intervention strategy became

lower than the mean daily costs in the do-nothing scenario (denoted as T). The 90% credibility intervals denote the uncertainty due to the inherent stochasticity of the dynamics of MRSA (with 5% of simulations yielding higher and 5% yielding lower results than the credibility interval).

Sensitivity analyses

Univariate sensitivity analyses were performed for all costs, the discount rate, and the probability to develop an infection. For the parameters with the highest sensitivity on results in the univariate analysis we investigated the dependence of T on the parameters.

Results

TThe model predicts a decrease of the mean hospital-wide prevalence of MRSA in five years after the start of the interventions from 5% to, depending on the strategy, a value between 3.7-3.9% when isolation efficacy is 25% and 0.8-1.2%, 2.5-2.9% and 4.3-4.5% when isolation efficacy is 100%, 50% and 10%, respectively (Figure 1). The mean prevalence in ICU is predicted to decrease from 20% to 15.9-17.2% for isolation efficacy of 25% and 3.8-5.6%, 11.6-13.0% and 18.4-19.2% for isolation efficacy 100%, 50% and 10%, respectively. Ten years after the start of the intervention, the hospital-wide prevalence is predicted to be 0.2-0.5%, 1.9-2.3%, 3.3-3.8% and 4.2-4.4% and the mean prevalence in ICU predicted to be 1.0-2.2%, 8.5-10.5%, 14.7-16.5% and 18.2-18.5% for an isolation efficacy 100%, 50%, 25% and 10%, respectively (Table 2). Naturally, universal screening leads to the largest decline in the prevalence, while S&I of flagged patients results in the smallest decline.

Only when isolation efficacy >50% the strategy to screen flagged and ICU patients is predicted to reduce the prevalence in both ICU and non-ICU units more than screening flagged and “frequent“ patients (Table 2). Universal screening leads to slightly lower prevalence in 10 years than other strategies. However, when isolation efficacy is low (10%), universal S&I is hardly more effective. S&I flagged patients only is less effective for all considered values of isolation efficacy. Differences in effects of interventions will increase with higher initial prevalence of MRSA (data are not shown).

Naturally, the number of isolation days needed varies considerably with the strategies and the isolation efficacy. The number of isolation beds needed increases immediately after the start of the intervention, most prominently for universal screening (Figure 1). The peak of the mean number of isolation days required for universal screening is 2.5, 2 and 1.4 times higher, as compared to screening flagged patients only, screening of flagged and ICU patients and screening of flagged and “frequent ‘ patients, almost independently of isolation efficacy.

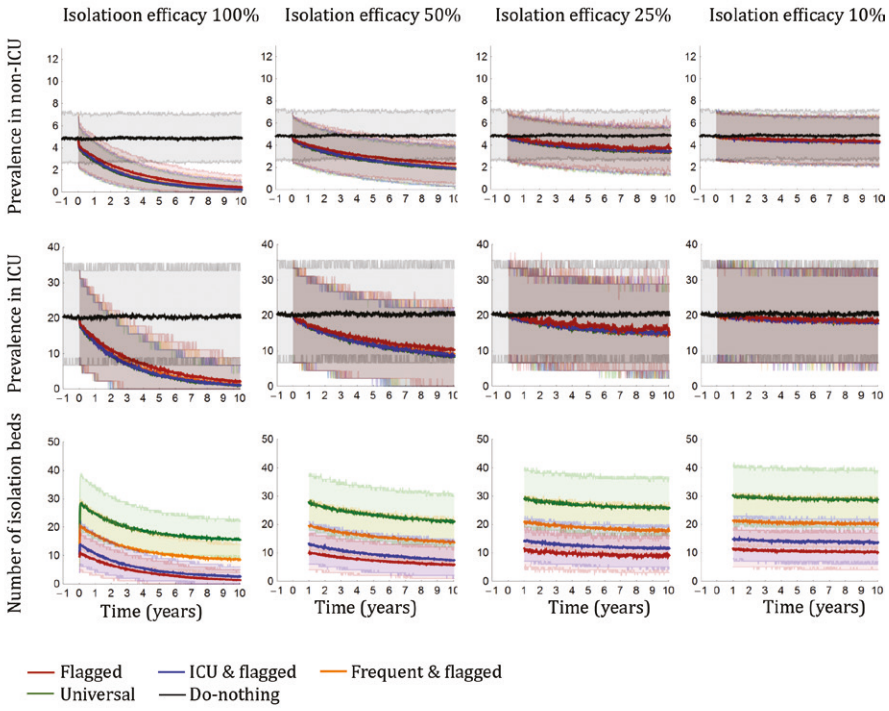


Figure 1. Prevalence of MRSA hospital-wide, in ICU wards and the number of isolation beds needed. The upper graphs denote the hospital-wide MRSA prevalence for different values of the isolation efficacy. The middle row of graphs depicts the prevalence of MRSA in ICU wards. The lower row of graphs depicts the number of isolation beds needed hospital-wide. Interventions start at time 0 and the lines for negative time correspond to the "do-nothing" scenario. Efficacy of patient isolation varied from left to right from 100%, 50%, 25% to 10%. The lines denote the mean of 1000 simulations; the coloured shaded areas denote the 90% credibility intervals due to stochasticity. All parameter values are at the default-value

Table 2. Results of the interventions for the default parameter values.

	Type of the intervention (targeted screening + isolation)				
Efficacy of isolation (%)	No intervention	Flagged only	ICU + flagged	"frequent" + flagged	Universal hospital
Mean intervention costs (tests + isolation costs) during 10 years (in millions €)					
100	0	0.179	0.845	3.27	6.29
50		0.23	0.909	3.32	6.35
25		0.26	0.949	3.35	6.38
10		0.279	0.972	3.37	6.4
Mean total Costs (intervention costs + costs of infections) during 10 years (in millions €)					
100	7.3	2.7	2.9	5.4	8.3
50		5.1	5.3	7.9	10.7
25		6.5	6.9	9.3	12.3
10		7.1	7.7	10	13.2
Mean prevalence in ICU 10 years after start of the intervention (%)					
100	20	2.2	1.1	1.3	1
50		10.5	8.6	9.2	8.5
25		16.5	15.0	15	14.7
10		18.5	18.2	18.2	18.2
Mean number of infections prevented in ICU over 10 years					
100	0	152	168	163	170
50		76	89	86	91
25		32	40	39	43
10		11	14	14	14
Mean number of infections prevented in non-ICU wards over 10 years					
100	0	131	142	141	146
50		76	86	86	90
25		41	48	48	51
10		22	25	25	25
Mean costs of intervention per infection prevented (in kilo €)					
100	-	0.6	2.7	10.8	19.9
50		1.5	5.2	19.3	35.1
25		3.6	10.8	38.5	67.9
10		8.4	24.9	86.3	164
Mean savings as compared to the do-nothing scenario during 10 years (in millions €)					

100	0	4.6	4.4	1.9	-0.96
50		2.2	1.96	-0.56	-3.4
25		0.85	0.42	-2.0	-4.9
10		0.19	-0.4	-2.8	-5.9
Median time till the daily expenses become less than in the do-nothing scenario (*T*) (years)					
100	-	<0.1	<0.1	1.6	5.4
50		<0.1	0.7	7.4	>10
25		3.3	6.0	>10	>10
10		7.6	>10	>10	>10
Mean screening and isolation costs (in millions €) till *T* (max 10 years)					
100	-	<0.1	<0.1	0.53	3.4
50		<0.1	0.1	2.5	>6.35
25		0.1	0.6	>3.35	>6.38
10		0.2	>0.97	>3.37	>6.4

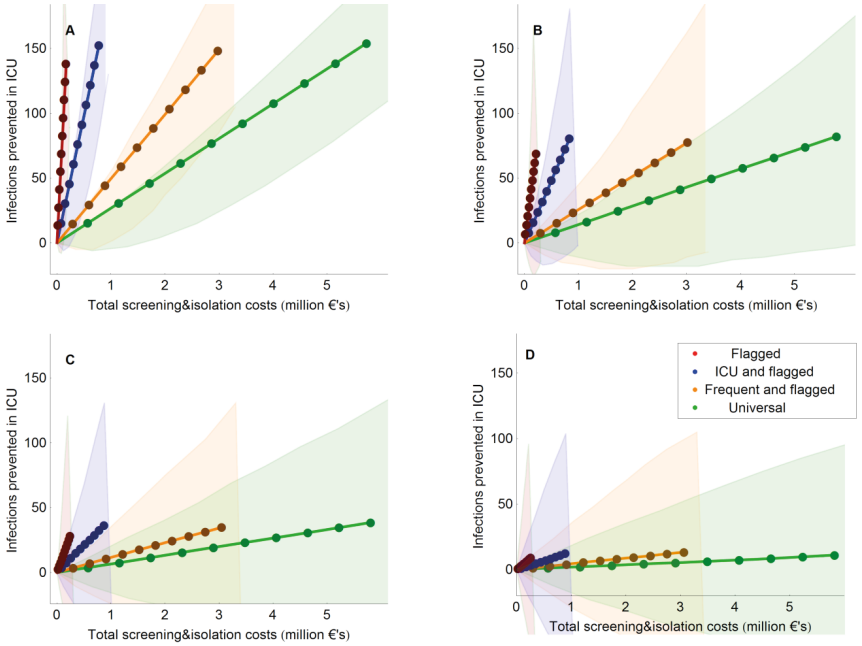


Figure 2. Number of infections prevented in ICUs and the cost of the intervention during the first 10 years after implementation. Isolation efficacy was 100% (A), 50% (B), 25% (C) and 10% (D). The credibility intervals denote the uncertainty due to the inherent stochasticity of the dynamics of MRSA and contain 90% of our simulation results. The 10 dots correspond to the means after 1,2,...,10 years.

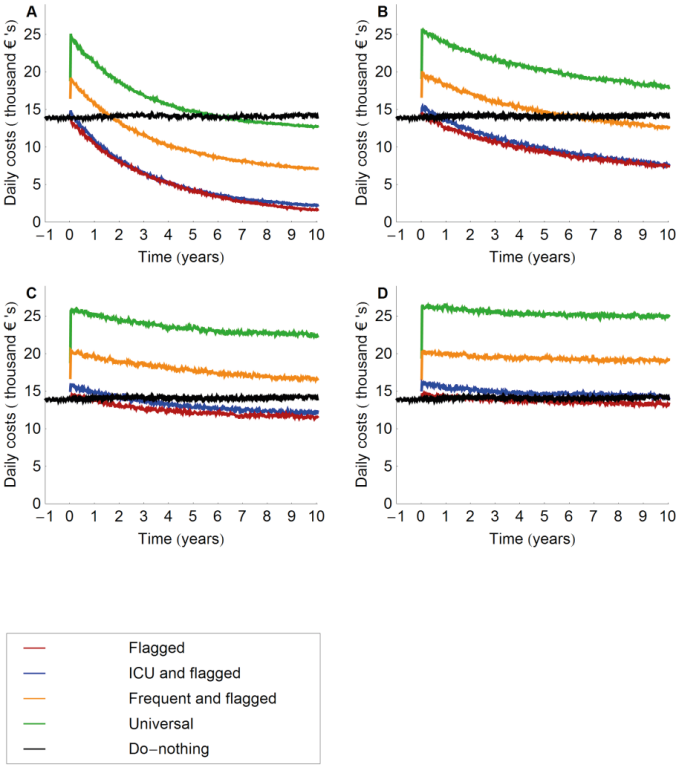


Figure 3. Mean total daily costs (intervention costs and costs due to infections) for different intervention strategies. Isolation efficacy was 100% (A), 50% (B), 25% (C) and 10% (D) and all other parameter values are at the default value (see Table 1). Credibility intervals are not shown because of large fluctuations in the daily costs due to stochasticity.

With isolation efficacy of 100%, 50%, 25% and 10%, screening of flagged and ICU patients will prevent on average 310, 175, 88 and 39 infections per hospital (168, 89, 40 and 14 in ICU) in 10 years time at the costs of €845.000, €909.000, €949.000 and €972.000 (Table 2). The costs of intervention measures per infection averted were lowest for screening of flagged patients only, being €632, €1.529, €3.598 and €8.447 for isolation efficacy levels of 100%, 50%, 25% and 10%, respectively. Universal screening was associated with the highest costs per infection averted, i.e., €19.918, €35.056, €67.857 and €164.093 for isolation efficacy levels of 100%, 50%, 25% and 10%, respectively. We have also compared the predicted number of infections prevented in ICUs and hospital, and the financial consequences of different strategies in high-endemicity settings (Figure 2 and Figure S1 in supplementary).

Whether a strategy will become cost-saving from the hospital perspective, as compared to the do-nothing scenario, critically depends on the isolation efficacy and

the costs per infection averted. With our default efficacy of isolation of 25%, only two strategies are expected to be cost-saving within 10 years: screening of flagged and ICU patients and screening of flagged patients only. The expected total gain in 10 years time is estimated to be €420.000 and €850.000 respectively (Table 2). When efficacy of isolation is 10%, screening of flagged patients only is the only cost-saving strategy within a time window of 10 years. Universal screening is not expected to be cost-saving within 10 years even if efficacy of isolation is 100%.

In the do-nothing scenario the number of infections caused by MRSA, and, therefore, the costs associated with these infections, will be –more or less– constant in time (Figure 3). The costs associated with the intervention will initially lead to increased hospital costs. Yet, due to prevention of infections the hospital costs per unit of time will decrease and may – at a time T – become lower than in the do-nothing scenario (Figure 3); For all values of the efficacy of isolation, our model indicates that T is minimal for screening of flagged and ICU patients and screening of flagged patients only. Universal screening has the largest value of T, which is only below 10 years when isolation efficacy is 100% (Figure 3 and Table 2).

Sensitivity analyses:

Univariate sensitivity analyses indicate that the total costs are rather insensitive to the costs of isolation, the costs per MRSA infection in non-ICU wards and the probability to develop an infection in non-ICU wards (Figure 4, supplementary figures S2, S3, S4). However, the total costs are sensitive to the costs associated with an infection in ICU wards and the probability per day for a colonized patient to develop infection in ICU wards. The dependence of total costs on the costs per screening test varies between screening strategies and is highest for universal screening.

Naturally the number of infections and the costs due to infections are more or less proportional to the number of colonized patient days. We, therefore, define a "constant of proportionality" as the "cost of an infection in ICU wards multiplied by the probability per day to develop an infection in ICU wards". This constant can be interpreted as the costs due to infections per colonized patient day in an ICU ward. The total costs of the interventions are sensitive to "the costs due to an infection per colonized patient day in an ICU ward" divided by the costs of a single screening test performed at admission (Figure 5). We denote the ratio of these two costs by q. When screening is cheap and the costs of infections in ICU are high (q is large), all four strategies will have lower daily costs as compared to the do-nothing scenario within 10 years (T<10 years) for high values of isolation efficacy. With isolation efficacies of 25% or 10% only S&I of flagged and S&I of flagged and ICU patients will reach T within 10 years in the considered range of q. With decreasing values of q, the time T increases and at some critical value of q, the number of infections prevented by a strategy becomes too low to compensate for the costs of the intervention. This critical value of q depends on the strategy and the isolation efficacy (Figure 5).

The value of T is relatively insensitive to the other costs. Only for relatively low infection costs per colonized patient day in ICU and high costs per test, the costs per isolation day will significantly impact T (data not shown).

Changing the discount rate to either 2% or 4% hardly influenced the results.

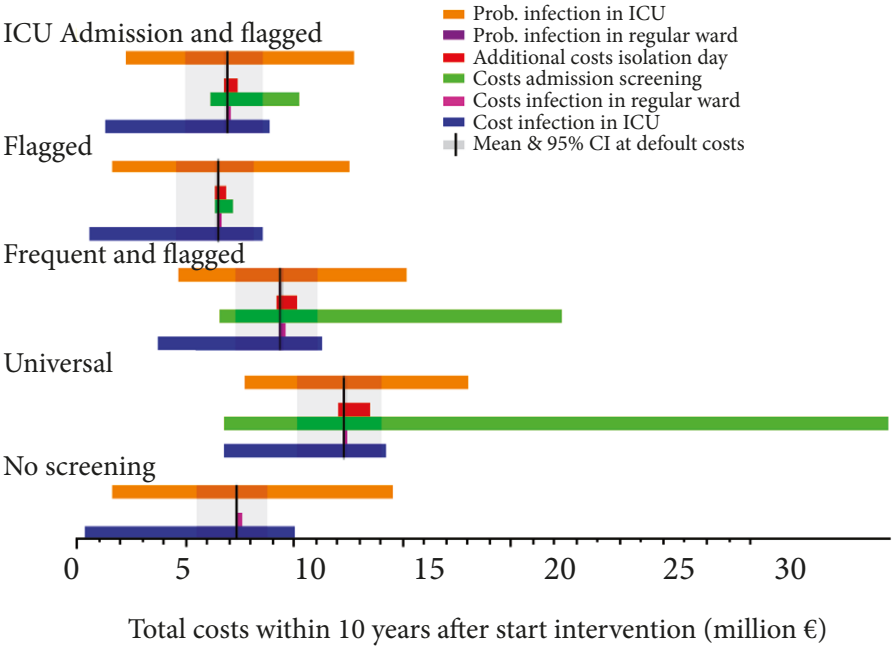


Figure 4. Univariate sensitivity analysis of the total costs during the first 10 years after implementation of the intervention when the isolation efficacy is 25%. The black line corresponds to the mean costs for the default parameter (see Table 1) and the grey area corresponds to the 90% credibility interval at the default values. All coloured bars correspond to the range of the mean total costs of an intervention strategy if one parameter is changed between its extreme ranges (Table 2).

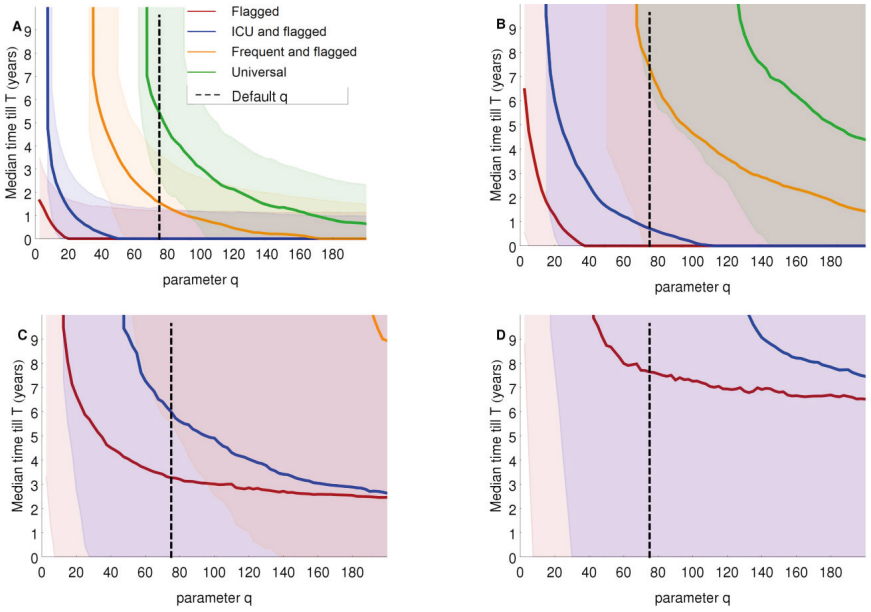


Figure 5. Time (T) till the median (and 10% and 90% quantile) weekly total costs with different intervention scenarios become lower than in the do-nothing scenario. The parameter q on the horizontal axis is the infection costs per colonized patient day in ICU wards divided by the costs of a single screening at admission. Isolation efficacy is A) 100%, B) 50%, C) 25% and D) 10%. The costs of an infection in non-ICU wards was set at €1.000 and additional costs of an isolation day at €20. If a curve for a strategy is not depicted in the figure, the median time till the weekly costs of the strategy become lower than the weekly costs in the do-nothing scenario exceeds 10 years.

Discussion

Using a dynamic stochastic simulation model, we have evaluated four intervention scenarios to control the spread of MRSA under comparable in silico conditions. Although universal screening at hospital admission leads to the fastest decline in both the hospital-wide and ICU prevalence of MRSA, it also requires the highest investment costs and the longest time till return of investment. In our analyses, screening all patients at ICU admission and those previously detected with MRSA (so-called flagged patients) or screening of flagged patients only were almost equally cost-saving in a 10 years period and were both associated with the fastest return of investment. These strategies should, therefore, be seriously considered by hospitals that aim to control the nosocomial spread of MRSA.

Our findings are complimentary to those of two other modelling studies on screening for carriage with antibiotic-resistant bacteria in hospitalized patients. In one study, Hubben and co-workers compared the effects of PCR-based and chromogenic screening tests [32]. Determination of the optimal screening was

not investigated in the current study, and we have, therefore, used a fixed time-to-result parameter. In the other modelling study, Robotham and co-workers investigated the effects of different screening tests in ICU patients, in combination with patient isolation and decolonisation [33]. The latter study did not include the effects of ICU-screening on the non-ICU hospital population and did not include the possibility of patients being readmitted while still colonized.

Yet, this is an important aspect of the dynamics of nosocomial MRSA as it explains why control measures may have not only a direct, almost instantaneous, effect on the prevalence of the nosocomial MRSA in the hospital, but also an indirect effect due to interruption of the so-called feedback loop; when less patients acquire colonization during hospitalization, less patients will be colonized upon readmission to the hospital (see supplementary Figure S5). This lower admission prevalence in time ensures that controlling spread of the nosocomial MRSA will become easier in time. Therefore, neglecting these feedback loop dynamics will underestimate the cost-savingness of interventions.

An important assumption of our model is that the pathogen spreads predominantly in health care settings. Interventions in health care settings will not be very effective in prevention of acquisitions in the community. With substantial spread in the community, a smaller fraction of the acquisitions can be prevented and also the fraction of the patients colonized on admission that are flagged will reduce. In the extreme case that transmission almost exclusively occurs outside health care settings, interventions in hospitals are ineffective and the cheapest strategy is the optimal one. For these reasons, our model is not applicable for community-associated MRSA, but is applicable for other pathogens with similar epidemiological characteristics as MRSA.

Although reductions in the occurrence of nosocomial MRSA infections have been reported [7, 10], multi-resistant Gram-negative bacteria, such as those producing extended-spectrum β-lactamases (ESBL) or carbapenemases are emerging in health care settings worldwide [34]. With no new antibiotics on the horizon to treat infections caused by these bacteria, effective transmission control strategies are needed. Yet, identifying the most effective control strategy for every possible setting through clinical trials seems impossible. Well-designed large clinical trials on rapid diagnostic testing of MRSA yielded highly variable results, varying from no effects on infection rates in surgical units [11, 12, 35] to 69.6% reductions in hospital-wide infection rates [10]. Moreover, the stochastic nature of ARB dynamics necessitates long study periods to avoid that conclusions are primarily based on chance events, rather than on true effects. We have, therefore, used mathematical modelling. Of note, mathematical models always are a simplification of real life complexities and cannot produce very precise predictions for a certain situation. For instance, we have assumed that all isolation measures were equally effective in all isolated patients and that all measures were executed with equal efficacy. One can easily think of scenarios in which these assumptions

do not hold [36]. Therefore, the main value of modelling is the comparison of different scenario analyses, while keeping other important parameters constant, rather than providing exact values.

In doing so, our analyses identified screening of flagged patients and ICU patients as a very powerful control strategy, even reducing prevalence levels in non-ICU wards. The central role of the ICU in our model follows from two assumptions. First, many patients discharged from ICU are transferred to other wards. Therefore, prevention of spread in ICUs will reduce the frequency at which MRSA is introduced in other wards. Second, the likelihood of cross-transmission is higher in ICUs than in non-ICU wards. This assumption is motivated by the more frequent (and possibly even more intense) contacts between patients and HCWs, allowing HCWs to act as transmission vectors of MRSA. Moreover, antibiotic selective pressure is higher in ICUs than in non-ICU wards, which may increase the likelihood that a HCW will pick up a pathogen during a physical patient contact and that another patient will be successfully colonized after being contacted by a temporarily contaminated HCW. Finally, the severity of disease of critically ill patients in ICU wards makes them more susceptible to acquire colonization with MRSA than patients in non-ICU wards. Several studies indeed support the potential effects of ICU-screening on hospital-wide resistance levels [37].

With regard to the costs of interventions, our analyses were most sensitive to the costs associated with an ICU-acquired infection caused by MRSA. Many studies have quantified the costs of ICU-acquired bacteremia and ventilator-associated pneumonia [30] and these estimates were all in the range of the €30,000 that we used. However, these costs sensitively depend on the additional length of stay that can be ascribed to infections, which is difficult to determine, see e.g. [38, 39]. Another important aspect is the role of the ICU in the patient flow. We have used data on patient admissions to 13 ICUs in the Netherlands. Naturally, patient flow may be different in other hospitals.

One of the simplification of the model is that patients should be colonized with MRSA before they are at risk of getting an infection with MRSA, i.e., we did not explicitly incorporate that some patients may acquire MRSA infection directly without being colonized first, i.e., due to invasive medical procedures. A slight increase in the daily probability for colonized patients to acquire an infection would lead to the same ratio of colonized and infected patients. Therefore, our sensitivity analysis on the daily probability for colonized patients to acquire an infection can also be interpreted as a proxy for a sensitivity analysis to the parameter which determines how often patients acquire an infection without being colonized.

We also assumed that the rates of conventional microbiological cultures performed for clinical reasons are independent of screening on admission (0.03 and 0.3 per patient day in non-ICU and ICU wards). We have assumed that a clinical suspicion of infection is the main reason for obtaining clinical cultures, and that

screening for MRSA-carriage on admission reduces the frequency of obtaining clinical cultures in case of a clinical suspicion of infection.

Our model contains many parameters and some parameter values are unknown, whereas others may differ between hospitals and countries. We have based our values on data from the literature and from our own hospital, where possible. To fully capture the effects of parameter uncertainty we would have considered to perform a probabilistic sensitivity analysis (PSA) for all parameters simultaneously, as was performed by Robotham et al. [33]. However, due to the higher complexity of our simulation model, as compared to the model of Robotham et al., this was computationally unfeasible. We, therefore, had to restrict our sensitivity analysis primarily to univariate sensitivity analysis. As a result, there may be more uncertainty in the results as we have presented here.

We did not include decolonization of detected carriers as a measure to control MRSA. Naturally, adding this measure (if successful at low costs) would increase intervention effects and would make the duration till return of investments shorter. Although persistently colonized HCWs were included as potential sources for MRSA transmission, we did not include screening and decolonization of them as intervention measure. This intervention measure would - in most settings – only slightly enhance the control of MRSA transmission, at the cost of significant expenses due to the necessity to replace colonized HCWs.

The (cost)-efficacy of admission screening strategies critically depends on the effectiveness of the infection prevention measures taken when a carrier of MRSA is detected. If these measures are not very effective, it may not be wise to invest lots of efforts in detecting carriers. The effectiveness of barrier precautions has been sufficiently high in the Netherlands and the Scandinavian countries to prevent high prevalence levels of MRSA. However, it is still debated whether patient isolation prevents transmission at all [23], and a recent estimate indicated that the efficacy is in the order of 25% [18], We, therefore, advocate to perform more clinical studies to determine the efficacy of decolonization, isolation or cohorting measures in different settings.

In conclusion, our study demonstrates marked and robust differences in the costs and effects of different infection control measures for MRSA. Because of the central role of ICU wards in patient flow in hospitals, the vulnerability of ICU patients to infections caused by MRSA and the high costs associated with these infections targeted infection control measures in ICU wards are likely to be the most effective and cost-saving from a hospital perspective.

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Supplementary material

Explanation of the calculation of the time T

For each strategy we define the time T as the median time of 1000 simulations till the daily total costs (of intervention and associated with infections) becomes lower than the mean daily costs in the do-nothing scenario. In the latter scenario the mean total costs are constant in time, but depend on the ratio q of the "costs due to an infection per colonized patient day in ICU divided by cost of a single screening".

Due to chance events, both the number of tests performed and the number of infections per week fluctuate per simulation, and so do the weekly total costs. To determine the time T for a single simulation, we performed a linear regression analysis for the weekly costs in a certain time window. The left point of the time window is the latest week where all weekly costs before that week exceed the mean weekly costs in the "do-nothing" scenario. The right point of the time window is defined by the first week for which all weekly costs after that week are lower than the mean weekly costs in the "do-nothing" scenario. This leads to 1000 values of T, some of which may exceed 10 years. In Figure 5 we plotted median values (and 10% and 90% quantiles) of time T as function of the ratio q.

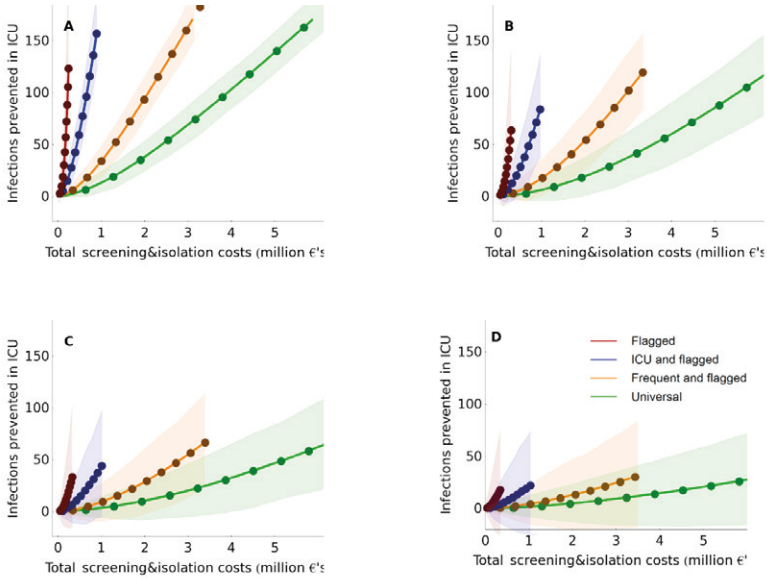


Figure S1. Number of infections prevented in ICUs and the cost of the intervention during the first 5 years after implementation in a high-endemicity settings (14% hospital-wide prevalence). Isolation efficacy was 100% (A), 50% (B), 25% (C) and 10% (D). The credibility intervals denote the uncertainty due to the inherent stochasticity of the dynamics of MRSA and contain 90% of our simulation results. The dots correspond to the means after 1,2,.. years.

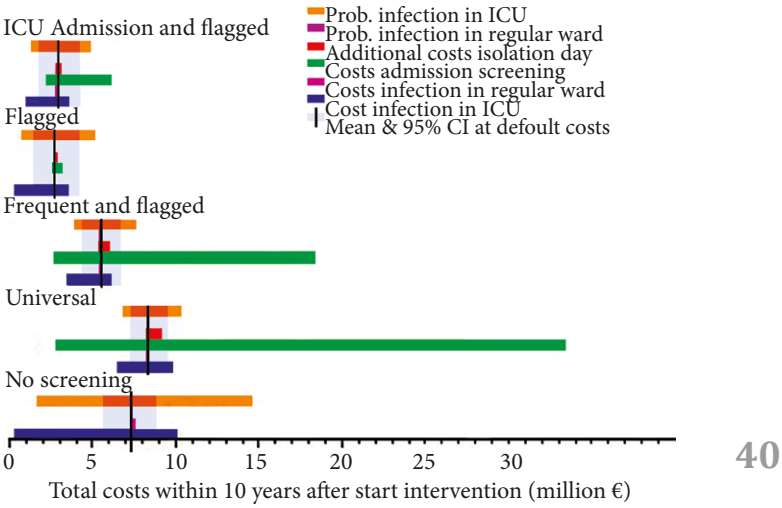


Figure S2. Univariate sensitivity analysis of the total costs during the first 10 years after implementation of the intervention when the isolation efficacy is 100%. The black line corresponds to the mean costs for the default parameter (see Table 1) and the grey area corresponds to the 90% credibility interval at the default values. All coloured bars correspond to the range of the mean total costs of an intervention strategy if one parameter is changed between its extreme ranges (Table 2).

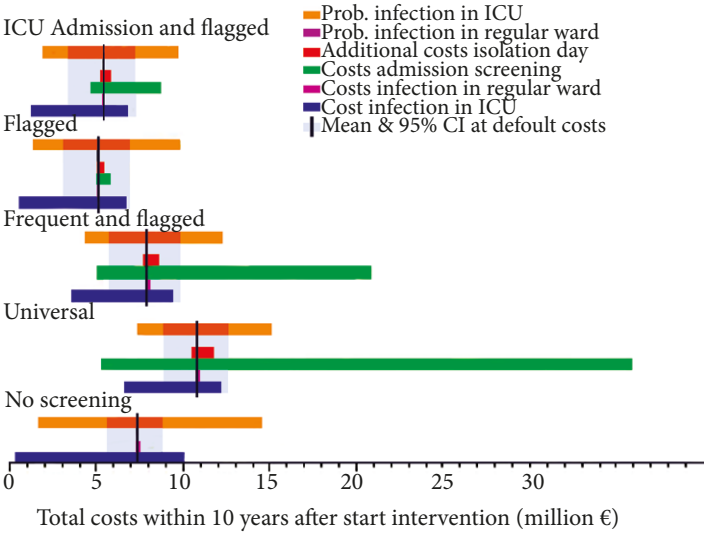


Figure S3. Univariate sensitivity analysis of the total costs during the first 10 years after implementation of the intervention when the isolation efficacy is 50%. The black line corresponds to the mean costs for the default parameter (see Table 1) and the grey area corresponds to the 90% credibility interval at the default values due. All coloured bars correspond to the range of the mean total costs of an intervention strategy if one parameter is changed between its extreme ranges (Table 2).

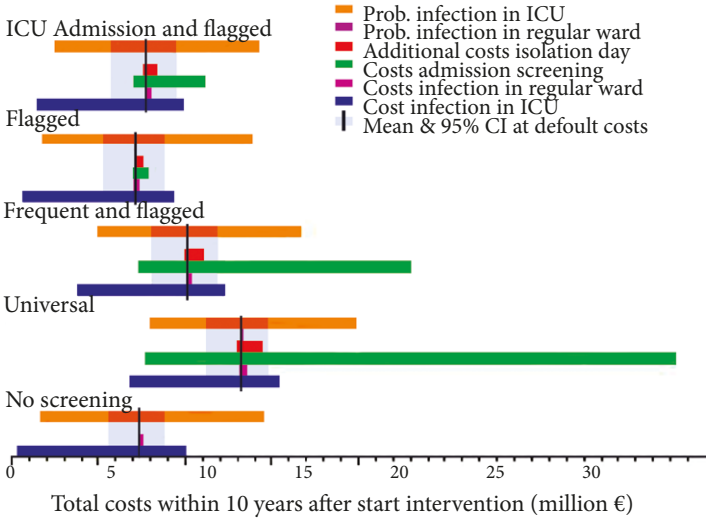


Figure S4. Univariate sensitivity analysis of the total costs during the first 10 years after implementation of the intervention when the isolation efficacy is 10%. The black line corresponds to the mean costs for the default parameter (see Table 1) and the grey area corresponds to the 90% credibility interval at the default values. All coloured bars correspond to the range of the mean total costs of an intervention strategy if one parameter is changed between its extreme ranges (Table 2).

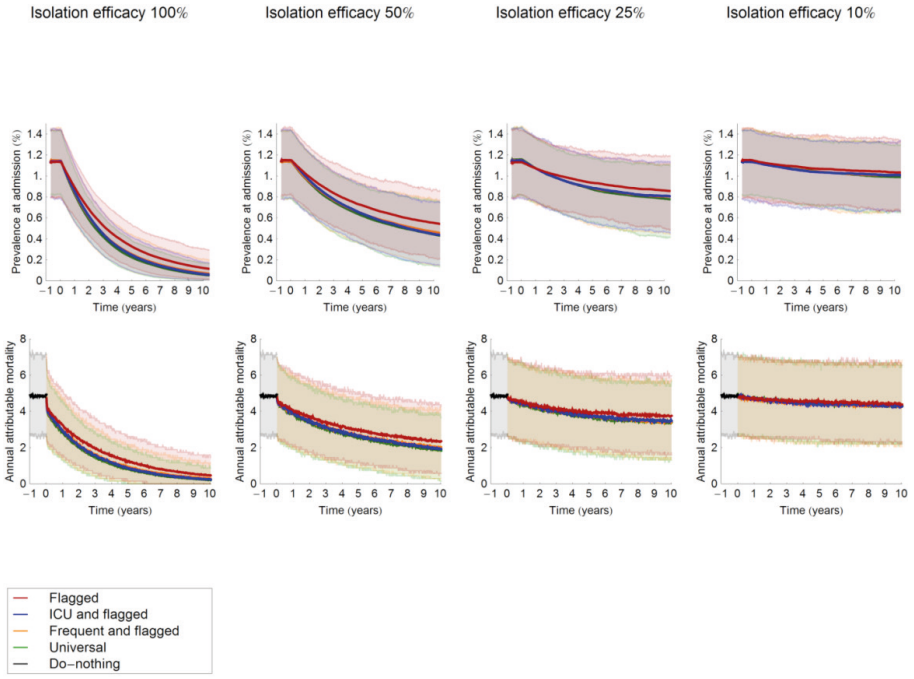


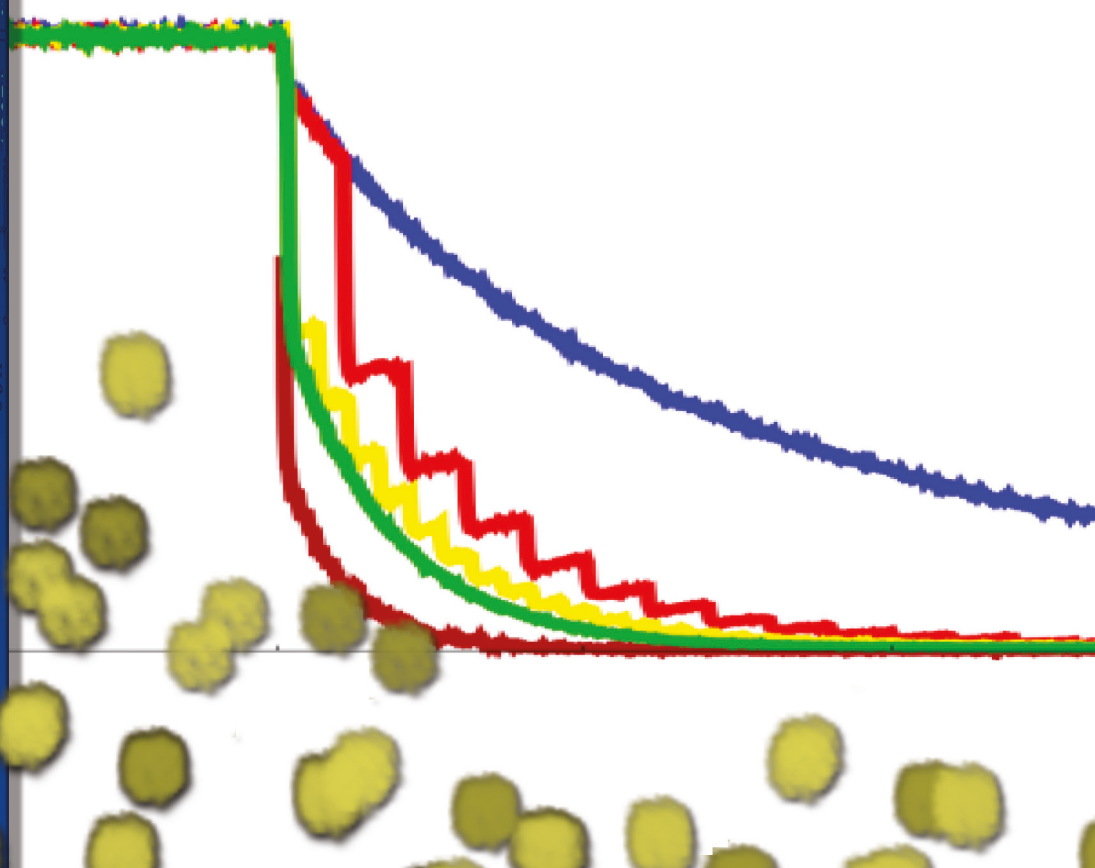
Figure S5. Admission prevalence of MRSA and the annual attributable mortality rates as function of the time since start of the intervention. The upper graphs denote the dynamics of the MRSA prevalence at admission for different values of the isolation efficacy . The lower graphs depict the dynamics of the annual attributable mortality rates. Both the admission prevalence and the attributable mortality e decrease due to the so-called feedback loop. Interventions in hospital start at time 0 and the lines for negative time correspond to the "do-nothing" scenario. Efficacy of patient isolation varies from left to right from 100%, 50%, 25% to 10%. The lines denote the mean of 1000 simulations; the coloured shaded areas denote the 90% credibility intervals due to stochasticity. All parameter values are at the default-value.

Chapter 3

Decolonization of patients and health care workers to control nosocomial spread of methicillin-resistant *Staphylococcus aureus*: a simulation study

Gurieva T V, Bootsma MC, Bonten MJ.

BMC Infect. Dis. 2012; 12:302.



Abstract

Background
Control of methicillin-resistant *Staphylococcus aureus* (MRSA) transmission has been unsuccessful in many hospitals. Recommended control measures include isolation of colonized patients, rather than decolonization of carriage among patients and/or health care workers. Yet, the potential effects of such measures are poorly understood.

Methods
We use a stochastic simulation model in which health care workers can transmit MRSA through short-lived hand contamination, or through persistent colonization. Hand hygiene interrupts the first mode, decolonization strategies the latter. We quantified the effectiveness of decolonization of patients and health care workers, relative to patient isolation in settings where MRSA carriage is endemic (rather than sporadic outbreaks in non-endemic settings caused by health care workers).

Results
Patient decolonization is the most effective intervention and outperforms patient isolation, even with low decolonization efficacy and when decolonization is not achieved immediately. The potential role of persistently colonized health care workers in MRSA transmission depends on the proportion of persistently colonized health care workers and the likelihood per colonized health care worker to transmit. As stand-alone intervention, universal screening and decolonization of persistently colonized health care workers is generally the least effective intervention, especially in high endemicity settings. When added to patient isolation, such a strategy would have maximum benefits if few health care workers cause a large proportion of the acquisitions.

Conclusions
In high-endemicity settings regular screening of health care workers followed by decolonization of MRSA-carriers is unlikely to reduce nosocomial spread of MRSA unless there are few persistently colonized health care workers who are responsible for a large fraction of the MRSA acquisitions by patients. In contrast, decolonization of patients can be very effective.

Background

Methicillin resistant *Staphylococcus aureus* (MRSA) is an important cause of nosocomial infections. The dynamics of MRSA transmission in health-care settings is characterized by high fluctuations in patient prevalence within units, resulting from patient-to-patient spread and admissions of colonized patients. So far, almost all interventions have been based on implementing barrier precautions for patients with documented MRSA carriage [1, 2], sometimes in combination with decolonization of carriage [3]. The evidence for the efficacy of patient isolation to control nosocomial spread of MRSA in high endemicity settings, though, is rather limited [4].

Especially for MRSA, health care workers (HCWs) might be important in the nosocomial transmission dynamics. First, temporary contaminated hands of HCWs are important vectors for MRSA transmission [5], and appropriate hand hygiene is considered the key intervention to minimize this transmission mode [6]. Second, HCWs may become persistently colonized with MRSA [7], e.g., in the nose or on injured skin, and act as a constant source for MRSA transmission [7]. The obvious difference between both transmission roles is that hand hygiene will not clear persistent carriage.

MRSA eradication therapies using mupirocin and chlorhexidine were extremely efficacious in decolonizing HCWs [8]. If persistent carriage among HCW is an important source for MRSA transmission, decolonization of HCWs could be effective in controlling MRSA among patients. To the best of our knowledge, though, the relative contribution of persistently colonized HCWs in the epidemiology of MRSA endemicity has never been determined, and, consequently, there is no information on the possible effects of decolonizing persistently colonized HCWs. In contrast the efficacy of eradication therapies applied to patients during hospitalization seems to be low [8]. Clinical decision making for the most appropriate infection control strategy is frequently hampered by the absence of prospective comparisons of different control strategies. Moreover, even if performed, the importance of stochastic events in small populations, such as in hospitals, would necessitate long periods of follow-up. In the absence of empirical evidence, mathematical models may offer the best alternative to determine the optimal control strategy [9].

Here, we use a computer simulation model to quantify the effects of patient isolation and antimicrobial treatment of carriage for patients and HCWs, as part of an infection control program for MRSA with universal hospital admission screening. We aim to identify scenarios in which HCW decolonization could be considered a sensible intervention.

Methods

Patient and transmission dynamics

We use an extended version of a previously described stochastic simulation model [10]. The model contains three hospitals of 693 beds, each with an extramural population of 220,000 subjects. Patients are subdivided into "core group" and "non core group" patients, distinguished by hospitalization rates of once per year (core-group) and once per ten years (non-core group). On average 50% of the hospital population consists of "core group" patients.

Each hospital comprises two types of wards: five 9-bed Intensive Care Units (ICUs) and 36 18-bed regular wards. In ICUs the staff-patient ratio is 9:9, in regular wards 5:18. Besides HCWs confined to a single ward, 80 HCWs are present who have contact with patients in different wards. HCWs work in 8-hours shifts. HCWs confined to a single ward will work in the same ward during their next shift. Upon hospitalization patients can be admitted to both types of wards. In ICUs, 70% of the patients stay, on average, 1.5 days, with an ICU mortality of 2%. After ICU discharge, these patients stay, on average, seven days in regular wards, before hospital discharge. The remaining 30% of ICU-patients stay, on average, 10 days in ICU and have an ICU-mortality of 25%. ICU survivors remain hospitalized for, on average, 15 days in regular wards. These figures are based on real patient data from a multi-center ICU study in the Netherlands [11]. Length of stay is assumed to be independent of the colonization status. Apart from transfer from ICUs to wards, patients can be transferred between regular wards, from regular wards to ICUs, between ICUs, and between hospitals, all with different rates. Important parameters used are listed in Table 1.

Patients are either carriers of MRSA or uncolonized and susceptible for colonization. Infection control interventions, however, are not based on the true colonization status, but on the available documentation of the colonization status only.

On hospital admission, MRSA carriage can be documented with a rapid diagnostic test that, for simplicity, provides a result in 24hours with sensitivity and specificity of 93% and 96% respectively [12]. Simultaneously, conventional microbiological tests, with assumed sensitivity and specificity of 100% and turnaround time of four days, are performed as back-up to adjust false test results of rapid tests. All patients should be screened on admission (i.e., universal screening), and we assume that compliance to this screening scenario is 88% (based on UMCU data) [10]. MRSA carriage may also be detected by clinical cultures, which are processed with conventional microbiological methods.

Patients can acquire MRSA by two modes: The first mode occurs via the hands of HCWs, which may have become contaminated after contact with a colonized patient. Appropriate hand hygiene will clean hand contamination and, therefore,

hand contamination is typically short-lived. As a consequence, the probability of transmission via hands of temporary colonized HCWs is proportional to the fraction of colonized patients in the unit. The second acquisition mode is through persistently colonized HCWs, e.g., with carriage in the nares. This type of colonization is not short-lived and is not eradicated through hand hygiene. We assume that the risk for HCWs to become persistently colonized is proportional to the number of patients being colonized.

Table 1. Parameters in the model

Parameter	Value	Source
Average length of stay in intensive care units, days	4	[17]
Average length of stay in regular ward, days	7	UMC
Admission from another hospitals, %	5	UMC
Staff : patient ratio in intensive care units	1:1	UMC
Staff : patient ratio in regular ward	5:18	UMC
Staff : patient ratio of HCWs not restricted to single wards	1:8.7	UMC
Duration of colonization in extramural population (mean), days	370	[13, 14]
Transmission risk intensive care units : regular ward	3:1	Assumption
Specificity of rapid diagnostic test, %	96	[12]
Sensitivity of rapid diagnostic test, %	93	[12]
Turnaround time of rapid diagnostic test, days	1	[12]
Specificity of conventional microbiological test (back-up test), %	100	Gold standard test assumed to be perfect
Sensitivity of conventional microbiological test (back-up test), %	100	Gold standard test assumed to be perfect
Turnaround time of conventional microbiological test (back-up test), days	4	[12]

UMC-parameters estimated from data from University Medical Center Utrecht.

HCWs and patients may lose MRSA carriage in the extramural community after a median time of 256 days (mean of 370 days) [13, 14]. Importantly, there is no patient-to-patient transfer of MRSA in the community, which limits our analyses to so-called hospital-acquired MRSA.

Most analyses are performed in settings with high endemicity levels of MRSA, i.e., in absence of any intervention specifically targeted at MRSA, the equilibrium patient prevalence of MRSA-carriage is around 14% and 40% in hospitals and

ICUs, respectively. A medium endemicity level of around 6% and 20% in hospitals and ICUs, respectively, was analysed as well. A medium endemicity level is most realistic [15]. However, an MRSA-prevalence of 20% is not uncommon [16]. Transmission parameters in regular wards and ICUs were chosen to obtain these patient prevalences of MRSA and to obtain a prevalence of persistently colonized HCWs of 1%, 5% or 10%, while 10%, 30% or 50% of the acquisitions in patients can be ascribed to persistently colonized HCWs (see Supplementary material). As the feedback loop, (i.e. colonized patients who are discharged and readmitted) is included in our model we obtain the MRSA admission prevalence as a result of the chosen transmission parameters.

Note that we do not specify 1) hand hygiene compliance levels, 2) cohorting levels, 3) environmental cleaning protocols, 4) the use of single/multi bed rooms, 5) the frequency of contact between patients and HCW, and other factors influencing MRSA transmission. The effectiveness of interventions depends on the prevalence and relative importance of transmission modes only, and not directly on the aforementioned parameters. For instance, a high hand hygiene compliance with a low cohorting level will have the same effect on transmission as a low compliance with a high cohorting level. On top of the dynamics of MRSA as described in this section, we model intervention strategies, as described below, to address our research questions.

Interventions

We consider two control strategies applied to patients with documented MRSA-carriage, and one applied to HCWs:

a) Isolation reduces both the likelihood for colonized patients to transmit MRSA and the likelihood for uncolonized patients (when isolated) to acquire colonization. The efficacy of isolation ranges from 0% (no effect of isolation) to 100% and is modelled as a multiplication factor (0 to 1) to transmission rates. Isolation with suboptimal efficacy could be considered to resemble strategies in which patients are not isolated in single-bed rooms, but in which other barrier precautions, e.g., gloves and gowns, are used instead. The number of beds available for patient isolation is unlimited, which allows quantification of the isolation needs for each intervention. Isolation measures are initiated when MRSA carriage (or infection) is documented. Isolation will be discontinued when screening cultures do not yield MRSA.

b) Decolonization of patients occurs a fixed number of days after the start of decolonization therapy. Until that time, or if decolonization is unsuccessful, the infectivity of a treated individual remains unaffected. If patients are discharged before the treatment is completed, the treatment will be continued extramurally. The efficacy of decolonization is denoted as the percentage of patients in which decolonization is successful. Decolonization is initiated on

the same day that MRSA-carriage is documented. A successfully decolonized patient is immediately susceptible for acquisition of MRSA. If not specified otherwise, decolonization occurs instantaneously.

c) Decolonization of HCWs is assumed to be 100% efficacious and occurs, for simplicity, instantaneously. We explore the effects of decolonizing all staff with frequencies ranging from monthly to annually. After decolonization, HCWs are immediately susceptible for acquisition of MRSA.

Simulations for which we report 95% credibility intervals are always based on 1000 1,000 independent runs of the stochastic simulation model. Mean values can be based on 50 independent runs. We define the effectiveness of an intervention a time after the intervention has been implemented as the mean relative reduction in the hospital-wide MRSA prevalence.

Results

Comparing patient isolation and decolonization

With similar levels of efficacy, decolonization is more effective than patient isolation (Figure 1). Decolonized patients cannot reintroduce MRSA when readmitted to the hospital, which interrupts the so-called feedback loop. Another benefit of decolonization is that the nosocomial patient prevalence of MRSA decreases faster as compared to isolation strategies, because decolonization decreases the number of colonized patients in the hospital directly while isolation only prevents new acquisitions while patients in isolation are still colonized.

Nosocomial MRSA patient prevalence will decrease slower with a lower efficacy of control measures. With a lower efficacy of decolonization and isolation, the difference in patient prevalence between both interventions decreases during the first months after implementation. Three months after the start of interventions, the absolute difference in nosocomial MRSA patient prevalence between decolonization and isolation is 3.9% with 100% efficacy and 3.7%, 3.1% and 1.7% with 75%, 50% and 25% efficacy, respectively with a high endemicity level (14% hospital-wide) and 2.2%, 2.0%, 1.6% and 1.1% with an efficacy of isolation of 100%, 75%, 50% and 25% with a medium endemicity level (6% hospital-wide). On longer time scales, though, differences in patient prevalence between interventions show opposite trends. After 5 years the difference is 0.7% with 100% efficacy, and 1%, 2.9% and 4.5% with 75%, 50% and 25% efficacy, respectively. With a medium patient prevalence endemicity level, the difference is 0.7% with 100% efficacy, and 1.2%, 1.6% and 1.6% with 75%, 50% and 25% efficacy, respectively (see Figure 1).

Using an arbitrary goal for the ultimate patient prevalence of 0.3%, this goal will be reached in 5 years if the efficacy of patient decolonization exceeds 75% (Fig-

ure 1). For isolation, the patient prevalence will decrease slower. Even with a 100% efficacy the patient prevalence will be 1.5% after five years and the patient prevalence will be 2.3% and 5.8% with 75% and 50% efficacy respectively.

The effect of non-instantaneous decolonization of patients and HCWs is discussed in the supplementary material.

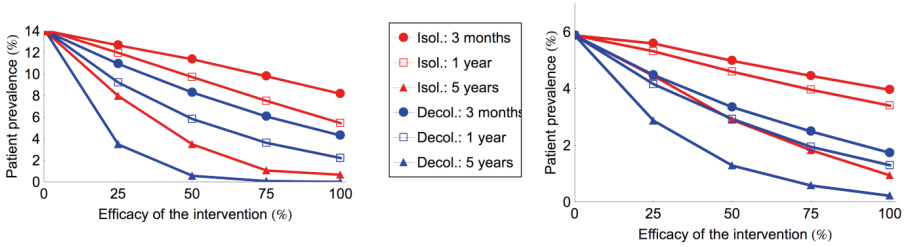


Figure 1. Patient prevalence level of MRSA as function of the efficacy of patient decolonization or isolation after 3 months, 1 year and 5 years. 88% of the patients are screened upon hospital admission. Carriers are either decolonized (red lines) or isolated (blue lines). The left figure corresponds to a high endemicity level, the right figure to a medium endemicity level.

Role of health care workers

The role of persistently colonized HCWs is composed of two aspects: the percentage of HCWs being persistently colonized (which depends on the probability for a non-colonized HCW to acquire colonization from a colonized patient) and the likelihood per colonized HCW to act as a source. Due to these different aspects few highly infectious persistently colonized HCWs may spread MRSA to the same number of patients as many persistently colonized HCWs who are individually less prone to spread MRSA. The benefits of decolonizing HCWs importantly depend on these parameters. Of note, this does not include their role as vectors with temporarily contaminated hands, which was considered as patient-to-patient transmission. We have evaluated the dynamics of the MRSA patient prevalence for several values of both aspects. The proportion of HCWs being persistently colonized ranged from 1% to 10%, and proportions of patient acquisitions resulting from persistently colonized HCW ranged from 10% to 50%. We quantified the effects of monthly, biannually and yearly decolonization of HCWs (Figure 2 and Figure A1 in the Supplementary material). The largest benefit from HCW decolonization is achieved when few persistently colonized HCWs are responsible for a large proportion of acquisitions. Naturally, monthly decolonization of HCWs is more effec-

tive than biannual and annual decolonization, but always less effective than decolonization of patients with documented MRSA carriage with an efficacy of 100%.

In practice, though, decolonization of patients will be less often successful than decolonization of HCWs [8]. We have, therefore, determined how efficacious patient decolonization should be to achieve the same MRSA patient prevalence (in 15 years after the start of the intervention) as 100% efficacious HCW decolonization (Table A1 in the supplementary material). The maximum efficacy needed is 55%-68% for scenarios in which 50% of acquisitions result from persistently colonized HCWs. Yet, when persistently colonized HCWs are responsible for 10% of all acquisitions, efficacy of patient decolonization need only be 8%-9%. With a medium endemic prevalence, it will take more time before HCWs become persistently colonized. Therefore, interventions targeted at HCWs become more effective in settings with a lower patient prevalence (data not shown).

As HCW decolonization has been used in combination with patient isolation in several countries, we also investigated the effects of perfect periodical decolonization of HCWs in combination with patient isolation (with 50% efficacy). In Figure 3 we have depicted the most extreme scenarios (i.e., 10% prevalence among HCWs being responsible for 10% of acquisitions, and 1% of HCWs being responsible for 50% of acquisitions) in settings with higher endemicity level . As expected, the additional benefit of HCW decolonization is much higher in the latter scenario (Figure 3) but differences between decolonization frequencies are relatively small. The effect of the combined intervention in settings with medium endemicity level is shown in the supplementary material (Figure A2).

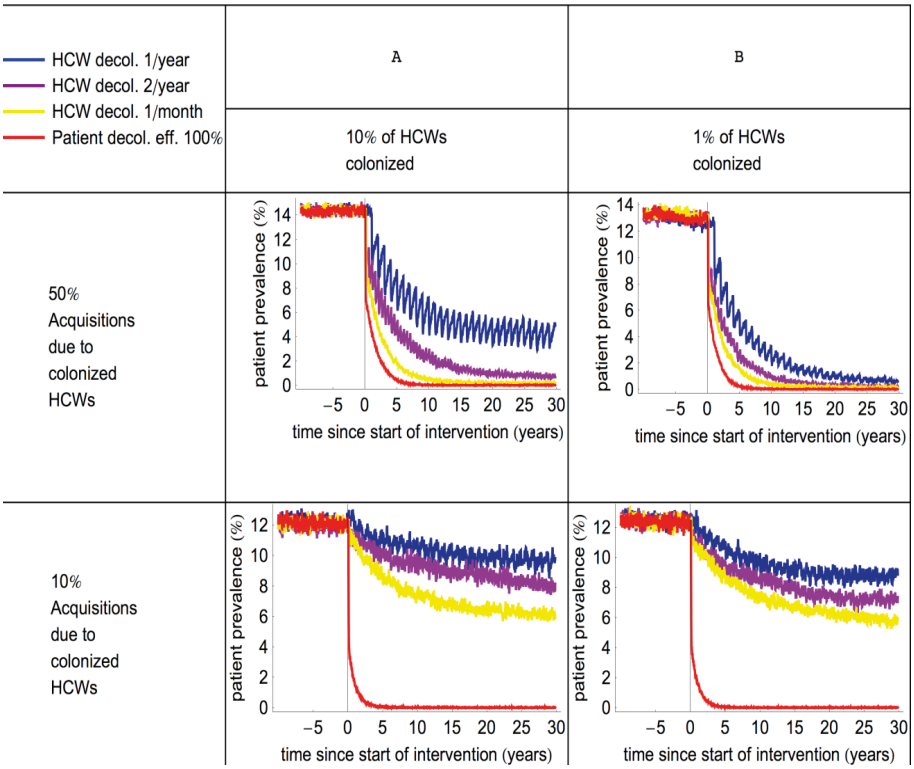


Figure 2. The effects of health care worker decolonization on the patient prevalence level of MRSA. Scenarios I and II, correspond to the relative importance of persistently colonized health care workers (HCW) in the spread of MRSA (being 50% and 10 %, respectively) in the endemic situation. Scenarios A and B correspond to different values for the percentage of persistently colonized HCWs. Results are based on 50 runs of the stochastic simulation model. The lines represent the average hospital-wide MRSA patient prevalence, starting from the baseline scenario of an average patient prevalence of 14% (high endemicity level). The red line represents the patient prevalence with patient decolonization (100% efficacious) and the other lines represent the patient prevalence with health care worker decolonization (100% efficacious) performed once per year (blue), twice per year (purple) and every month (yellow).

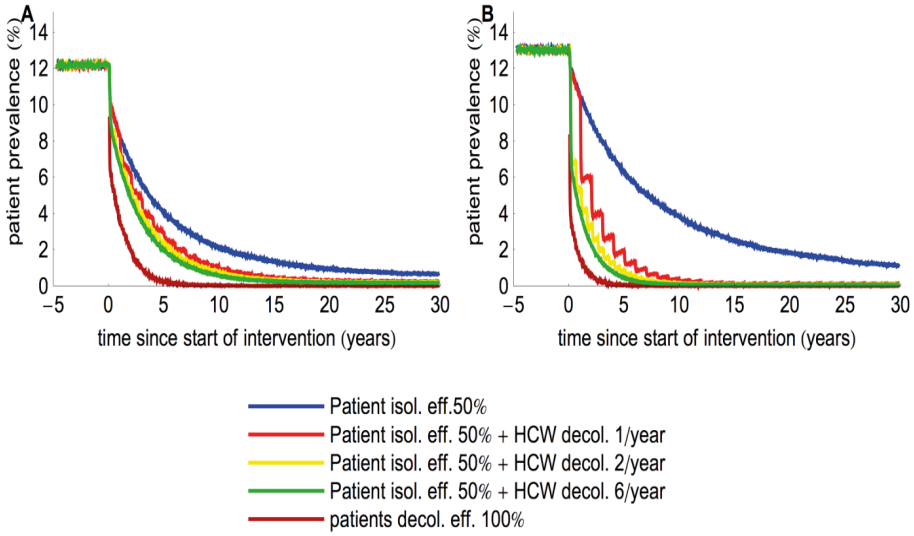


Figure 3. Effect of combining patient isolation with decolonization of health care workers. The two graphs correspond to scenarios with minimum effect of decolonization of HCWs (A) (10% of HCWs are persistently colonized and responsible for 10% of acquisitions) and maximum (B) (1% of HCWs is persistently colonized and responsible for 50% of acquisitions). The effect of patient decolonization (100% efficacious) is added for comparison.

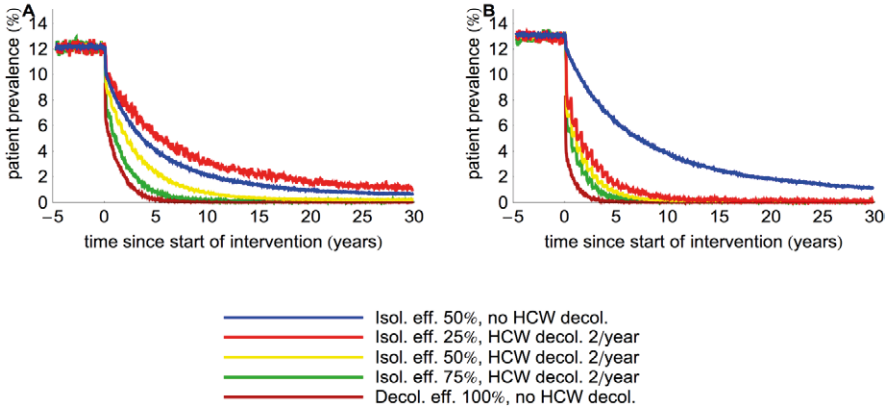


Figure 4. Effect of the patient isolation efficacy when combined with biannual decolonization of health care workers. The two graphs correspond to scenarios with minimum effect of decolonization of HCWs (A) (10% of the HCWs are persistently colonized and responsible for 10% of acquisitions) and maximum (B) (1% of the HCWs is persistently colonized and responsible for 50% of acquisitions). The efficacy of HCW decolonization is 100%. Lines with patient decolonization (100% efficacious) and only isolation (50% efficacious) are added for comparison.

In real life, multiple interventions are usually applied simultaneously. We, therefore, also determined the incremental effect of HCW decolonization to patient isolation and decolonization together. When isolation efficacy of patients with MRSA is 50% and decolonization efficacy among patients would be 90%, additional effects of HCW decolonization will be small, even for the `best-case scenario` of monthly decolonization with 1% of HCW being persistently colonized and responsible for 50% of acquisitions (data not shown). When the efficacy of patient decolonization is only 10% and isolation efficacy is 50%, monthly decolonization of HCWs will only substantially reduce MRSA patient prevalence in the extreme scenario with 1% of the HCW being persistently colonized and responsible for 50% of the acquisitions.

Discussion

We have used a mathematical model to investigate the effects of isolation strategies for patients and of decolonization for patients and HCWs. Our findings demonstrate that – with similar levels of efficacy - patient decolonization is more effective than patient isolation and that active decolonization of persistently colonized HCWs only has a significant impact if a considerable proportion (e.g., 50% or more) of the MRSA acquisitions by patients can be ascribed to persistently colonized HCWs.

Our analyses clearly illustrate the two processes that determine the potential role of persistently colonized HCWs in MRSA transmission. One of these parameters, the proportion of HCWs being colonized, can easily be determined. Reported point-prevalence rates of HCW colonization in the nares range from <0.1% in Dutch hospitals with low endemic levels of MRSA [17] to 5-6% in hospitals with high endemic levels [18-21]. The other parameter, though, the relative contribution of these colonized HCWs for MRSA acquisition, is much more difficult to quantify, as both extensive screening among patients and HCWs and genotyping to demonstrate genetic similarities of MRSA isolates would be needed. Despite multiple, usually anecdotal, reports about MRSA carriage in HCWs, (as reviewed in [7]), this parameter has to the best of our knowledge never been quantified.

Naturally, the relative effects of HCW decolonization depend on the parameters used in the model. For instance, at lower endemic levels of MRSA the effects of HCW decolonization would be relatively higher. However, the dependency of two parameters, the fraction persistently colonized HCWs and the percentage of acquisitions resulting from them, remains important in all settings and estimation of these parameters in clinical settings will allow more precise determination of the effectiveness of HCW decolonization in reducing nosocomial MRSA-transmission.

Several studies have attempted to quantify the effects of bacterial eradication therapies in hospitalized patients [22,23]. In a systematic review, nasal applica-

tion of mupirocin had, as compared to placebo, an estimated pooled relative risk of failure to eradicate nasal *S. aureus* carriage after one week of 0.10 (0.07-0.14), and effects were similar for patients and healthy subjects as well as in studies including only MSSA or both MSSA and MRSA carriers [8]. In a recent study, a combined approach of universal screening of MRSA carriage with PCR testing, followed by topical decolonization with mupirocin and isolation precautions for carriers, was associated with a 69.6% reduction in the aggregate hospital-associated MRSA disease incidence [24]. However, in the latter study, as in most studies in the systematic review, several interventions were tested simultaneously, hampering accurate quantification of the effects of decolonization.

In a Spanish intensive care burn unit topical application of vancomycin in the nose, oropharynx and intestines was evaluated in an observational before-after study during nine years [25]. Although no data are presented about the decolonization efficacy on a patient level, acquisition rates and average endemic patient prevalence levels were 80% lower with vancomycin use.

Another option, which we did not investigate, would be to restrict HCW decolonization to outbreak settings only. This strategy could lower the decolonization frequency of HCWs, especially when outbreaks are rare. However, the effectiveness of this strategy strongly depends on the definition of an outbreak and the sensitivity of detecting outbreaks.

Our analysis of non-instantaneous decolonization in the supplementary material is limited to patients. Indeed, instantaneous decolonization of HCWs may always be achieved in practice by temporary dismissal of known colonized HCWs and by replacing those by uncolonized ones."

Although decolonization of patients seems, at least theoretically, an effective measure, these benefits should be balanced with potential adverse events. Topical use of mupirocin and antibiotics are considered safe, but selection of antibiotic resistance remains a potential threat. Especially the use of topical vancomycin should be carefully judged, as vancomycin is one the few remaining antibiotics available for intravenous treatment of MRSA infections.

Naturally, the model used is a simplification of reality. For instance, there are many specialized hospital wards with different patient populations and different patient transfer rates to other wards. Also, the susceptibility of patients to acquire MRSA will differ. Furthermore, we assumed that length of stay was not affected by colonization status, that all HCWs work in shifts of 8 hour, that direct transmission of MRSA between HCWs did not occur and that HCWs could not acquire persistent colonization outside hospital settings, e.g. from their colonized homes or families. Also, isolation was assumed to be equally efficacious in all isolated patients, which may not be true if the number of isolation beds available is limited. Finally, we did not explicitly model resistance development as a result of decolonization strategies. Our findings should, therefore, not be interpreted as

a definitive argument in favour of widespread use of antibiotics for controlling the nosocomial spread of MRSA, but more as an illustration that different approaches might be more effective than our current strategies. Furthermore, we have identified research targets that could be pursued in epidemiological studies that are needed to further quantify the potential benefits of HCW decolonization.

Conclusions

Based upon a theoretical framework, we have identified the scenarios in which decolonization of persistently colonized HCWs, either as a stand-alone measure or when added to interventions targeted at colonized patients, can significantly improve MRSA control in health care settings. In general, decolonizing HCWs becomes more beneficial when their carriage rates decrease and – simultaneously – their contribution to patient acquisition (per colonized HCW) increases.

Yet, decolonization of MRSA carriage among patients will be more efficacious than decolonization of HCWs in most scenarios with high endemicity levels, even for a low decolonization efficacy among patients. Furthermore, patient isolation, albeit conceptually less efficient than patient decolonization, will also be more effective than HCW decolonization. Note that if decolonization therapy in patients would not eradicate MRSA carriage, but only suppresses infectiousness by lowering the bacterial load, decolonization is conceptually similar to patient isolation as both reduce infectiousness without interrupting the feedback loop of colonized patients being readmitted. Considering the continuously rising patient prevalence levels of MRSA and the repeatedly reported failures of isolation policies to control its spread, our findings support further evaluation of pharmacological (and other) strategies to actively achieve eradication of MRSA carriage in patients.

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Supplementary material

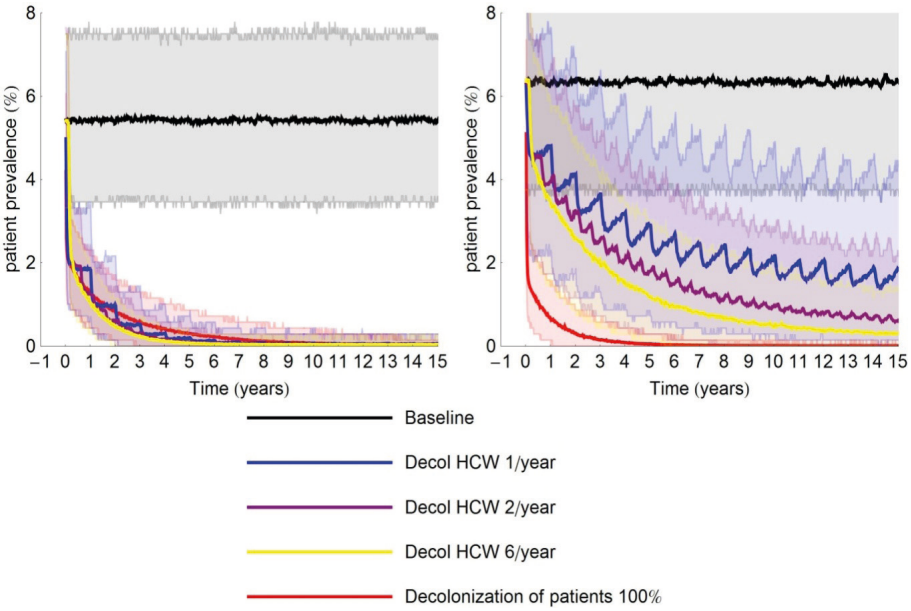


Figure A1. The effects of health care worker decolonization on the patient prevalence level of MRSA. The left figure corresponds to a relative importance of persistently colonized health care workers (HCW) on the spread of MRSA before interventions of 50%, the right figure to 10%. 5% percent of the HCWs are persistently colonized. Results are based on 1000 runs of the stochastic simulation model. The lines represent the average hospital-wide patient prevalence level of MRSA, starting from the baseline scenario of an average patient prevalence of 6%. The red line represents patient decolonization (100% efficacious). The other lines represent health care worker decolonization (100% efficacious) performed once per year (blue), twice per year (purple) and every month (yellow). Shaded areas correspond to 95% credibility intervals.

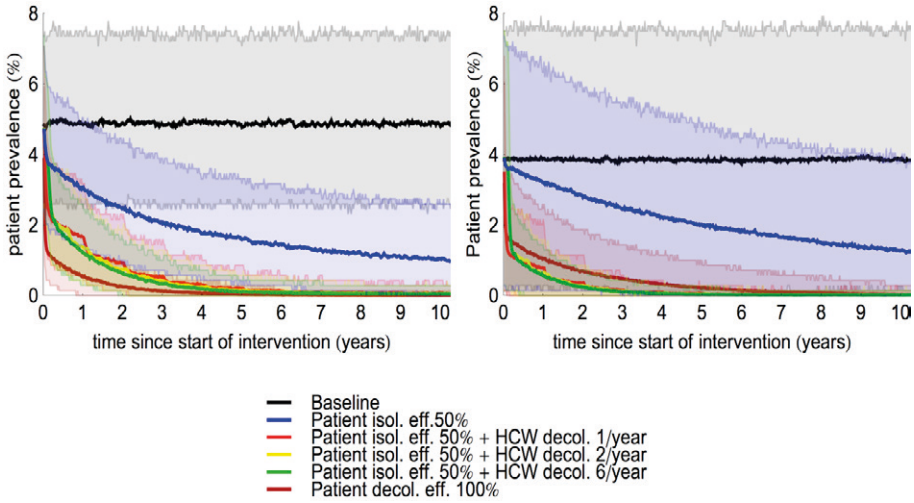


Figure A2. The effects of combining patient isolation with 100% efficacious decolonization of health care workers. The lines represent the average hospital-wide patient prevalence level of MRSA, starting from a medium endemic setting. The effect of decolonization of HCWs is minimal in the left figure (10% of the HCWs are persistently colonized and they are responsible for 10% of the acquisitions in the endemic situation) and maximal in the right figure (1% of the HCWs are persistently colonized and they are responsible for 50% of the acquisitions in the endemic situation). The effect of patient decolonization (100% efficacious) is added to compare these strategies. Shaded areas correspond to 95% credibility intervals.

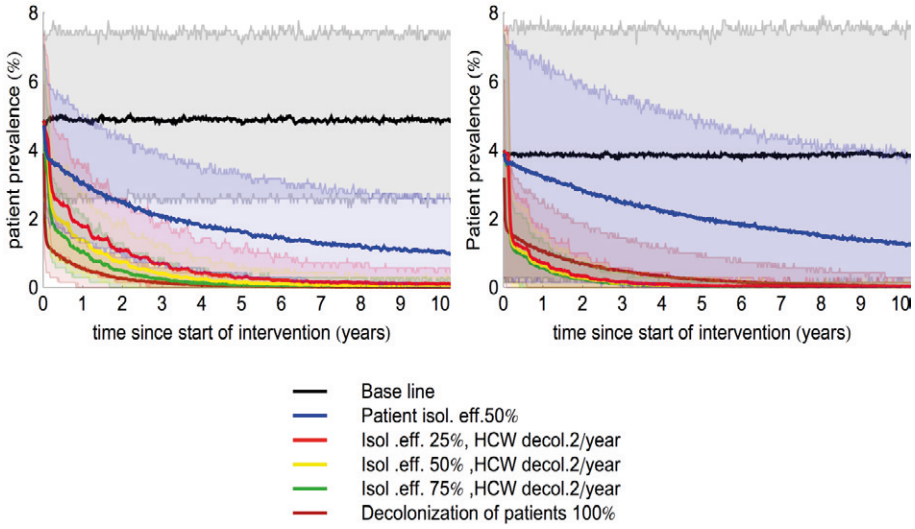


Figure A3. The effects of the patient isolation efficacy when combined with biannual 100% efficacious decolonization of health care workers. The lines represent the average hospital-wide patient prevalence level of MRSA, starting from the baseline scenario of a medium endemic settings. The effect of decolonization of HCWs is minimal in the left Figure (10% of the HCWs are persistently colonized and they are responsible for 10% of the acquisitions in the endemic situation),and maximal in the right Figure (1% of the HCWs are persistently colonized and they are responsible for 50% of the acquisitions in the endemic situation). Lines with patient decolonization (100% efficacious) and only isolation (50% efficacious) are added to compare the strategies. Shaded areas correspond to 95% credibility intervals.

Non-instantaneous decolonization

Where isolation can be achieved quickly, the decolonization process may take several days. When decolonization works not instantaneously, isolation will initially be more effective. For instance, isolation will reduce MRSA prevalence more effectively in the first 2 months if decolonization takes 10 days or more. However, even if decolonization takes that long, decolonization will ultimately be more effective. Here we assumed a constant time till decolonization, which is the worst-case scenario compared to all other distributions for the time till decolonization with the same mean (data not shown).We did not explicitly analyze non-instantaneous decolonization of HCWs. Yet, instantaneous decolonization of HCW can be realized, for example, by temporary dismissal of known colonized HCWs and by replacing those by uncolonized ones.

Parameterization.

We choose the patient prevalence of MRSA hospital-wide and in ICUs as well as the fraction HCWs who are persistently colonized and which fraction of the acquisitions of MRSA by patients are due to persistently colonized HCW. We varied 4 transmission parameters in our simulation code to obtain these desired values. These 4 parameters are 1) the susceptibility of HCWs for acquisition of persistent colonization, 2) the infectivity of persistently colonized HCWs, 3) the susceptibility for MRSA acquisitions of patients (increased susceptibility increases the acquisition rate of all modes) and 4) the relative difference in transmission rates in ICUs and other wards. We used a gradient based algorithm to obtain the best parameters, where we ran our coded for 50 years after a burn-in period for a given set of parameters. We started the algorithm at several initial values to avoid local minima. However, because our model is stochastic in nature, the obtained parameters may lead to slightly different values as desired for the patient prevalence of MRSA hospital-wide and in ICUs and the fraction HCWs who are persistently colonized and which fraction of the acquisitions of MRSA by patients are due to persistently colonized HCW .

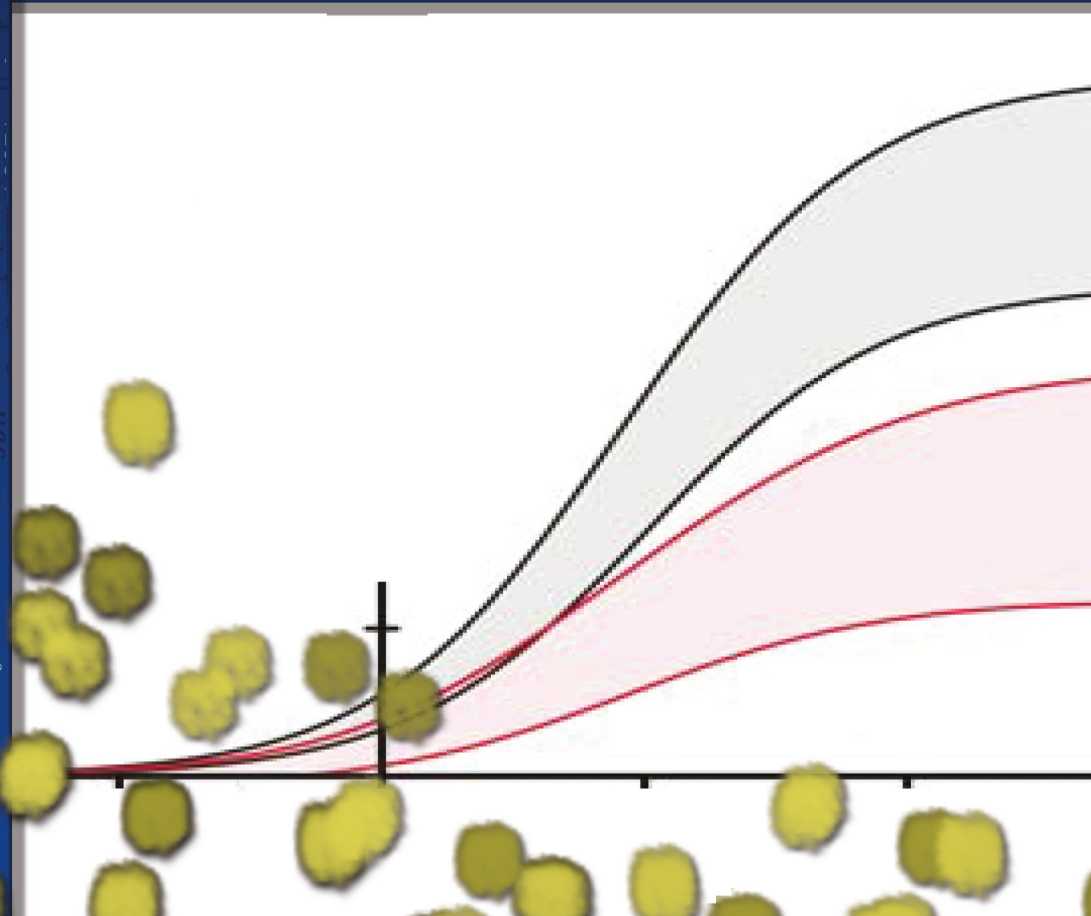
Table A1. Efficacy of patient decolonization needed to be equally effective as decolonization of health care workers. We assume that health care worker (HCW) decolonization is 100% effective and is performed once a year, twice a year or every month. We have determined how efficacious universal screening followed by decolonization of known carriers should be in order to achieve the same hospital-wide MRSA patient prevalence (in 15 years after the start of the intervention) as HCW decolonization. Before the start of the intervention, 1%, 5% or 10% of the HCW are persistently colonized, while they are responsible for 10%, 30% and 50% of all MRSA acquisitions by patients.

	HCW decolonization	10% of HCW colonized	5% of HCW colonized	1% of HCW colonized
50% Acquisitions due to colonized HCW	Once per year	28%	32%	25%
	Once per half year	43%	47%	45%
	Once per month	65%	68%	55%
30% Acquisitions due to colonized HCW	Once per year	15%	16%	15%
	Once per half year	23%	22%	20%
	Once per month	32%	30%	27%
10% Acquisitions due to colonized HCW	Once per year	4%	4%	4,5%
	Once per half year	6%	6%	6%
	Once per month	9%	8%	8%

Chapter 4

Successful veterans affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections revisited

Gurieva T, Bootsma MCJ, Bonten MJM.
Clin. Infect. Dis. 2012; 54:1618–1620.



Abstract

In 2011 Jain et al reported a 62% reduction of healthcare-associated methicillin-resistant Staphylococcus aureus infections that resulted from an intervention bundle. Here we present a mathematical model and prove, using parameters from the study by Jain et al, that the universal screen and isolate strategy can have contributed only marginally to the reduction in infections.

Introduction

Infections caused by antibiotic-resistant bacteria, such as methicillin-resistant Staphylococcus aureus (MRSA), frequently occur in hospitalized patients and are associated with increased disease burden and worse patient outcome [1]. Curtailing nosocomial transmission of MRSA to prevent hospital-acquired MRSA infections is an important goal of hospital infection prevention. The application of barrier precautions for patients infected or colonized with MRSA has been effective in several countries with low-endemicity MRSA levels [2], yet implementation of universal MRSA screening and isolation of identified carriers has remained controversial in countries with high-endemicity MRSA-levels, primarily because several studies have shown reductions in MRSA infections [3, 4] while others have not [5, 6]. Recently, implementation of a MRSA bundle in 153 hospitals was associated with a 62% reduction in rates of healthcare-associated MRSA infections [7]. Like all quasi-experimental studies, controlling for confounding variables is difficult and causality between interventions and observed changes cannot be automatically assumed [8]. The bundle, which was fully implemented in October 2007 and observed until June 2010, comprised 3 interventions: (1) universal nasal MRSA surveillance of admitted and transferred patients followed by contact precautions for colonized patients, (2) improved adherence to hand hygiene protocols, and (3) an institutional culture change whereby everyone with patient contact is responsible for infection control. The first 2 interventions aim to reduce the number of transmission events. Indeed, Jain et al observed a 17% reduction in MRSA acquisition events in intensive care units (ICUs) and a 21% reduction in non-ICUs (from 3.02 and 2.54 per 1000 patientdays in October 2007 to 2.50 and 2.00 per 1000 patient-days in June 2010, respectively). With a constant colonization prevalence of MRSA of 13.6% at admission [7], the decline in point prevalence of MRSA should be relatively less than the decline in acquisition rates. One would expect the incidence of MRSA infections to decrease more or less proportionally to the decrease in the point prevalence of MRSA colonization. However, Jain et al observed incidence reductions as high as 62% (1.64 to 0.62 per 1000 patient-days from October 2007 to June 2010) in ICUs and 45% (0.47 to 0.26 per 1000 patientdays) in non-ICUs. During this program 1 712 537 surveillance- screening tests were obtained and other significant financial efforts—eg, manpower to obtain, transport, and perform tests, and to communicate results—are likely to have been used. Here we assess the extent to which prevention of MRSA transmission, through either better hand hygiene or barrier precautions, contributed to the observed reduction in MRSA infections.

Methods and Results

We consider 2 simple models for the dynamics of MRSA colonization (see Supplementary Material for details on model choice). In both models there is a constant probability, $\alpha = 0.136$, that an admitted patient is colonized with MRSA [7]. Independent of colonization status, patients have a median length of stay (LOS)

of 3.0 days [6], which, for simplicity, we assume to be exponentially distributed (see Supplementary Material for 9 other distributions). In model 1, we ascribe the reductions in MRSA carriage acquisition rates after bundle implementation fully to improved hand hygiene without effects of barrier precautions. Bundle implementation reduces the transmission parameter from β to $\beta 1$. In model 2, we ascribe the reductions in MRSA carriage acquisition rates fully to contact precautions without improvement in hand hygiene if contact precautions are absent (see Supplementary Material for modeling details).

Although the point prevalence of MRSA colonization was not directly reported, patients were screened at admission and at discharge. Based on reported numbers of MRSA acquisitions per 1000 patient-days (T) in ICUs and non-ICUs, we can estimate the point prevalence (P) according to: $P = \alpha + T \cdot \langle LOS \rangle / 1000$, with $\langle LOS \rangle$ the average LOS (1.44 times the median LOS for exponential distributions). If MRSA dynamics were stable before bundle implementation, estimated MRSA transmission parameters at the start of interventions are $\beta = 0.024$ for ICUs and $\beta = 0.020$ for non-ICUs. This corresponds to reproduction numbers per hospital admission ($RA = \beta \langle LOS \rangle$) of 0.10 in ICUs and 0.09 in non-ICUs. After bundle implementation, MRSA dynamics are expected to change, but we can assume that the equilibrium is reached when the observation period ends after 33 months (see Supplementary Material). With this assumption and model 1, we obtain $\beta 1 = 0.84 \cdot \beta$ for ICUs and $\beta 1 = 0.80 \cdot \beta$ for non-ICUs; a 16% hand hygiene efficacy improvement in ICUs and a 20% improvement in non-ICUs. Other distributions for the LOS gave similar results (see Supplementary Material).

In the second scenario, the MRSA transmission parameter β is reduced to $\beta 1$ only for isolated patients; bundle implementation does not affect spread by unisolated colonized patients. If MRSA colonization is detected only by means of admission and discharge screening and not by means of clinical cultures or during transfer between wards, colonized patients will face contact precautions either during their entire hospital stay or not at all. Although unrealistic, this assumption maximizes the estimated isolation efficacy. Of admitted patients, 96% [7] were screened. Assuming 100% sensitivity of screening tests, instantaneous availability of test results, and immediate treatment with barrier precautions for detected carriers, we find that $\beta 1 = 0.82 \cdot \beta$ in ICUs and $\beta 1 = 0.78 \cdot \beta$ in non-ICUs, for an isolation efficacy of 18% and 22%, respectively. With test sensitivity of 93% and a 1-day delay before installation of barrier precautions, estimated isolation efficacy increases to 24% in ICUs and 29% in non-ICUs.

Assuming a constant daily risk (k) for colonized patients to develop an infection, we can calculate this risk based on numbers of healthcare-associated infections, as reported by Jain et al [7]. Independent of model choice, the daily infection risk needs to decrease by 64% in ICUs and by 44% in non- ICUs to explain the observations. Based on estimates obtained for efficacy of the intervention on transmission prevention and daily infection risk, we can predict how healthcare-as-

sociated infection rates would decline if the intervention affected either only the parameter k or only the transmission parameter. We conclude (see Supplementary Material) that in ICUs 1%–4% of the reduction in infection rate is attributable to prevention of acquisition of colonization. In non-ICUs, this range is 3%–6%. Even if patients who became colonized during their stay had a 10 times higher daily infection risk compared with patients already colonized at admission, only 6%–15% of the reduction in infection rates in ICUs and 17%–26% in non-ICUs (see Figure 1) is attributable to transmission prevention. If, in addition to this high daily infection risk after acquisition, acquisition was 20% less effectively detected before bundle implementation than after it, 16%–33% of the reduction in infections in ICUs and 36%– 50% in non-ICUs would be attributable to transmission prevention measures.

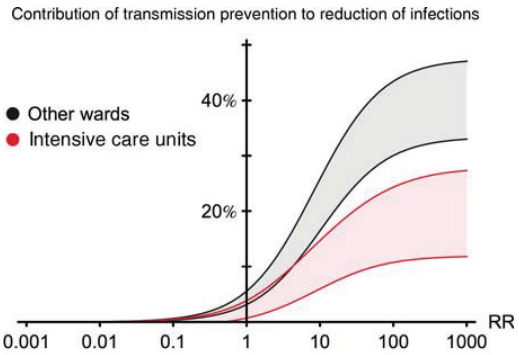


Figure 1. Possible range for the contribution of transmission prevention to the reduction in the number of infections as a function of the relative daily risk to developing an infection for patients who became colonized during their hospital stay compared with those who were already colonized at admission. Abbreviation: RR, relative daily risk.

Discussion

Only a small fraction of the phenomenal effects on MRSA infection rates described by Jain et al can result from interventions aimed at transmission prevention, simply because transmission rates before bundle implementation were already low and most patients with MRSA colonization were already colonized at admission. Unless barrier precautions reduce the daily infection risk for colonized patients, admission screening and isolation could not have caused the observed reduction in infections. We therefore hypothesize that other practices have changed, eg, better management of intravascular lines. This is supported by concurrent reduction in infections caused by vancomycin-resistant enterococci and *Clostridium difficile*, as reported voluntarily by some participating hospitals.

We deliberately determined the maximum possible effects of both interventions by excluding any effect of the other intervention and no identification of MRSA

carriage after admission screening. Including these possibilities would reduce the estimated efficacy of each intervention. The efficacy of patient isolation on MRSA transmission prevention has not been determined frequently. The other best estimate (25%) was also obtained in US hospitals [9] and coincides with our estimate. The calculated reproduction number per hospital admission (RA) was much lower than previous estimates of RA values for MRSA. Ranges of 0.1–0.6 in 8 ICUs in the United States [9] and 0.68–0.93 in The Netherlands [10] were reported, and modeling studies suggest that RA should be in the range of 0.5–1 [11, 12]. The combination of low nosocomial transmission rates and the 13.6% admission MRSA prevalence implies either that patients have had multiple previous hospital admissions or that MRSA was acquired outside hospitals. Unfortunately, no information is available on patient transfers from other hospitals or long-term care facilities or on community-acquired MRSA proportions.

Naturally, our analyses can provide only crude estimates, because we considered aggregated data from 153 hospitals. Therefore, some individual hospitals may have had higher efficacy levels of transmission interruption measures. Furthermore, most hospitals started implementation in the months before the baseline measurement was taken in October 2007. However, incidences of healthcare-associated MRSA infections started to decline only in April 2008 in ICUs and even later in non-ICUs. Therefore, reductions in transmission before October 2007, if present, were not associated with fewer healthcare-associated MRSA infections.

Furthermore, in the cluster-randomized trial by Huskins et al [6], admission screening followed by barrier precaution did not prevent MRSA colonization or infection. These and our findings have important implications for translating the results of Jain et al into practice guidelines. The low efficacy of both measures aimed at interrupting MRSA transmission should be balanced with universal screening costs. Therefore, policy makers should be reluctant to recommend adaptation of universal screening and patient isolation of MRSA carriers. However, more cluster-randomized trials are needed to determine the key factors for isolation success or failure.

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Supplementary Material

Introduction

In the next section we discuss two models for the spread of MRSA based on differential equations in which the length of stay of patients is exponentially distributed. Later on in the supplementary material we will also discuss other distributions for the length of stay. Some other distributions fit the interquartile ranges for the observed length of stay better than the exponential distribution, but the formulas are more complicated and the results are essentially the same.

All our analyses are based on deterministic models. This has the advantage that the modeling is relatively easy, but may be less accurate when stochasticity is important. In this case, for example, an agent-based model could have been used. As long as we group together all 153 hospitals and consider it as one hospital, the population size is sufficiently large to expect that stochastic effects will be small. Modeling each hospital separately would require much more details of individual hospitals, which are not available, and is, therefore, considered not feasible. Moreover, the aim of this study is not to provide the most accurate parameter estimates possible, but to show that the admission screening and subsequent isolation of carriers of MRSA cannot explain the reported decrease in the rate of hospital-associated MRSA infections. Even if the relative contribution of the screen and isolate strategy on the reduction of hospital-associated MRSA infections would be a few percent too high or too low, this would not affect our conclusions.

Finally, there is a substantial amount of MRSA transmission models in the literature, such as caricatural models to estimate important transmission parameters [S1-S4] or to determine which assumptions are essential to observe certain phenomena [S5, S6]. These models typically are not specific for MRSA but for antibiotic resistant pathogens in general. Furthermore, more detailed models exist, which aim to predict the efficacy/cost-effectiveness of interventions [S7-S12]. Here we use mathematical modeling to re-analyze data from a recently published nonrandomized trial [S13]. This approach is novel, but may be a helpful tool to understand the implications of clinical trials.

The study of Jain et al. [S13] was a quasi-experimental trial in 153 hospitals in the US. A bundle of interventions (see [S13] and main article for details) was implemented in October 2007 and the results in terms of hospital-acquired MRSA infections in intensive care units (ICUs) and non-intensive care units (non-ICUs) and transmission episodes in ICUs and non-ICUs were observed till June 2010.

Basic models for the dynamics of colonization with MRSA

U, C and *I* respectively, denote the fraction of hospitalized patients who are uncolonized, colonized but not treated with barrier precautions and colonized and

treated with barrier precautions *(U+C+I=1)*. In both models there is a constant probability α=0.136 that an admitted patient is colonized with MRSA [S13]. Patients have, independent of their colonization status, a median length of stay (LOS) of 3.0 days [S13], which is exponentially distributed (see further on in the supplementary material for nine other distributions). The parameter of the exponential distribution is given by *Log(2)/3.0*.

Although data on the point prevalence of colonization prevalence of MRSA in the hospital weren't directly available, patients were screened on admission and at discharge. Based on the estimate of the number of MRSA acquisitions per 1000 patient days (*T*) in ICUs and non-ICU wards (see Supplementary Table 1), we can calculate the point prevalence of colonization (*P*) according to:

$$P = \alpha + T\frac{< LOS >}{1000},$$

where *<LOS>* is the mean LOS. The prevalence of colonization before and after implementation of the bundle and in ICUs and non-ICU wards is given in Supplementary Table 1.

Model 1

To quantify the potential role of improved hand hygiene we ascribe the reduction in the MRSA carriage acquisition rate after implementation of the bundle fully to improved hand hygiene with no effects of barrier precautions. Bundle implementation reduces the transmission parameter from β to β_1 and we neglect patients treated in isolation (*I*), i.e., *I*=0. The model is represented by the following differential equations per period (see Supplementary Figure 1 for a schematic representation):

$$\begin{aligned} \frac{dU}{dt} &= \frac{C-\alpha}{\langle LOS \rangle} - \beta UC & & \frac{dU}{dt} = \frac{C-\alpha}{\langle LOS \rangle} - \beta_1 UC \\ \frac{dC}{dt} &= \frac{\alpha - C}{\langle LOS \rangle} + \beta UC \quad \xrightarrow{\text{Intervention}} & \frac{dC}{dt} &= \frac{\alpha - C}{\langle LOS \rangle} + \beta_1 UC \\ U + C &= 1 & U + C &= 1 \end{aligned}$$

If we assume that MRSA dynamics were stable before implementation of the bundle, the MRSA transmission parameter in ICUs and non-ICU wards can be calculated as follows:

$$\frac{dC}{dt} = 0 \Rightarrow \beta = \frac{1}{\langle LOS \rangle}\frac{C-\alpha}{(1-C)C}$$

In model 1, the fraction *C* equals the point prevalence *P*. Therefore, we have that $C=\alpha+T<LOS>/1000$. α equals 0.136 and before the intervention, *T* equals 3.02 and 2.54 per 1000 patient-days in ICUs and non-ICUs respectively. This leads (with $<LOS>=3/log(2)$) to *C*=0.149 and 0.147 in ICU and non-ICUs respectively at the start of the intervention.

Calculated MRSA transmission parameters are 0.024 and 0.020 for ICUs and non-ICU wards, respectively. This implies that the expected number of transmission

events from a colonized patient during his/her length of stay, i.e., the reproduction number per hospital admission ($R_A=\beta\langle LOS\rangle$), equals 0.10 in ICUs and 0.09 in non-ICU wards. Note that the mean length of stay equals *1/log(2)* times the median length of stay if the length of stay is exponentially distributed.

MRSA dynamics are expected to change after implementation of the bundle, but a stable MRSA prevalence is expected to be reached within a month (see last section of the supplementary material). We, therefore, assume that an equilibrium has been reached at the end of the observation period, 33 months after bundle implementation. With this assumption we obtain for ICUs, $\beta_1=0.84\cdot\beta$, which corresponds to an improvement of hand hygiene efficacy of 16%. In non-ICU wards, $\beta_1=0.80\cdot\beta$, which corresponds to an improvement of hand hygiene efficacy of 20%.

Model 2

To quantify the potential role of barrier precautions, we ascribe the reduction in the MRSA carriage acquisition rate after implementation of the bundle fully to the barrier precautions with no effects of improvement of hand hygiene if contact precautions are absent.

The model contains three compartments (*U, C, I*). The MRSA transmission parameter β is reduced only for isolated patients (*I*), as the spread of MRSA due to non-isolated colonized patients is the same as before bundle implementation (as we assume no improvement of hand hygiene). If we assume that MRSA colonization is only detected by screening at admission and discharge and not by clinical cultures or during transfer between wards, colonized patients won't switch from treatment without contact precautions (*C*) to treatment with contact precautions (*I*), i.e., colonized patients will either face contact precautions during their entire hospitalization or not at all. Naturally, this assumption isn't realistic, but it maximizes the estimated efficacy of isolation. A fraction f=0.96 of the admitted patients were screened, and assuming 100% sensitivity of screening tests, instantaneous availability of test results, and immediate treatment with barrier precautions for all detected carriers, the fraction uncolonized (*U*), colonized but not isolated (*C*), colonized and isolated (*I*) and the point prevalence (*P*) satisfy:

$$\begin{aligned}
&\frac{dU}{dt}=\frac{1-\alpha-U}{\langle LOS\rangle}-\beta UC && \frac{dU}{dt}=\frac{1-\alpha-U}{\langle LOS\rangle}-U(\beta C-\beta_1 I)\\
&\frac{dC}{dt}=\frac{\alpha-C}{\langle LOS\rangle}+\beta UC \quad \xrightarrow{\text{intervention}} && \frac{dC}{dt}=\frac{\alpha(1-f)-C}{\langle LOS\rangle}+U(\beta C+\beta_1 I)\\
&I=0 && \frac{dI}{dt}=\frac{\alpha f-I}{\langle LOS\rangle}\\
&U+I+C=1 && U+C+I=1\\
&P=C && P=I+C
\end{aligned}$$

The fraction of the patients in isolation (*I*) satisfies $I=\alpha f$. Assuming again an equilibrium situation, we find that in ICUs $\beta 1$=0.82·β, which corresponds to efficacy of isolation of 18%. In non-ICU wards, $\beta 1$=0.78·β, which corresponds to efficacy

of isolation of 22%. If we use a sensitivity of the test of 93% and a delay of 1 day before colonized patients are isolated, the efficacy of isolation is 24% and 29% in ICUs and non-ICU wards respectively (see next section for the model which incorporates a delay between admission and isolation of colonized patients).

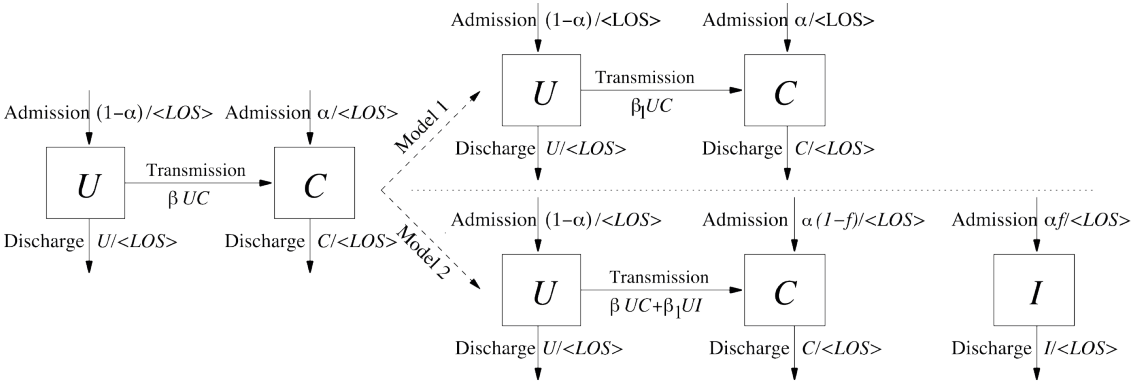

Figure S.1. Schematic representation of the two models.

Other distributions for the length of stay

We fitted 10 distributions (Inverse Gaussian, Lognormal, Suzuki, Generalized Gamma, K, Gamma, Weibull, Exponential, Nakagami and Hoyt) to the interquartile ranges for the length of stay (2.0, 3.0 and 7.0) using a least square error approach in Mathematica (Wolfram Research, Inc., Mathematica, Version 8.0, Champaign, IL (2010)), where we allowed the interquartile ranges for the length of stay to be in the interval (1.95-2.05), (2.95-3.05) and (6.95-7.05). The parameters of the 10 distributions are shown in Supplementary Table 2 and 3. (Note that the parameter of the exponential distribution is slightly different from the parameter estimate based on the median only as used before.)

Let T be the number of MRSA acquisitions per 1000 patient days and α=0.136 the admission prevalence. The probability that a randomly chosen patient will acquire colonization is $T<LOS>/1000$. At the start of the observation period (October 2007), T=3.02 and T=2.54 in ICUs and non-ICUs respectively. At the end of the study period (June 2010), T=2.50 and T=2.00 in ICUs and non-ICUs respectively.

We now want to calculate the probability that a patient acquires colonization in our model. Only patients uncolonized on admission (probability $(1-\alpha)$) can acquire colonization. If a patient has a length of stay of τ, the probability that he/she will acquire colonization depends on the force of infection λ and this probability is given by: $1-e^{-\lambda\tau}$. If we integrate over all possible values of the length of stay, we obtain the probability that a randomly chosen patient acquires colonization. When we assume that the observed probability equals the model probability, we obtain an implicit relation for the force of infection:

$$\frac{T<LOS>}{1000} = (1-\alpha)\int_0^\infty d\tau\, f(\tau)\left(1-e^{-\lambda\tau}\right),$$

where $f(\tau)$ is the probability density function of the length of stay (LOS) and $<LOS>$ is the mean LOS. As we know the value of T at the start of the study and at the end of the study for both ICUs and non-ICUs, we obtain estimates for the force of infection for ICUs and non-ICUs at the start and at the end of the intervention.

In model 1, we assume that the reduction in the number of transmissions could be fully ascribed to improved hand hygiene and that the barrier precautions had no effect, i.e., we do not differentiate between colonized patients in isolation and colonizaed patients not in isolation. Furthermore we assume that colonization has no influence on the length of stay. In this setting the mean fraction of patients colonized (C) can be calculated by observing that a fraction α of the patients is colonized on admission (and will remain colonized during their entire stay), while patient who were uncolonized on admission and remain hospitalized for a period τ may acquire colonization. If this occurs, the moment of acquisition t should be smaller than τ, the moment of discharge. If we integrate over all possi-

ble durations of the length of stay and over all possible moments of acquisitions, we observe that the mean fraction of patients colonized (*C*) satisfies:

$$C = \alpha + \frac{(1-\alpha)}{<LOS>} \int_0^\infty d\tau f(\tau) \int_0^\tau dt \lambda e^{\lambda t} (\tau - t)$$

The transmission parameter β can be obtained from the formula: $\beta = \lambda / C$.

In model 2, we assume that the reduction in the number of transmissions could be fully ascribed to the barrier precautions, while the level of hand hygiene didn't change. The total force of infection has two components; one due to colonized patients in isolation and one due to non-isolated colonized patients.

Furthermore we assume no identification of MRSA carriage after admission screening, that a fraction *f*=0.96 is screened on admission and that the sensitivity the test is ϕ, the specificity of the test is 1, and that the test results are available after *z* days.

If a patient is isolated, he/she had to be an MRSA carrier upon admission (probability α), he/she has to be screened (probability *f*) and the test results should be positive as well (probability ϕ). If the results of the screening would be immediately available (no turn around time), a fraction αfϕ of the patients would be isolated, and also a fraction αfϕ of all patient days would be patient days in isolation. If the results of the screening are available after *z* days, only patients with a length of stay greater than *z* will become isolated. The fraction of the patients in isolation (*I*) in this case can be written as:

$$I = \frac{1}{<LOS>} \int_0^\infty d\tau f(\tau) \alpha f \phi \max(0, \tau - z)$$

There are four ways in which a colonized patient can be not-isolated.

1. The patient was colonized on admission, but not screened on admission (probability $\alpha(1-f)$). Patients are colonized and unisolated during their entire length of stay.

2. The patient was colonized on admission but the screening was false negative (probability $\alpha f(1-\phi)$). Patients are colonized and unisolated during their entire length of stay.

3. The patient was colonized on admission and detected as such through screening. These patients are not isolated during their entire length of stay if their length of stay is less than the turn around time *z* of the screening results. If their length of stay exceeds *z*, these patients are unisolated only during their first *z* days.

4. The patient was uncolonized on admission and acquired colonization during stay. These patients are colonized from the moment of acquisition onwards.

This leads to the following expression for the fraction colonized but unisolated patients*C*:

$$
\begin{aligned}
C &= \alpha(1-f) + \alpha f(1-\varphi) + \alpha f\varphi \frac{1}{\langle LOS \rangle} \int_0^\infty d\tau f(\tau) \min(\tau, z) \\
&+ (1-\alpha) \frac{1}{\langle LOS \rangle} \int_0^\infty d\tau f(\tau) \int_0^\tau dt \lambda e^{-\lambda t} (\tau - t) \\
&= \alpha(1 - f\varphi) + \frac{1}{< LOS >} \int_0^\infty d\tau f(\tau) \left[\alpha f\varphi \min(z, \tau) + (1-\alpha) \left(\tau - \frac{1 - e^{-\lambda\tau}}{\lambda} \right) \right]
\end{aligned}
$$

The force of infection can be written as $\lambda = \beta C + \beta_1 I$ and $1 - (\beta_1/\beta)$ denotes the efficacy of isolation.

The relative reduction of the transmission parameter (based on model 1) is shown in Supplementary Table 4, the efficacy of isolation (based on model 2) is shown in Supplementary Table 5. We conclude that the efficacy of isolation is at most 30% and that the reduction in the transmission parameter due to improved hand hygiene is at most 20%.

Number of infections

If we assume a constant risk (*k*) per day of developing an infection given that a patient is colonized, the number of health care-associated infections per 1000 patient days (*X*), defined as a positive clinical culture obtained 48 hours after admission (*z*=2) provides us with a way to calculate the risk *k*. The risk *k* should satisfy:

$$
\frac{X < LOS >}{1000} = \int_2^\infty d\tau f(\tau) \left[\alpha \left(\int_2^\tau dt k e^{-kt} \right) + (1-\alpha) \left(\int_0^\tau dt \lambda e^{-\lambda t} \int_{\max(t,2)}^\tau ds k e^{-k(s-t)} \right) \right]
$$

The efficacy of the intervention on the risk per day for a colonized to develop an infection is given in Supplementary Table 4. The number of infections per 1000 patient days is a function of the transmission parameter β and the infection rate *k*, i.e., *X(β, k)*. With the notation that a subscript "1" corresponds to a parameter at the end of the observation period and absence of a subscript to a parameter at the start of the intervention, the maximum contribution of the total reduction that can be ascribed to a reduction in the transmission parameter is given by:

$$
\frac{X(\beta, k) - X(\beta_1, k)}{X(\beta, k) - X(\beta_1, k_1)} \cdot 100\%
$$

Note that this estimate is an upper bound for the contribution of transmission prevention because there are two competing prevention events, i.e., some patients that didn't acquire colonization because of the lower transmission risk wouldn't have developed an infection anyway because of the lower risk k_1 of getting an infection once a patient is colonized. Therefore, the under bound is given by:

$$\left(1-\frac{X(\beta,k)-X(\beta,k_1)}{X(\beta,k)-X(\beta_1,k_1)}\right)\cdot 100\%$$

In SupplementaryTable 6 we have shown the minimum and maximum percentage of the reduction in the number of health care-associated infections that can be ascribed to prevention of transmission. The complementary percentages are the maximum and minimum percentage of the reduction in the number of health care-associated infections that can be ascribed to a reduction in the parameter *k*.

Supplementary Table 6 clearly shows that prevention of transmission, the main reason to isolate colonized patients, hardly contributed to the reduction in the number of health care-associated infections. At most 5% of the prevented infections in ICUs can be ascribed to transmission prevention and at most 7% in non-ICU wards. We also tested what the impact of transmission reduction could have been if patients who acquired colonization during their stay would have a 10 times higher daily infection risk as compared to patients already colonized on admission. This increases the impact of transmission prevention, but the percentage of the reduction in the number of health care-associated infections that can be ascribed to a reduction in the transmission parameter changes not very fast (see Supplementary Figure 2). For example, if colonization acquired during stay leads 10 times more likely to infection, at most 16% in ICUs and 28% in non-ICU wards of the reduction in the number of health care-associated infections can be ascribed to a reduction in the transmission parameter.

Finally, we tested whether our results would change if we assume that detection of transmission would have been imperfect, for example because not all patients are screened for colonization on discharge. Such an imperfect detection of transmission has the largest effect on our results if we assume that before the intervention a substantial fraction of the acquisitions isn't detected, while at the end of the intervention all acquisitions are detected. If we consider this extreme scenario, and we assume that before the intervention only 80% of the acquisitions is detected as such, the true number of acquisitions have decreased from 1/0.8·3.02=3.78 to 2.50 in ICUs and from 1/0.8·2.54=3.18 to 2.00 in non-ICU wards, a decrease of 34% and 37% respectively. If we redo our analysis with these numbers, and assume that patients who acquire colonization during their stay are equally likely to develop an infection as compared to patients who were colonized on admission, the minimum-maximum percentage of the reduction in the number of infections that can be ascribed to prevention of transmission of colonization is 2%-11% in ICUs and 5%-15% in non-ICU wards.

If patients who acquired colonization during their stay have a 10 times higher chance per day to develop an infection, these numbers increase to 13%-34% and 30%-53% respectively.

The equilibrium assumption

In our analysis we assumed that the dynamics of MRSA is in equilibrium, i.e., the mean number of patients colonized (or isolated) doesn't change over time. The intuitive justification of this assumption is that the mean length of stay of patients is very short compared to the length of the study period and we don't expect that the colonization status of patients who stayed a long time ago have a significant impact on the current colonization prevalence. We also checked this assumption numerically with the model parameters. Both for model 1 and 2, we found that within 10 times the mean length of stay, the fraction colonized patients differs less than 0.01% from the equilibrium value.

Table S.1. The observed admission prevalence and acquisition rate by Jain et al. and our estimated point prevalence in ICUs and non-ICU-wards at the start of the bundle implementation (October 2007) and at the end of the observation period (June 2010).

	ICUs	Non-ICUs
Admission prevalence at start & end	13.6%	13.6%
Acquisitions per 1000 patient days (*T*) at start	3.02	2.54
Acquisitions per 1000 patient days (*T*) at end	2.50	2.00
Point prevalence at start	14.9%	14.7%
Point prevalence at end	14.7%	14.5%

Table S.2. Least squared error (LSE) and the parameters of the fit of 10 distributions to the interquartile ranges for the length of stay. NA=not applicable. The density function of the 10 distributions are shown in Supplementary Table 3. All densities are defined only for x>0. Parameter 1, 2 and 3 in Table 2 corresponds to the first, second and third mentioned parameter in the first column of Table 3 respectively.

Distribution	Parameter 1	Parameter 2	Parameter 3	LSE
Inverse Gaussian	5.39	4.26	NA	0.00279
Lognormal	1.22	0.968	NA	0.00347
Suzuki	1.14	0.791	NA	0.00410
Generalized Gamma	14.3	2.08e-4	0.271	0.00441
K	0.658	41.0	NA	0.00569
Gamma	1.22	3.89	NA	0.00577
Weibull	1.12	4.93	NA	0.00602
Exponential	0.195	NA	NA	0.00708
Nakagami	0.426	34.2	NA	0.00745
Hoyt	4.36e-4	28.9	NA	0.00955

Table S.3. The density function of the 10 distributions used. The parameters of the distributions are listed in Supplementary Table 2.

Distribution	Density function	Mean	Variance
Inverse Gaussian(μ,λ)	$x^{-3/2}\ e^{-\lambda(x-\mu)^2/(2x\mu^2)}$	μ	μ^3/λ
Lognormal(μ,σ)	$1/(x\sqrt{(2\pi\sigma^2)})e^{-((\ln x-\mu)^2/(2\sigma^2))}$	$e^{\mu+\sigma^2/2}$	$e^{2\mu+\sigma^2}(-1+e^{\sigma^2})$
Suzuki(μ,ν)	No closed form	$\sqrt{(\pi/2)}e^{\mu+\nu^2/2}$	$e^{2\mu+\nu^2}(2e^{\nu^2}-\pi/2)$
Generalized Gamma(α,β,γ)	$x^{\alpha\gamma-1}e^{-(x/\beta)^{\gamma}}$	$\beta\Gamma(\alpha+1/\gamma)/\Gamma(\alpha)$	$\beta^2(-\Gamma(\alpha+1/\gamma)^2+\Gamma(\alpha)\Gamma(\alpha+2/\gamma))/\Gamma(\alpha)^2$
K(ν,w)	$x^{\nu}K_{\nu-1}(2x\sqrt{(\nu/w)})$, where *K* is a modified Bessel function of the second kind	$\frac{1}{2}\sqrt{\pi}\sqrt{(w/\nu)}$ Pochhammer(ν,½)	w(1-(π Pochhammer(ν,½)^2)/(4ν)
Gamma(α,β)	$e^{-x/\beta}x^{\alpha-1}$	αβ	$\alpha\beta^2$
Weibull(α,β)	$x^{\alpha-1}e^{-(x/\beta)^{\alpha}}$	$\beta\Gamma(1+1/\alpha)$	$\beta^2(-\Gamma(1+1/\alpha)^2+\Gamma(1+2/\alpha))$
Exponential(λ)	$\lambda e^{-\lambda x}$	$1/\lambda$	$1/\lambda^2$
Nakagami(μ,ω)	$x^{2\mu-1}e^{-\mu x^2/\omega}$	$\sqrt{(\omega/\mu)}$ Pochhammer(μ,½)	ω-(Pochhammer(μ,½)^2/μ
Hoyt(q,ω)	$xe^{-((1+q^2)^2x^2/(4q^2\omega)}$ $I_0((1-q^4)x^2/(4q^2\omega))$	$\sqrt{(2\omega/(\pi(1+q^2)))}$ EllipticE(1-q^2)	ω(1-2EllipticE(1-q^2)^2/(π(1+q^2))

Table S.4. Relative reduction in the transmission parameter and infection rate due to the intervention if we assume that isolation wasn't effective and all prevented acquisitions can be ascribed to improved hand hygiene.

Distribution	Reduction transmission in ICUs (%)	Reduction transmission in non-ICU wards (%)	Reduction in risk of developing an infection in ICUs (%)	Reduction in risk of developing an infection in non-ICU wards (%)
Inverse Gaussian	15.8	19.8	64.4	44.0
Lognormal	15.7	19.7	64.6	43.9
Suzuki	15.8	19.8	64.5	44.0
Generalized Gamma	16.0	20.0	64.3	44.0
K	16.2	20.2	63.9	44.2
Gamma	16.2	20.2	63.9	44.2
Weibull	16.2	20.2	63.9	44.2
Exponential	16.0	20.0	64.0	44.1
Nakagami	16.3	20.3	63.8	44.2
Hoyt	16.4	20.4	63.9	44.3

Table S.5. Efficacy of isolation if we assume that the efficacy of hand hygiene remained constant during the study period and that all prevented acquisitions could be ascribed to the barrier precautions. The perfect test has a sensitivity of 100% and results are immediately available, the imperfect test has a sensitivity of 93% and results are available after 24 hours.

	Perfect test		Imperfect test	
Distribution	Efficacy isolation in ICUs (%)	Efficacy isolation in non-ICU wards (%)	Efficacy isolation in ICUs (%)	Efficacy isolation in non-ICU wards (%)
Inverse Gaussian	18.3	22.5	24.1	29.6
Lognormal	18.4	22.6	24.0	29.5
Suzuki	18.3	22.5	24.0	29.5
Generalized Gamma	18.3	22.5	24.1	29.7
K	18.2	22.4	24.3	30.0
Gamma	18.2	22.4	24.3	29.9
Weibull	18.2	22.4	24.3	29.9
Exponential	18.2	22.4	23.8	29.3
Nakagami	18.1	22.4	24.4	30.1
Hoyt	18.1	22.3	24.9	30.6

Table S.6. Minimal and maximal percentage of the reduction in the number of infections that can be ascribed to prevention of transmission of colonization. 100% minus this percentage is the maximal/minimal percentage that can be ascribed to a lower infection risk once a patient is colonized. In the left two columns, the risk per day to develop an infection is the same for all colonized patients. In the right two columns, the risk per day to develop an infection is 10x higher for patients who acquire colonization during their stay as compared to patients who were colonized on admission.

	Constant infection risk		Acquired colonization 10x higher infection risk	
Distribution	Reduction ascribed to transmission prevention in ICUs (%)	Reduction ascribed to transmission prevention in non-ICU wards (%)	Reduction ascribed to transmission prevention in ICUs (%)	Reduction ascribed to transmission prevention in non-ICU wards (%)
Inverse Gaussian	1.0-4.5	3.8-6.6	6.4-15.4	17.9-27.7
Lognormal	1.1-4.8	4.1-7.2	6.6-15.6	18.5-28.4
Suzuki	1.0-4.5	3.8-6.7	6.4-15.3	18.0-27.7
Generalized Gamma	0.9-4.2	3.5-6.2	6.2-15.0	17.3-26.9
K	0.6-3.5	2.8-5.0	5.6-13.9	15.4-24.3
Gamma	0.6-3.5	2.8-5.0	5.6-14.0	15.4-24.4
Weibull	0.5-3.4	2.8-4.9	5.6-13.9	15.3-24.3
Exponential	0.7-3.9	3.2-5.6	6.0-14.8	16.5-25.9
Nakagami	0.4-3.1	2.5-4.4	5.3-13.4	14.5-23.0
Hoyt	0.3-2.9	2.3-4.1	5.0-12.8	13.7-22.0

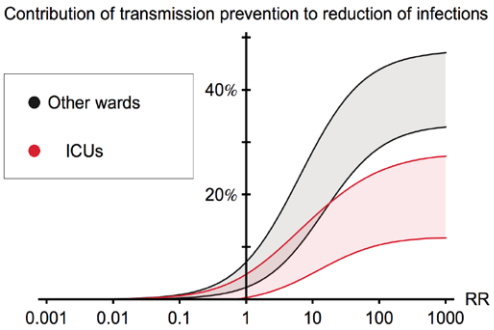

Figure S.2. The possible range for the contribution of transmission prevention on the reduction in the number of infections as function of the relative daily risk to develop an infection for patients who acquired colonization as compared to patients who were already colonized on admission. For each relative risk, the lower line corresponds to the minimum over all 10 distributions for the LOS of the minimal percentage that needs to be ascribed to a reduction in transmission; the upper line corresponds to the maximum over all 10 distributions for the LOS of the maximal percentage that can be ascribed to a reduction in transmission.

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Chapter 5

The transmissibility of antibiotic-resistant Enterobacteriaceae in intensive care units

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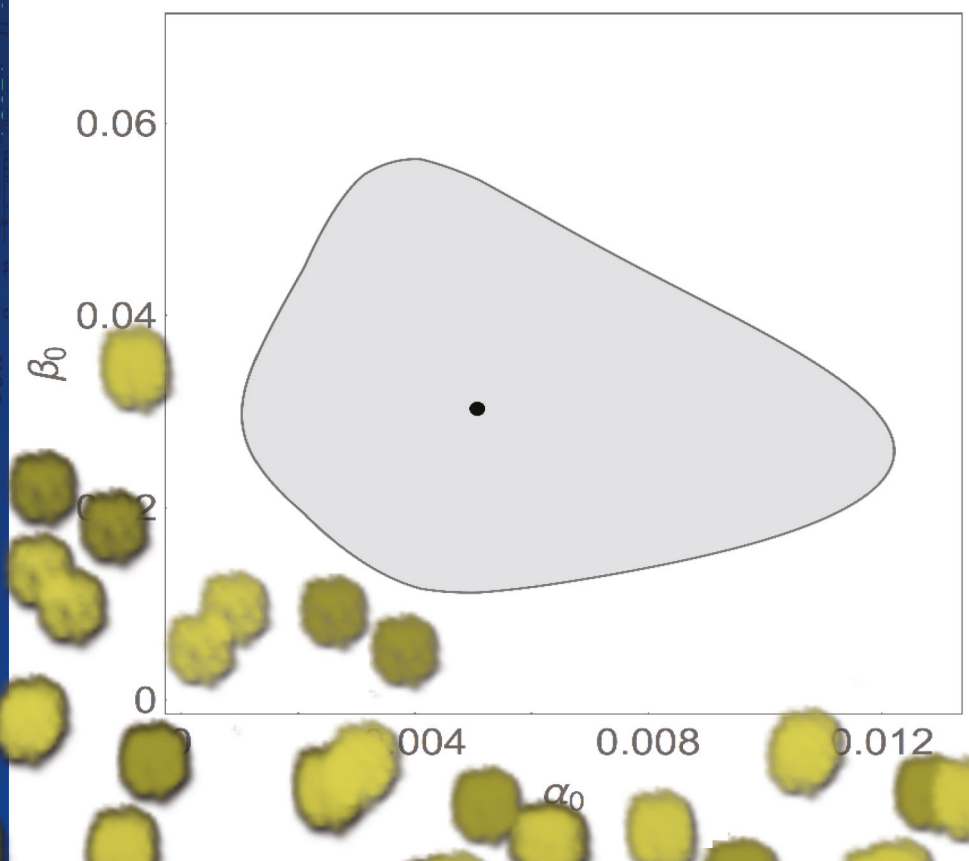
Clin. Inf. Dis. 2017, cix825



Summary

In an international study in 13 European intensive care units using protocolized surveillance and microbiological analysis, the transmission capacity of bacteria resistant to expanded-spectrum cephalosporins was 3.7 times higher for non-*Escherichia coli* Enterobacteriaceae (mainly *Klebsiella pneumoniae*) than for *E. coli.*

Abstract

Background: The global emergence of infections caused by Enterobacteriaceae resistant to expanded-spectrum cephalosporins (ESCs) in intensive care units (ICUs) is, at least partly, driven by cross-transmission. Yet, individual transmission capacities of bacterial species have not been quantified.

Methods: In this post-hoc analysis of a multicenter study in 13 European ICUs prospective surveillance data and a mathematical model were used to estimate transmission capacities and single admission reproduction numbers (R_A) of *Escherichia coli* and non-*E. coli* Enterobacteriaceae, all being ESC-resistant. Surveillance was based on a chromogenic selective medium for ESC-resistant Enterobacteriaceae, allowing identification of *E. coli* and of *Klebsiella*, *Enterobacter*, *Serratia*, *Citrobacter* species, grouped as non-*E. coli* Enterobacteriacea (non-EcE).

Results: Among 11,420 patients included, the admission prevalence was 3.8% for non-EcE (74% being *Klebsiella pneumoniae*) and 3.3% for *E. coli*. Acquisition rates were 7.4 and 2.6 per 100 admissions at risk for non-EcE and *E. coli*, respectively. The estimated transmission capacity of non-EcE was 3.7 (95% credibility interval 1.4-11.3) times higher than of *E. coli*, yielding single admission reproduction numbers (R_A) of 0.17 (95% credibility interval 0.094-0.29) for non-EcE and 0.047 (0.018-0.098) for *E. coli*.

Conclusions: In ICUs non-EcE, mainly being *K. pneumonia*e, are 3.7 times more transmissible than *E. coli*. Estimated R_A values of these bacteria were below the critical threshold of one, suggesting that in these ICUs outbreaks typically remain small with current infection control policies.

Introduction

Incidences of infections caused by Enterobacteriaceae resistant to expanded-spectrum cephalosporins (ESCs) have increased in the last decade, especially in intensive care units (ICUs) [1,2]. Most infections are preceded by asymptomatic carriage, especially in the intestine, which may not be apparent at the time of ICU-admission. ICU-acquired colonization with these bacteria may originate from an exogenous source, for instance through patient to patient transfer of bacteria, from horizontal transfer of resistance genes located on mobile genetic elements, or from within-host selection of previously undetectable bacteria.

In recent years, the understanding of the epidemiology of ESC-resistant Enterobacteriaceae in ICUs has increased. For instance, several studies have demonstrated that spontaneous decolonization during ICU stay is rare, as about 80% of the carriers of ESBL genes were still colonized after one month [3]. Yet, other quantities, such as horizontal gene transfer rates have not been determined, and it is unknown whether there is heterogeneity in transmission potential of different Gram-negative bacteria. Quantification of these parameters is essential for understanding the transmission dynamics and, hence, for the design of effective infection control measures in ICUs.

Yet, estimation of the relative importance of the different acquisition routes is complex. The main difficulty is that the exact timing of acquisition of bacteria cannot be demonstrated accurately. Clinical culture results will miss many episodes of carriage, as carriage infrequently leads to infection. Results from regularly obtained surveillance cultures are more useful, but even these suffer from limited sensitivity and interval censoring, as screening cultures are collected at discrete time points precluding determination of the exact times of acquisition. Recent work, though, has provided statistical methods to better address this problem [4-6].

Here we have used screening culture results from 11,420 patients during 48 months (122,301 patient days) in 13 European ICUs that participated in the MOSAR-ICU trial [7]. Screening on a chromogenic selective medium, followed by microbiological analysis distinguished *Escherichia coli* from other bacteria, such as *Klebsiella*, *Enterobacter*, *Serratia* or *Citrobacter* species, here grouped as non-*E. coli* Enterobacteriaceae (non-EcE). We used a Bayesian random-effect method [6] to estimate the transmission capacity for *E. coli* and non-*E. coli* Enterobacteriaceae, and confirmed the findings with typing by the Raman spectroscopic analysis.

Methods

Setting and patients

Our analyses are based on the detailed data and molecular characterization of isolates from the MOSAR-ICU trial [7], a study in 13 ICUs in 8 European countries carried out between May 2008 and April 2011. This consisted of a 6-month baseline period, followed by a 6-month period in which a hand hygiene improvement program was implemented in combination with chlorhexidine body washing of all patients. Finally, ICUs were cluster-randomized to different approaches of screening and isolation of carriers of antibiotic-resistant bacteria. In all three study periods carriage with ESC-resistant Enterobacteriaceae was determined on admission and twice weekly by obtaining perianal swabs. In the first and second period, there was no feedback of screening results to physicians, precluding adaptation of infection prevention measures. In the third study period screening was followed by contact precautions for identified carriers. Patients aged 18 years or older with an expected length of stay of three days or longer, and of a sample of patients with shorter expected length of stay were included. There was no statistically significant effect of any of the interventions on acquisition rates of ESC-resistant Enterobacteriaceae [7].

Microbiological analysis

Swabs were plated onto the Brilliance™ ESBL 2 Agar (Oxoid Limited, Cambridge, UK) and colonies from the groups of *E. coli* and *Klebsiella/ Enterobacter/ Serratia/ Citrobacter* (non-EcE) were selected.

One colony of each morphotype per patient was frozen and transported to the National Medicines Institute, Warsaw, Poland, for further analysis. The Vitek 2 system (bioMérieux, Marcy l'Etoile, France) was used for species identification, followed by more specific analyses of Enterobacteriaceae with extended-spectrum β-lactamase (ESBL)-, AmpC-type cephalosporinase- or carbapenemase-mediated phenotypes of ESC resistance, as described previously [8-10].

Mathematical modeling

We assumed that the risk for an uncolonized patient per day to acquire colonization equals $\alpha+\beta\, I(t)/N(t)$. The term $\beta\, I(t)/N(t)$ describes the rate of cross-transmission where $N(t)$ is the total number of patients present in ICU at day t and $I(t)$ is the number of colonized patients in the ICU at day t. The constant term α represents the risk of acquisition due to all routes which do not depend on the number of colonized patients present in the ICU. This includes transmission due to visitors or persistently colonized health care workers, de novo mutations in

the patient and outgrowth of previously undetectable colonization, stimulated by antimicrobial use. The parameter β represents the effective transmissibility of the bacteria in the ICU, taking infection control measures like hand hygiene into account. The effective single admission reproduction number R_A, defined as the average number of secondary cases per primary case during the ICU admission of the index case when all other patients in the ICU are susceptible for acquisition [11, 12], is approximately $\beta<LOS>$, with $<LOS>$ the mean length of stay of patients in the ICU. Note that secondary cases may remain undetected when they are discharged before samples for microbiological testing have been obtained, and that secondary cases may be detected after discharge of the index case. Tertiary cases (infected by secondary cases) are not part of the definition of R_A.

We estimated the parameters α and β for *E. coli* and non-EcE (as a group) and the relative cross-transmission capacity of non-EcE versus *E. coli* ($\beta^{non\text{-}EcE}/\beta^{E.\ coli}$), using data on the days of admission, days of discharge of patients, the surveillance culture dates and culture results. For simplification, we assume that the specificity and sensitivity of the tests were 100% (see supplementary material 3 for a discussion of the impact of this assumption). We assumed that colonization with *E. coli* does not change the hazard rate to acquire non-EcE colonization (and vice versa) and that colonization does not disappear during ICU-stay (which seems reasonable as the length of ICU-stay is short and antibiotic pressure in ICU is high). We calculated the likelihood of values of α and β by averaging over all possible transmission paths that are in agreement with the culture results. For more details about the method, see supplementary methods and Bootsma et al. [6]. In this way, we obtained, for both *E. coli* and non-EcE, the likelihood of the transmission parameters α and β per study period and per ICU on a (α, β)-grid.

Because of the uncertainty levels around the transmission parameters per period and per ICU, results of 13 ICUs were pooled using a random effects model as ICUs differ in many aspects (such as bed occupancy, admission prevalence, case-mix and adherence to infection prevention measures). We assumed that the parameters α and β in a single ICU are drawn from two independent folded normal distributions with means α_0 and β_0 and standard deviations σ_α and σ_β, all with uninformative priors. Using the likelihoods obtained in the previous step, we obtained a posterior probability density for each point on the (α_0, β_0)-grid by numerical integration over all possible values of the transmission parameters in each ICU (see supplementary material 2). In performing these analyses for non-EcE species and *E. coli* we determined both the transmission parameters and the relative cross-transmission capacity of *E. coli* and non-EcE with the highest posterior probability. As the studied interventions did not reduce acquisition with ESC-resistant Enterobacteriaceae [7], we assumed in our primary random effect analysis that transmission parameters within an ICU did not change between study periods. In the supplementary material, we also present results per period and for a scenario in which interventions may have had an effect on trans-

mission. In contrast to Derde et al. [7], we base our estimates of the admission prevalence only on patients for whom a swab was obtained within two days after admission. This leads to slightly higher estimates of the admission prevalence.

Raman spectroscopic analysis

To confirm differences in cross-transmission rates, we further typed relevant *K. pneumoniae* and *E. coli* isolates from ICUs with at least 25 patients being colonized with *K. pneumoniae* and *E. coli*, by Raman spectroscopic analysis (RSA) (SpectraCell RA, River Diagnostics BV, Rotterdam, the Netherlands). Typing was performed according to the manufacturer's instructions [16]. In short, isolates were inoculated on trypticase soy agar (TSA), incubated overnight at 35°C, and then checked for purity. Biomass (free lying colonies) was collected from the TSA plates to fill a 1μL loop, and suspended in 20 μL sterilized water. 20 μL of the suspension was inoculated and spread on a new TSA plate, and allowed to dry for 10 minutes. The plates were incubated at 35°C for 20h (+/- 30 minutes). Using a 1 μL inoculation loop the biomass was suspended in 10 μL of sterilized water, and centrifuged for 3 minutes at high speed (circa 10,000 g) to remove possible air bubbles. After removal of 4 μL supernatant the pellet was re-suspended, 4 μL of suspension was pipetted into the indicated well of the MicroSlide, and dried in an incubator for 20-30 minutes. Raman spectra were measured using the SpectraCell Bacterial Strain Analyzer. The similarity between pairs of spectra was calculated using the squared Pearson correlation coefficient (R^2). The cut-off values used for the calculation of clusters of clonally related isolates were based on species-dependent criteria determined by the manufacturer.

Linkage and cross-transmission

Epidemiological and microbiological linkages were used to identify possible cross-transmission events. Epidemiological linkage was defined as the presence of two patients with an overlapping stay in ICU. Microbiological linkage was defined as two patients being colonized with identical species belonging to a defined Raman cluster. Cross-transmission was defined as acquired colonization in a patient with negative cultures on admission, and both epidemiological and microbiological linkage to at least one other patient.

Cross-transmission rates were expressed as the number of cross-transmission events per 1,000 patient days at risk (DAR). DAR included all patient days of uncolonized patients in ICU with at least one colonized patient in ICU. To account for colonization pressure, weighted days at risk (wDAR) were calculated by multiplying the DAR each day with the number of colonized patients during that day in the ICU. The overall averaged transmissibility ratio was determined using a mixed effects Poisson model with number of transmissions as the outcome, species and log(wDAR) as fixed effects, and a random effect for hospital. Analyses were performed using SPSS version 20 and R version 2.15.1.

Results

For 11,420 out of the 14,390 patients in the study there was at least 1 culture result available (see Table 1 and Derde et al.[7] for more details), of whom 637 patients were colonized with *E. coli* and 1,184 with non-EcE. Admission prevalence was 3.8% for non-EcE species and 3.3% for *E. coli*. Of patients uncolonized at admission for non-EcE species, 7.4% had non-EcE in at least one subsequent culture. For *E. coli,* this was 2.6%. From 1,046 of the 1,184 patients colonized with non-EcE species frozen isolates were available for further analysis and of these 777 (74.3%) were *K. pneumoniae*. The production of ESBL only was the predominant phenotype of ESC resistance (88.7%).

Table 1. Estimation of transmission parameters of non-*E. coli* Enterobacteriaceae (non-EcE) and *E. coli* in 13 European intensive care units using a random effect model with no effect of the interventions. Only the 11420 out of the 14390 patients with at least one culture result were used in this analysis.

	Patients included (n=11,420)	
	Non-EcE	*E. coli*
No. of patients colonized at admission (%)	401 (3.8%)	356 (3.3%)
No. of patients with documented acquisition	783	281
Acquisition rate/100 uncolonized admissions	7.4	2.6
Cross transmission parameter β_0, (95% CI)	0.029 (0.016-0.049)	0.0078 (0.0029-0.016)
Single admission reproduction number R_A (95% CI)	0.17 (0.094-0.29)	0.047 (0.018-0.098)
Transmission parameter α_0, (95% CI)	0.0048 (0.0022-0.011)	0.0024 (0.0013-0.0039)
The relative transmission capacity of non-*E. coli* Enterobacteriaceae versus *E. coli* ($\beta_0^{non\text{-}EcE}/\beta_0^{E.\ coli}$) (95% CI)	3.7 (1.4-11.3)	

CI: credibility interval. Estimates are the values with the highest posterior probability density.

Maximum likelihood estimates for α and β differed between ICU's and between periods, ranging from 0.0001 to 0.013 and 0.0001 to 0.045 for α and β for *E. coli*, respectively, and from 0.0001 to 0.040 and 0.0001 to 0.105 for α and β for non-EcE, respectively, see Supplementary Table S1. The random effects analysis (assuming constant transmission parameters for all study periods in each ICU) yielded values with the highest posterior probability density and 95% credibility intervals of 0.0024 (0.0013-0.0039) and 0.0078 (0.0029-0.016) for α_0 and β_0 for *E. coli*, respectively, and 0.0048 (0.0022-0.011) and 0.029 (0.016-0.049) for α_0

and β_0 for non-EcE, respectively (see Figure S.1 and Table 1). Using the observed mean length of stay of 6 days, these transmission parameters correspond to effective single admission reproduction numbers of 0.047 (0.018-0.098) for *E. coli* and 0.17 (0.094-0.29) for non-EcE. The cross-transmission parameter is, therefore 3.7 (95% CI 1.4-11.3) times higher for non-EcE compared to *E. coli*. Higher relative cross transmission parameters for non-EcE as compared to *E. coli* were also obtained when data were analyzed per study period, being 3.6 (95% CI 1.0-11.2), 2.4 (95% CI 0.83-7.1) and 4.4 (1.2-13.0) in periods 1, 2, and 3 respectively (see Supplementary Table S2). The ratio was 4.3 (2.1-7.6) when all study periods in all ICUs were considered to be independent from each other (See supplementary Figure S.1, and Table S.3 for more details).

Raman spectroscopy

In total, 1,015 isolates (385 *E. coli* and 630 *K. pneumoniae*) from 877 patients from 4 ICUs (in Greece, France, Latvia and Slovenia) were typed with RSA. For *K. pneumoniae*, 173 patients (174 isolates) were colonized on admission (4.1% admission prevalence), and 449 acquired carriage (456 isolates, 10.7% acquisition rate). For *E. coli*, 214 patients (215 isolates) were colonized on admission (5.1%), and 169 acquired carriage (170 isolates, 4.0%). Transmission rates ranged across ICUs from 1.66 to 29.74/1,000 DAR for *K. pneumoniae* and from 0 to 3.31/1,000 DAR for *E. coli* (Table S4). Assuming equal transmissibility ratios in hospitals and using the wDAR the combined transmissibility ratio is 5.0:1 (95% CI for the population average 3.6-7.1:1). The estimated transmissibility ratio in these four ICUs based on modelling with random effects was 6.1 (1.3:1-35.0:1). When we performed our mathematical model with a random effect analysis for these 4 hospitals only, we found as value for the transmissibility ratio with the highest posterior probability density: 6.1 with as 95% credibility interval (0.69-58.6).

Discussion

Based on extensive microbiological surveillance in 13 ICUs during a 24-month period and mathematical modelling the estimated relative cross-transmission capacity of non-EcE (mainly consisting of *K. pneumoniae*, but also *Enterobacter*, *Serratia* and *Citrobacter* species) was found to be 3.7 times higher than that of *E. coli.* Importantly, external factors influencing transmission could be considered equal during the study period for all species. The estimates in a subset of four ICUs using bacterial typing by the Raman spectroscopy analysis were very similar to the estimates of the random effects model based on the same four ICUs. The per admission reproduction numbers were 0.17 for non-EcE and 0.047 for *E. coli*.

This was a post-hoc analysis of a large international prospective study, and, therefore, inevitably has study limitations. The surveillance method as used may have resulted in misclassification of some patients. Only the first isolate of each morphotype identified on chromogenic media was selected for species determination. Therefore, carriage with *K. pneumoniae* could have been missed in patients colonized with either *Enterobacter*, *Serratia* or *Citrobacter* species, as no further isolates were harvested and tested. Furthermore, for confirmation of our results, we used the high-throughput typing method by the Raman spectroscopy (see supplementary material S3), for *K. pneumoniae* and *E. coli* isolates of four ICUs. Although validated for typing antibiotic-resistant Enterobacteriaceae [13], whole-genome sequencing might have provided more granularity and, thereby, more accurate estimates of transmission parameters.

When using mathematical modeling it is inevitable to make assumptions. Naturally, transmission will differ between ICUs, but the study was underpowered for reliably estimating transmission ratios per ICU. However, by using a random effect model, differences between ICUs were taken into account. Furthermore, we assumed that the sensitivity and specificity of the microbiologic tests was 100%, mainly to reduce the computational burden. However, this assumption affected both *E. coli* and non-EcE, and it is, therefore, unlikely that it will impact the estimated relative transmission capacity of *E. coli* and non-EcE.

The higher estimates for these 4 ICUs (although not statistically significant) compared to the analysis for all 13 ICUs could be the result of selection bias. As we required that at least 25 patients were colonized with *K. pneumoniae* and *E. coli*, we might have selected for ICUs with a *K. pneumoniae* outbreak during the study period.

Our findings are in line with previous results suggesting that in-hospital transmission was higher for ESBL-producing *K. pneumoniae* than for ESBL-producing *E. coli*, although the observed transmission rates of 13.9 and 5.6 cases per 1,000 exposure days for *K. pneumoniae* and *E. coli*, respectively, were based on only 2 and 4 transmission events in a hospital-wide setting, respectively [14]. In another study patient-to-patient transfer, based on epidemiological linkage and PFGE typing, was observed in 14 (52%) of 27 acquisitions with ESBL-producing *K. pneumoniae* and in three (13%) of 23 acquisitions with ESBL-producing *E. coli* [15, 16]. Because of these small numbers, it was not possible to quantify the amount of and uncertainty in transmission capacity of the different species in those studies.

Our study estimates that per admission effective reproduction numbers for non-EcE and *E. coli* were well below one (0.17 and 0.047, respectively), suggesting that outbreaks typically remain small with current infection control policies. These findings support the observation that treating carriers of these bacteria in isolation, which was the cluster-randomized intervention in this study, failed to reduce the prevalence of carriage in the ICUs. In fact, our findings also suggest

that the implementation of universal chlorhexidine body washing and improving hand hygiene adherence from 52% to 77% did not reduce the transmission capacity of these bacteria. Yet, our estimated R_A of 0.17 for non-EcE should not be interpreted as evidence for ineffectiveness of isolation measures for *K. pneumoniae*. Firstly, isolation will only be effective if there is cross transmission. In our setting, with low transmission rates, the potential gain of isolation is limited. In settings with high rates of cross transmission, i.e., settings with a different epidemiology, isolation may be effective. Note that isolation in high-endemicity settings will not be effective if the high-endemicity levels are primarily caused by a high prevalence on admission of ESC-Enterobacteriaceae , e.g., due to extramural reservoirs. Secondly, the estimate is for the group of bacteria, and the individual estimate for *K. pneumoniae* could be higher. Moreover, as compared to *E. coli*, *K. pneumoniae* is more frequently also resistant to carbapenem antibiotics, providing further arguments to prevent cross-transmission.

In conclusion, the analysis of extensive longitudinal carriage data from 13 European ICUs demonstrated that the transmission rate of non-EcE (mainly consisting of *K. pneumoniae*) is 3.7 times higher than of *E. coli.* If problems emerge, e.g., outbreaks of colistin-resistance Enterobacteriaceae, more measures are are needed to control a *K. pneumoniae* outbreak than are needed to control an *E. coli* outbreak.

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Supplementary material 1

From the MOSAR ICU trial [6] we have data on the admission and discharge day of patients in 13 ICU in Europe and data on their colonization status at certain points in time (day of screening and result of screening), i.e., at admission and afterwards twice per week. The study consisted of 3 phases, which we initially analyze separately.

We assumed that the probability to acquire colonization equals $\alpha + \beta\ I(t)/N(t)$ where α represents the risk due to routes which do not depend on the number of colonized patients present in the ICU, the so-called endogenous route, and $\beta\ I(t)/N(t)$ describes the rate of cross-transmission where $I(t)$ is the number of colonized patients in the ICU at time t and $N(t)$ is the total number of patients present in ICU at time t. The parameter β represents the effective transmissibility of the bacteria in the ICU, taking infection control measures like hand hygiene into account. We want to know what the probability is to observe the data as were observed in one of the ICUs if the transmission parameters were (α,β). An existing algorithm, written in C++, can be used [5] to determine the likelihood of the data for given values of the parameters α and β. Below we shortly describe the algorithm.

We divide the stay of each patient into at most three periods:

- The period when the patient is known to be uncolonized, i.e., from admission to the last negative test;
- The period when the colonization status of a patient is unknown, i.e., from the last negative test to first positive test (if there was such) or from the last negative test to discharge;
- The period when the patient is known to be colonized, i.e., from first positive test to discharge.

Note that this distinction can be made because we assume that colonization is persistent during ICU stay and the test results are 100% reliable. If we would know the exact moment of colonization of each patient, calculation of the likelihood is easy[5]. Our algorithm calculates the likelihood of the observed culture results by a (weighted) summation over all possible moments of acquisition of all patients.

The likelihood was calculated on a grid of step size 0.005 for α and 0.0005 for β. In this way for each ICU for each period we obtained the likelihood of the data for each point of the grid. For values close to the maximum likelihood estimates of α and β we refined our grid to obtain more precise estimates. The likelihood for parameters α and β between grid points was determined by linear interpolation.

Supplementary material 2: Random effects model

To reflect that the transmission parameters may differ between ICUs we assume that the transmission parameters of a certain ICU are realizations of two independent folded normal distributions, i.e., $\alpha \sim N(\alpha_0, \sigma_\alpha)$ and $\beta \sim N(\beta_0, \sigma_\beta)$. Formally, this implies a switch to a Bayesian perspective. We assume non-informative (improper) priors for $\alpha_0, \sigma_\alpha, \beta_0$ and σ_β

Case 1: We assume here, for simplification, that the transmission parameters of a certain bacteria in a certain ICU in the three periods (baseline and 2 intervention periods) are independent of each other (different bundle, treatment during different periods of the trial).

We calculate the posterior distribution *H* for each point (α_0, β_0) on the grid by the formula:

$$H(\text{icu}, \text{phase}, \alpha_0, \sigma_\alpha, \beta_0, \sigma_\beta) \sim$$

$$\sim \frac{1}{\sigma_\alpha \sqrt{2\pi}} \frac{1}{\sigma_\beta \sqrt{2\pi}} \iint e^{-\frac{(\alpha-\alpha_0)^2}{2{\sigma_\alpha}^2}} e^{-\frac{(\beta-\beta_0)^2}{2{\sigma_\beta}^2}} \cdot$$

$$\cdot L(icu, phase, \alpha, \beta)\, d\alpha\, d\beta,$$

where *L(icu,phase,α,β)* is the likelihood of the observed data during the trial if the transmission parameters are α and β for endogenous and cross-transmission respectively (see Supplementary Material 1).

The overall posterior distribution is obtained by the product over all ICUs and all phases of the posterior distribution per ICU and per phase, i.e.,

$$H_{all}(\alpha_0, \sigma_\alpha, \beta_0, \sigma_\beta) \sim \prod_{all\ icu, all\ phases} H(icu, \text{phase}, \alpha_0, \sigma_\alpha, \beta_0, \sigma_\beta)$$

Case 2: Despite different measures during the three phases, no significant effect of the intervention on the spread of Gram-negative bacteria was found [Derde et al]. Therefore, in our main analysis, we assume that the transmission parameters in phase 2 and 3 were the same as in period 1.

Now the formula for the posterior distribution per ICU is:

$$H(\text{icu}, \alpha_0, \sigma_\alpha, \beta_0, \sigma_\beta) \sim \frac{1}{\sigma_\alpha\sqrt{2\pi}} \frac{1}{\sigma_\beta\sqrt{2\pi}} \iint e^{-\frac{(\alpha-\alpha_0)^2}{2\sigma_\alpha{}^2}} e^{-\frac{(\beta-\beta_0)^2}{2\sigma_\beta{}^2}} \cdot$$

$$\cdot L(icu, phase = 1, \alpha, \beta) L(icu, phase = 2, \alpha, \beta) \cdot$$

$$\cdot L(icu, phase = 3, \alpha, \beta)\, d\alpha\, d\beta$$

The overall posterior distribution is obtained by the product over all ICUs of the posterior distribution per ICU, i.e.,

$$H_{all}(\alpha_0, \sigma_\alpha, \beta_0, \sigma_\beta) \sim \prod_{all\ icu} H(icu, \alpha_0, \sigma_\alpha, \beta_0, \sigma_\beta)$$

Supplementary material 3: Effects assumptions perfect sensitivity of the test

A formal investigation of how the assumption of perfect sensitivity and specificity of the test impact our estimates would be a manuscript on its own. To try to shed some light, we have run 10 simulations of a ward of 10 beds for a period of 1000 days with the parameter values for non-EcE observed in this study (α=0.0048, β =0.029 and the admission prevalence is 3.8%, with cultures performed on admission and afterwards twice per week and with a mean length of stay of 6 days). In our simulation we assumed a sensitivity of the test of 80% and a specificity of 100%. For each simulated data set we subsequently estimated the transmission parameter β for two cases: 1) if we assume a 100% sensitivity of the test and 2) if we estimate the sensitivity simultaneously with the estimate of the parameter β (we used an Bayesian approach described in Worby et al. Am J Epidemiol (2013) 177 (11): 1306-1313). In all 10 simulations, the estimate of the sensitivity was close to the true value of 80%. The median values for β was, on average, 4.5% lower with an assumed sensitivity of 100% as compared to the value of β obtained when the sensitivity was estimated simultaneously. The range of the ratio of the two estimates was (0.88-1.17), so the maximum deviation observed was 17%, which is also the maximum error in the estimate of R_A. This suggest that the errors made by assuming a test with perfect sensitivity and specificity are moderately low.

The relative transmission capacity of *E.coli* and non-EcE does depend even less on the sensitivity and specificity of the test, as long as the sensitivity and specificity for E. coli and non-EcE are comparable. The reason is that the estimates of the R_A-value for *E. coli* and for non-EcE are calculated in the same way, and the

systematic errors in the estimate are therefore expected to be of the same relatively size , which implies that they are cancelled out when taken the ratio of the two R_A-values

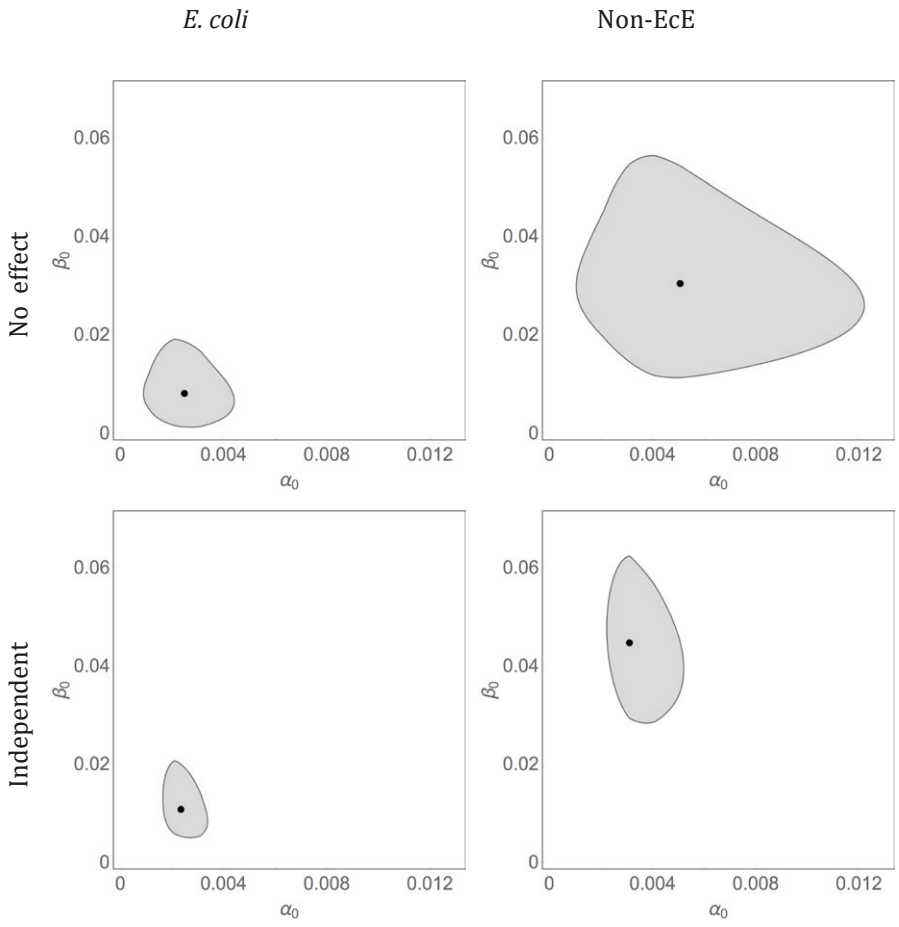


Figure S1. Estimates of the transmission parameters (α_0, β_0) and 95% credibility areas for *E. coli* (left) and non-*E. coli* Enterobacteriaceae (non-EcE) (right) using a random effect model with the assumption that the intervention had no effect the transmission parameters (upper panels) and with the assumption that the transmission parameters in each period were independent (lower panel). The transmission parameter of the endogenous route is on the horizontal axis and the cross-transmission parameter is on the vertical axis.

Table S1. Estimation of transmission parameters *(α,β)* and 95% confidence interval of non-*E. coli* Enterobacteriaceae (non-EcE) and *E. coli* in 13 European intensive care units per ICU per period.

phase		1		2		3	
		α	β	α	β	α	β
ICU							
1	non-EcE	0.0046	0.0251	0.0151	0.0001	0.0051	0.0051
		(0.0006-0.0126)	(0.0001-0.0551)	(0.0031-0.0201)	(0.0001-0.0401)	(0.0016-0.0076)	(0.0001-0.0351)
	E. coli	0.0011	0.0001	0.0011	0.0001	0.0031	0.0051
		(0.0006-0.0026)	(0.0001-0.0201)	(0.0006-0.0026)	(0.0001-0.0351)	(0.0016-0.0046)	(0.0001-0.0351)
2	non-EcE	0.0001	0.1001	0.0011	0.0001	0.0006	0.0001
		(0.0001-0.0021)	(0.0051-0.2951)	(0.0001-0.0051)	(0.0001-0.2951)	(0.0001-0.0016)	(0.0001-0.1601)
	E. coli	0.0016	0.0451	0.0016	0.0301	0.0036	0.0001
		(0.0001-0.0081)	(0.0001-0.1251)	(0.0001-0.0061)	(0.0001-0.1351)	(0.0021-0.0061)	(0.0001-0.0301)
3	non-EcE	0.0121	0.0001	0.0026	0.0251	0.0016	0.0201
		(0.0051-0.0201)	(0.0001-0.0701)	(0.0006-0.0091)	(0.0001-0.1051)	(0.0006-0.0041)	(0.0001-0.0601)
	E. coli	0.0001	0.0251	0.0001	0.0251	0.0011	0.0301
		(0.0001-0.0026)	(0.0051-0.0801)	(0.0001-0.0026)	(0.0001-0.1101)	(0.0006-0.0031)	(0.0051-0.0701)
4	non-EcE	0.0011	0.0351	0.0026	0.0101	0.0016	0.0301
		(0.0001-0.0036)	(0.0001-0.1751)	(0.0006-0.0091)	(0.0001-0.0551)	(0.0006-0.0046)	(0.0051-0.0651)
	E. coli	0.0006	0.0001	0.0016	0.0101	0.0026	0.0001
		(0.0001-0.0031)	(0.0001-0.0551)	(0.0001-0.0066)	(0.0001-0.0851)	(0.0011-0.0056)	(0.0001-0.0301)
5	non-EcE	0.0086	0.0351	0.0076	0.0201	0.0051	0.0201
		(0.0026-0.0176)	(0.0001-0.0851)	(0.0026-0.0151)	(0.0001-0.0651)	(0.0011-0.0101)	(0.0001-0.0501)
	E. coli	0.0046	0.0001	0.0041	0.0001	0.0056	0.0001
		(0.0016-0.0076)	(0.0001-0.0401)	(0.0016-0.0071)	(0.0001-0.0301)	(0.0036-0.0071)	(0.0001-0.0101)
6	non-EcE	0.0401	0.0251	0.0276	0.0401	0.0106	0.0201
		(0.0056-0.0401)	(0.0001-0.1101)	(0.0061-0.0401)	(0.0001-0.1051)	(0.0031-0.0236)	(0.0001-0.0501)
	E. coli	0.0001	0.0001	0.0006	0.0001	0.0001	0.0001
		(0.0001-0.0021)	(0.0001-0.1451)	(0.0001-0.0031)	(0.0001-0.2301)	(0.0001-0.0006)	(0.0001-0.1051)

7	non-EcE	0.0056	0.0301	0.0136	0.0001	0.0091	0.0751
		(0.0001-0.0191)	(0.0001-0.0701)	(0.0066-0.0241)	(0.0001-0.0351)	(0.0001-0.0401)	(0.0001-0.1251)
	E. coli	0.0041	0.0001	0.0026	0.0001	0.0036	0.0001
		(0.0001-0.0091)	(0.0001-0.0751)	(0.0006-0.0081)	(0.0001-0.0451)	(0.0016-0.0066)	(0.0001-0.0351)
8	non-EcE	0.0006	0.0001	0.0001	0.0101	0.0016	0.0001
		(0.0001-0.0016)	(0.0001-0.1251)	(0.0001-0.0016)	(0.0001-0.0501)	(0.0006-0.0026)	(0.0001-0.0201)
	E. coli	0.0006	0.0001	0.0006	0.0001	0.0021	0.0001
		(0.0001-0.0016)	(0.0001-0.1801)	(0.0001-0.0016)	(0.0001-0.2951)	(0.0016-0.0036)	(0.0001-0.0101)
9	non-EcE	0.0016	0.0001	0.0021	0.0351	0.0011	0.0001
		(0.0006-0.0041)	(0.0001-0.1851)	(0.0006-0.0056)	(0.0001-0.1401)	(0.0006-0.0021)	(0.0001-0.1151)
	E. coli	0.0031	0.0001	0.0021	0.0001	0.0011	0.0151
		(0.0011-0.0066)	(0.0001-0.0501)	(0.0006-0.0056)	(0.0001-0.0401)	(0.0006-0.0026)	(0.0001-0.1051)
10	non-EcE	0.0401	0.0051	0.0401	0.0651	0.0136	0.1051
		(0.0186-0.0401)	(0.0001-0.0601)	(0.0121-0.0401)	(0.0401-0.1251)	(0.0001-0.0366)	(0.0501-0.1501)
	E. coli	0.0126	0.0001	0.0046	0.0251	0.0071	0.0251
		(0.0066-0.0176)	(0.0001-0.0401)	(0.0006-0.0126)	(0.0001-0.0601)	(.0036-0.0116)	(0.0051-0.0451)
11	non-EcE	0.0026	0.0251	0.0036	0.0551	0.0041	0.0101
		(0.0006-0.0081)	(0.0001-0.0801)	(0.0011-0.0076)	(0.0001-0.1851)	(0.0021-0.0071)	(0.0001-0.0301)
	E. coli	0.0016	0.0301	0.0016	0.0401	0.0021	0.0001
		(0.0001-0.0061)	(0.0001-0.0801)	(0.0006-0.0051)	(0.0001-0.1701)	(0.0011-0.0036)	(0.0001-0.0101)
12	non-EcE	0.0026	0.0001	0.0026	0.0351	0.0061	0.0301
		(0.0006-0.0061)	(0.0001-0.0301)	(0.0006-0.0086)	(0.0001-0.1401)	(0.0026-0.0116)	(.0001-0.1051)
	E. coli	0.0041	0.0001	0.0021	0.0001	0.0011	0.0301
		(0.0016-0.0091)	(0.0001-0.0251)	(0.0006-0.0066)	(0.0001-0.0301)	(0.0001-0.0036)	(0.0001-0.1351)
13	non-EcE	0.0036	0.0001	0.0061	0.0001	0.0011	0.0001
		(0.0011-0.0091)	(0.0001-0.0651)	(0.0026-0.0116)	(0.0001-0.0751)	(0.0006-0.0036)	(0.0001-0.0501)
	E. coli	0.0031	0.0301	0.0001	0.0001	0.0001	0.0001
		(0.0006-0.0086)	(0.0001-0.2451)	(0.0001-0.0016)	(0.0001-0.2951)	(0.0001-0.0011)	(0.0001-0.0751)

Table S2. Estimation of transmission parameters of non-*E. coli* Enterobacteriaceae (non-EcE) and *E. coli* in 13 European intensive care units per phase using a random effects model.

	Period 1 (0.5 year)		**Period 2 (0.5 year)**		**Period 3 (1 year)**	
	non-EcE	*E. coli*	non-EcE	*E. coli*	non-EcE	*E. coli*
Number of patients	2819		2523		6078	
Patients colonized at admission	102	91	94	57	205	208
Acquisitions	181	69	213	47	389	165
Cross transmission parameter β_0, (95% CI)	0.041 (0.020-0.067)	0.011 (0.0041-0.031)	0.041 (0.019-0.070)	0.017 (0.0066-0.020)	0.040 (0.017-0.067)	0.0093 (0.0034-0.022)
Transmission parameter α_0 (endogenous route), (95% CI)	0.0035 (0.0019-0.0095)	0.0026 (0.0014-0.0045)	0.0048 (0.0027-0.0099)	0.0016 (0.0008-0.0035)	0.0025 (0.0015-0.0047)	0.0025 (0.0014-0.0039)
Single admission reproduction number R_A (95% CI)	0.25 (0.12-0.40)	0.068 (0.024-0.18)	0.25 (0.11-0.42)	0.10 (0.040-0.21)	0.24 (0.10-0.40)	0.056 (0.021-0.13)
Relative transmission capacity of non-EcE versus *E. coli* ($\beta_0^{\text{non-EcE}}/\beta_0^{\text{E. coli}}$) (95% CI)	3.6 (1.0-11.2)		2.4 (0.83-7.1)		4.4 (1.2-13.0)	

CI: credibility interval. Estimates are the values with the highest posterior posterior probability density.

Table S3. Estimates of the transmission parameters of non-*E. coli* Enterobacteriaceae (non-EcE) and *E. coli* in 13 European intensive care units using a random effects model while we assumed that the transmission parameters in different periods are independent.

	Patients included (n=11,420)	
	non-EcE	*E. coli*
Patients colonized at admission (%)	401 (3.5%)	356 (3.1%)
Acquisitions	783	281
Acquisition rate/100 uncolonized admissions	7.4	2.6
Cross transmission parameter β_0, (95% CI)	0.044 (0.031-0.058)	0.010 (0.0061-0.019)
Transmission parameter α_0 (endogenous route), (95% CI)	0.0031 (0.0025-0.0049)	0.0023 (0.0018-0.0032)
Single admission reproduction number R_A (95% CI)	0.26 (0.19-0.35)	0.061 (0.037-0.11)
The relative transmission capacity of non-EcE versus *E. coli* ($\beta_0^{non\text{-}EcE}/\beta_0^{E.\ coli}$) (95% CI)	4.3 (2.1-7.6)	

CI: credibility interval. Estimates are the values with the highest posterior probability density.

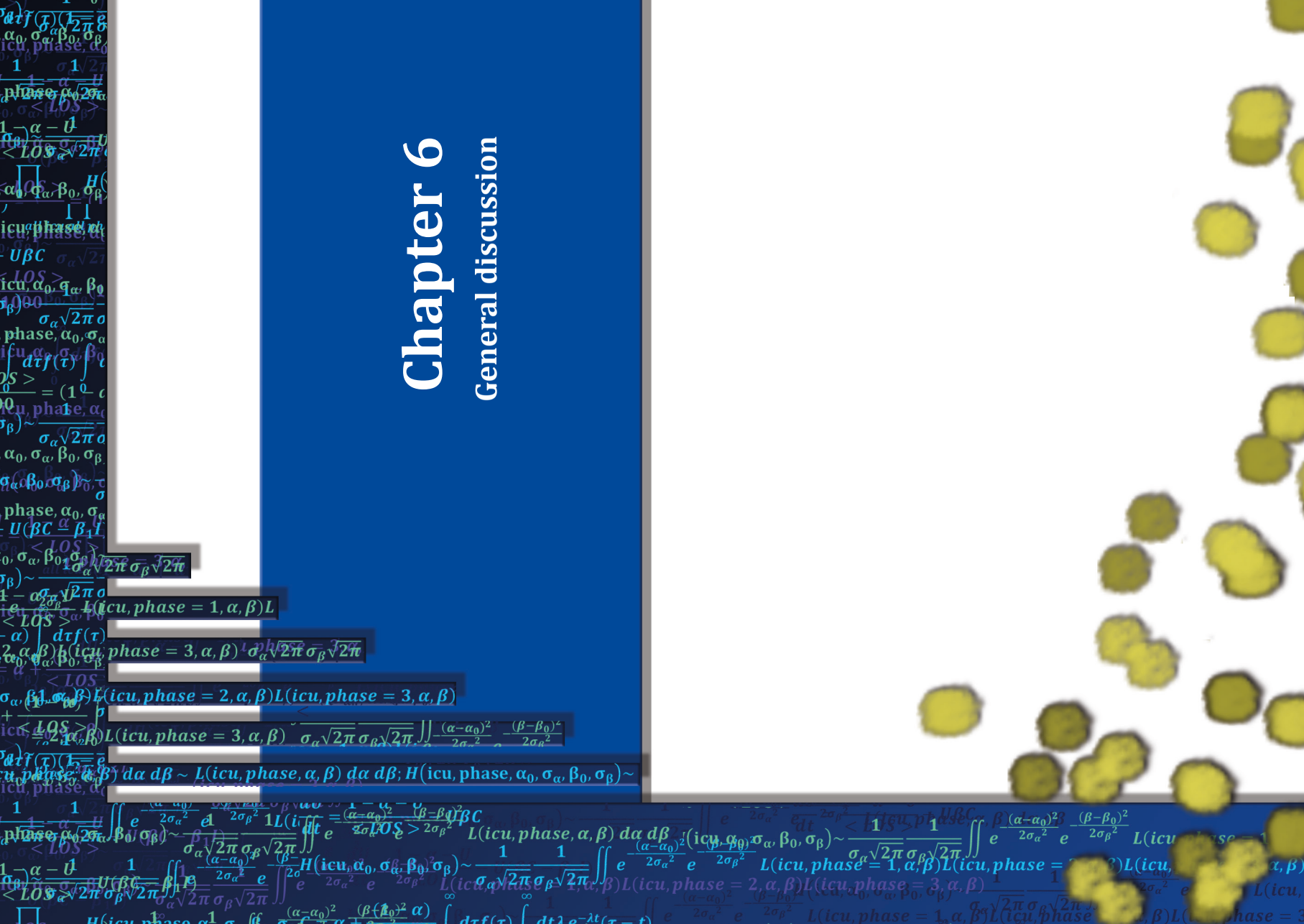
Table S.4. Transmissibility of *K. pneumoniae* and *E. coli* isolates in four European intensive care units using Raman spectroscopy.

	ICU 1 (N=779)		ICU 2 (N=1532)		ICU 3 (N=625)		ICU 4 (N=1309)	
	KP	EC	KP	EC	KP	EC	KP	EC
On admission prevalence[a]	6.4	1.5	4.9	7.2	8.6	3.7	8.3	5.7
Number of patients with isolate(s) available[b]	72	33	112	159	76	29	362	162
Number of patients colonized on admission	23	13	49	112	22	18	79	70
Number of patients acquiring colonization	49	20	63	47	54	10	283	92
Number of transmissions	29	0	19	3	28	0	246	33
DAR	11896	10184	11440	11764	4373	2482	8271	9974
Transmissions/ 10000 DAR	2.44	0	1.66	0.26	6.40	0	29.74	3.31
wDAR	31937	14571	23058	26109	9351	3369	49567	27354
Transmissions/ 10000 wDAR	0.91	0	0.82	0.11	2.99	0	4.96	1.21
Number of extra transmissions using 7-day window	0	0	4	1	4	0	6	7

DAR: Days at risk. EC: *Escherichia coli*. ICU: Intensive care unit. KP: *Klebsiella pneumoniae*. wDAR: weighted days at risk. [a] On admission prevalence of *E. coli* and non-*E. coli* Enterobacteriaceae . [b] For 10 patients 2 isolates were available (for EC 0, 1, 0 and 1 patients and for KP 2, 1, 1 and 4 patients for ICUs 1, 2, 3 and 4 respectively).

Chapter 6

General discussion



In this thesis, we have presented the investigation of several actual problems of infection control in hospital settings.

In chapter 2, we have assessed the costs and effects of four admission screening strategies followed by isolation and contact precaution with 100%, 50%, 25% and 10% effectiveness of isolation. As expected, the screening strategy in which most patients are screened, i.e., universal screening at hospital admission, is the most expensive strategy. However, it also decreases the prevalence of MRSA faster than the other scenarios considered. On the other hand, two other strategies, 1) screening all patients at ICU admission together with screening those that were previously detected as carrier, and 2) screening only those patients that were previously detected as carrier, become cost-saving within 10 years, even when the efficacy of isolation is low. Both strategies lead to a reduction of the prevalence of MRSA and have the shortest time till return of investment. These strategies are serious candidates to control MRSA. In several clinical trials [1] a number of questions remain about the effectiveness of active surveillance. METHODS We searched the literature for studies that examined MRSA acquisition, MRSA infection, morbidity, mortality, harms of screening, and resource utilization when screening for MRSA carriage was compared with no screening or with targeted screening. Because of heterogeneity of the data and weaknesses in study design, meta-analysis was not performed. Strength of evidence (SOE, the effects of admission screening of different groups of patients, followed by contact precautions, were investigated. However, comparison of the efficacy of the different screening strategies is complicated, because of the different settings, the different extramural prevalence, the different effectiveness of contact precautions/ isolation and so on. Mathematical modeling allowed us to compare the relative effectiveness and costs of different screening strategies, while all the remaining parameters could be kept the same. Moreover, the mathematical modeling also allowed us to identify critical parameters. In particular, the dynamics of costs of an intervention and whether an intervention becomes cost-saving within a few years depend critically on the costs of screening, the isolation efficacy and the costs per infection event in ICU.

Analyses of the costs of interventions can be divided into two types: i) evaluations based on data of clinical trials [2], e.g., based on systematic reviews and/or meta-analyses or applied to only some single concrete intervention [2] ii) comparison of different strategies based on simulation models to predict the optimal (cost-effective, lowest number of infections) strategy, like in the study of Hubben et al. [3]using both PCR-based and chromogenic media-based tests in various settings. METHODOLOGY/PRINCIPAL FINDINGS A simulation model of MRSA transmission was used to determine costs and effects over 15 years from a US healthcare perspective. We compared admission screening together with isolation of identified carriers against a baseline policy without screening or isolation. Strategies included selective screening of high risk patients or universal admission screening, with PCR-based or chromogenic media-based tests, in medium (5% in

which the cost-effectiveness of different tests was compared or the study of Robotham et al. [4] in which several screening, isolation and decolonization strategies were compared. Our study falls into the second category and complements the first by considering the screening of different groups of patients and by taking into account the effect of ICU-screening on the hospital population in general and by including the possibility to readmit patients while they are still colonized.

An important characteristic of our study is the fact that it accounts for the possibility to readmit patients, who can still be colonized from previous admission. Interventions in hospitals do not only have an effect on the prevalence of MRSA in the patient population in the hospital, but also, as a consequence, on the prevalence of MRSA of patients at discharge. A lower prevalence at discharge implies that less patients will enter the extramural population while being colonized, and, consequently, less patients will be colonized upon readmission to the hospital. In this way, interventions in the hospital can interrupt the feedback loop, which leads to an additional, delayed effect on the prevalence of the nosocomial MRSA in the hospital. Therefore, as the admission prevalence will decline in time, the efforts required to control MRSA will decline in time as well. However, this is only valid for HA-MRSA, where pathogens spread predominantly in health care settings. This delayed effect of interventions will be significantly smaller for pathogens which spread extramurally as well, like community-associated MRSA.

In chapter 3, we switched our attention to health care workers, as they contribute to the transmission process, either as vectors, when their hands may be temporarily colonized after contact with a colonized patient, or as a permanent source, when the health care worker is persistently colonized himself/herself, for example in the nose. However, it was not well understood in which settings healthcare workers are responsible for a significant amount of acquisitions. Therefore, we tried to determine the key-parameters for the importance of health care workers to the spread of MRSA.

In chapter 3 we demonstrated that interventions targeted at detection of carriers among patients followed by decolonisation or isolation is more effective than screening all health care workers followed by active decolonization or a replacement strategy of persistently colonized health care workers, even when the efficacy of isolation is relatively low. The standalone intervention to target persistently colonized health care workers is an ineffective measure in endemic settings. In case of sporadic outbreaks in non-endemic settings, this need not be true. Interventions targeted at persistently colonized health care workers only have a significant effect on the prevalence of MRSA among hospitalized patients when a high proportion of the MRSA acquisitions are due to a small number of persistently colonized health care workers.

We have indicated two key parameters for the effectiveness of interventions targeted at persistently colonized health care workers: the proportion of health

care workers being persistently colonized and the proportion of acquisitions of MRSA among patients which can be ascribed to persistently colonized health care workers. While the first parameter was estimated in earlier studies [5–8] respectively, the second one is difficult to estimate and requires screening of patients and health care workers and, preferably, genotyping of all MRSA isolates.

Many clinical studies have been performed aimed at reducing the transmission of MRSA and infections with MRSA. Our attention was drawn to a study by Jain et al. [9], which showed a reduction of almost 70% in infections with MRSA. This truly remarkable reduction was ascribed to screening and isolation of patient. This study may convince policy makers that transmission preventions measures are enough to achieve such a decrease in the number of infections. However, if the reduction was not only caused by the screening and isolation strategy, but also by other components of the bundle of interventions, implementation of a screening and isolation strategy may not be as effective as expected. To prevent this, we assessed the possible effect of barrier precaution and better hand hygiene on the reduction of MRSA infections and what fraction of the reduction, observed in the study published by Jain et al, could be ascribed to the components of the bundle of interventions.

In chapter 4, we have shown, using a mathematical model, that only a small fraction of the phenomenal reduction in infection rate described by Jain et al. could be the result of transmission prevention. Simply said, the transmission rates before bundle implementation were already low and most patients with MRSA colonization were already colonized at admission, so transmission prevention in the hospitals could not have had a large impact.

Therefore, we hypothesized that the striking reduction of infection rates described by Jain et al. could be explained by a reduction of the risk for a colonized patient to develop an infection as other practices may have changed as well, e.g., better management of intravascular lines, rather than by reduction in acquisition rates.

While the incidence of nosocomial infections with MRSA are decreasing in some countries during the last few years, infections with Gram-negative bacteria are emerging. For instance, infections with Enterobacteriaceae resistant to third-generation cephalosporins increased substantially during the last 10 years [10].

Although cross-transmission is only responsible for a part of the nosocomial infections with third-generation cephalosporin resistant Enterobacteriaceae, this route can be controlled by standard measures such as contact precaution, isolation and so on.

In chapter 5 we have estimated the rates of cross-transmission of *E.Coli* and non-*E.coli* (mainly Klebsiella) Enterobacteriaceae and have found that non-*E. coli* bacteria have a 3.7 times higher cross-transmission capacity than *E.coli*. The

estimations were based on 24 month extensive microbiological surveillance in 13 ICUs. As the data for *E.coli* and non-*E.coli* species were collected at the same time, in the same ICUs, with the same surveillance protocol, all external factors which could influence transmission were the same for the bacteria types.

The per admission reproduction numbers were estimated to be below one for both non-*E.coli* (0.17) and *E.coli* (0.047), suggesting that transmission of third-generation cephalosporin resistant Enterobacteriaceae in hospitals is not a major problem with the currently implemented transmission prevention measures. Therefore, implementation of additional transmission prevention measures in hospital, like isolation of colonized patients, is unlikely to be very effective.

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Summary & Acknowledgments

Summary

Infections with antibiotic-resistant bacteria are a worldwide problem in hospitals and their rates remain high in many countries despite efforts to reduce the rates. Infection prevention is complicated by asymptomatic carriers, who do not suffer from colonization, but can spread these bacteria to other patients, often via the hands of temporary colonized health care workers (HCWs). Using mathematical methods this thesis addresses several actual problems of infection control in hospital settings.

First of all, asymptomatic carriers can be detected by screening, which can be based on conventional or rapid molecular techniques and which may target different patient populations. After detection of carriage, the patient may be placed in an isolation room, treated with antibiotics or antiseptics to eradicate the colonization or other measures can be taken in order to reduce the chance to transmit the bacteria to other patients.

The costs and effects of four admission screening strategies followed by 100%, 50%, 25% and 10% effective isolation are estimated in chapter 2. As expected, screening of all patients at hospital admission is the most expensive but also most effective strategy to reduce methicillin-resistant *Staphylococcus aureus* (MRSA). Two other strategies, *i*) screening all patients at admission to intensive care units (ICUs) together with screening those patients with a history of MRSA colonization, and *ii*) screening only patients with a history of MRSA colonization are much cheaper, but still reduce the prevalence of MRSA significantly. Moreover, these two strategies become cost-saving within 10 years, even when the efficacy of isolation is low. Both interventions result in the shortest time till return of investments, and are, therefore attractive candidates to control MRSA.

Not only patients can carry bacteria, such as MRSA, HCWs may become persistently colonized (for example in their nose) as well. HCWs have multiple contacts with different patients and, once colonized, can spread the bacteria to uncolonized patients. The contribution of persistently colonized HCWs to the transmission process in endemic settings is investigated in chapter 3. It is shown that, in most endemic settings, screening of patients, followed by isolation and/or decolonization of those with a positive test is a more effective strategy than screening of HCWs followed by decolonization and/or replacement of identified carriers. This holds true even when the efficacy of patient isolation is relatively low. The only exception is the situation when a low amount of persistently colonized HCWs is responsible for large amount of transmissions. Next to that, key parameters for the effectiveness of the interventions targeted at HCWs were determined. These were the fraction of colonized HCWs and the proportion of the MRSA acquisitions they are responsible for. The prevalence of colonization among HCWs was estimated earlier in seldom clinical studies, but the second critical parameter is hard to estimate, but essential for the potential gain of interventions targeting HCWs.

Many clinical studies have been performed to reduce the transmission of infections with MRSA. Some of them claimed success, others did not find any reduction in MRSA infection rates. The study of Jain et al showed a reduction of almost 70% in infections with MRSA. This phenomenal reduction was ascribed to screening and isolation of patients, while the intervention consisted of complex bundle of measures. To prevent possible inappropriate expectations from single measures by policy makers, the maximal impact of screening and isolation of patients on MRSA infection rates is determined in chapter 4. Using a mathematical model, it was shown that only a small fraction of the remarkable reduction in infection rate described by Jain et al. could be the result of transmission prevention. Transmission prevention could not have had a huge effect on infection rates, because transmission rates within these hospitals were low already before the start of the intervention. Most of the carriers of MRSA were already colonized when they entered the hospital. The huge reduction in infections was probably the result of other measures, for example, better management of intravascular lines.

Gram-negative bacteria, such as Enterobacteriaceae that are resistant to third-generation cephalosporins, are another emerging problem in the last years. Transmission of the bacteria from patient to patient is only one possible route of spreading resistant genes, but it can be controlled by standard measures such as isolation, hand hygiene, contact precaution, decolonized treatments, cohorting patients or/and health care workers and so on. Transmission capacities of *E. coli* and non-*E. coli* (mainly *Klebsiella*) Enterobacteriaceae are estimated in chapter 5. It is shown, that non-*E. coli* bacteria are 3.7 times more transmissible than *E. coli* in the same conditions. The estimations were based on the data from 24 months extensive microbiological surveillance in 13 ICUs. Still the per admission reproduction numbers were below one for both bacteria, which means the transmission of the bacteria in ICUs is already low. In such cases additional measures targeted on prevention of transmission within hospitals are unlikely to be very effective.

Samenvatting

Infecties met antibiotica-resistente bacteriën zijn een probleem in ziekenhuizen wereldwijd. Ondanks pogingen om de incidentie te verlagen blijven infecties veelvoorkomend in veel landen. Infectiepreventie is gecompliceerd doordat mensen de bacteriën bij zich kunnen dragen zonder ziek te zijn. Deze zogenaamde asymptomatische dragers kunnen de bacteriën wel verspreiden naar andere patiënten, vaak via tijdelijk besmette handen van medisch personeel. In dit proefschrift worden met behulp van wiskundige methoden verschillende actuele problemen uit de infectiepreventie in ziekenhuizen onderzocht.

Infectiepreventiemaatregelen gericht op asymptomatische dragerschap vereisen kennis van welke patiënten de bacterie bij zich dragen. Detectie van dragerschap kan met behulp van conventionele, op kweek-gebaseerde, technieken of met moleculaire technieken die minder tijd vergen. Ook de te screenen patiëntenpopulatie kan variëren. Na detectie van de dragers kunnen maatregelen worden genomen om de besmettelijkheid van de patiënten te verminderen; dit kan isolatieverpleging zijn of behandeling met antibiotica of antiseptica.

In hoofdstuk 2 worden, voor ziekenhuizen met een hoge prevalentie van meticilline-resistente *Staphylococcus aureus* (MRSA), de kosten en effecten van vier verschillende screeningsstrategieën berekend, indien detectie van dragerschap gevolgd wordt door isolatieverpleging (met een effectiviteit 100%, 50%, 25% of 10%). Zoals verwacht is het screenen van alle patiënten bij ziekenhuisopname de duurste maar ook de meest effectieve strategie om de prevalentie van MRSA te verminderen. Twee andere strategieën, i) het screenen van alle patiënten bij intensive care (IC) opname samen met het screenen van patiënten met een geschiedenis van MRSA-dragerschap en ii) het screenen van alleen patiënten met een geschiedenis van MRSA-dragerschap zijn veel goedkoper, en verminderen de prevalentie van MRSA ook aanmerkelijk. Bovendien worden deze twee strategieën binnen 10 jaar kostenbesparend, zelfs wanneer de effectiviteit van isolatie laag is. Omdat beide interventies bovendien de kortste tijd hebben tot de initiële investeringen zijn terugverdiend, zijn het aantrekkelijke infectiepreventie strategieën.

Niet alleen patiënten kunnen bacteriën, zoals MRSA, bij zich dragen, ook ziekenhuismedewerkers kunnen langdurig dragers zijn (bijvoorbeeld in de neus). Medewerkers, zoals verpleegkundigen en artsen, hebben contact met verschillende patiënten en kunnen daarom, als ze MRSA bij zich dragen, de bacterie naar meerdere patiënten verspreiden. In hoofdstuk 3 wordt de bijdrage van persistent gekoloniseerde medewerkers aan het transmissieproces onderzocht in instellingen waar MRSA endemisch is. Het blijkt dat het screenen van patiënten, gevolgd door isolatie en/of dekolonisatie van degenen met een positief testresultaat een effectievere strategie is dan het screenen van medisch personeel gevolgd door dekolonisatie en/of vervanging van als drager geïdentificeerde medewerkers door niet-gekoloniseerde medewerkers. Dit geldt zelfs wanneer de effectiviteit van patiëntisolatie relatief laag is. De enige uitzondering is de situatie wan-

neer een klein aantal persistent gekoloniseerde medewerkers verantwoordelijk is voor een groot deel van de transmissies. Daarnaast werden de belangrijkste parameters voor de effectiviteit van interventies gericht op medewerkers bepaald. Dit waren: de fractie gekoloniseerde medewerkers en het aandeel van de MRSA-acquisities waarvoor zij verantwoordelijk zijn. De prevalentie van MRSA onder medewerkers is eerder gerapporteerd in een paar klinische studies, maar de tweede kritische parameter is moeilijker te bepalen.

Er zijn veel klinische studies uitgevoerd om de incidentie van MRSA-infecties te verminderen, met sterk wisselende resultaten. Jain et al. beschreven een omvangrijke studie waarbij de interventie leidde tot een afname van bijna 70% in MRSA-infecties. Deze reductie werd aan screening en isolatie van patiënten toegeschreven, terwijl de interventie een complexe bundel maatregelen omvatte. Om mogelijke onjuiste verwachtingen van individuele maatregelen door beleidsmakers te voorkomen, wordt in hoofdstuk 4 de maximale impact van de screening en isolatie van patiënten op de incidentie van MRSA-infecties bepaald. Met behulp van een wiskundig model wordt aangetoond dat slechts een klein deel van de indrukwekkende afname van MRSA-infecties die door Jain et al. beschreven is, het gevolg van transmissiepreventie kan zijn. Transmissiepreventie kan het aantal infecties niet enorm hebben beïnvloed, omdat er binnen deze ziekenhuizen voor het begin van de interventie al nauwelijks transmissie was. De meeste dragers van MRSA waren reeds gekoloniseerd toen ze in het ziekenhuis kwamen. De grote vermindering van infecties was waarschijnlijk het resultaat van andere maatregelen, bijvoorbeeld een beter verzorging van intravasculaire lijnen.

Gram-negatieve bacteriën, zoals Enterobacteriaceae die resistent zijn tegen derde generatie cefalosporines, zijn in de afgelopen jaren een toenemend probleem. Transmissie van deze bacteriën van patiënt naar patiënt is slechts een mogelijke verspreidingsroute van de resistentiegenen, maar het belang van deze route kan door standaardmaatregelen, zoals isolatie van patiënten en handhygiëne, worden beperkt. Het transmissiepotentieel van *E. coli* en andere Enterobacteriaceae (vooral Klebsiella) wordt in hoofdstuk 5 geschat. De schattingen zijn gebaseerd op de gegevens van een 24 maanden durende studie in 13 IC's. Klebsiella bleek, onder dezelfde omstandigheden, 3,7 keer besmettelijker te zijn dan *E. coli*. De reproductiegetallen per ziekenhuisopname waren echter beduidend lager dan één voor beide bacteriën, wat betekent dat transmissie van de bacteriën in IC's beperkt is. In dergelijke gevallen is het onwaarschijnlijk dat aanvullende maatregelen, gericht op preventie van transmissie binnen ziekenhuizen, zeer effectief zullen zijn om de verspreiding van Enterobacteriaceae, die resistent zijn tegen derde generatie cefalosporines, tegen te gaan.

Резюме

Инфекционные заболевания, вызванные антибиотико-резистентными бактериями, являются актуальной проблемой в больницах во всём мире. Несмотря на все попытки уменьшить частоту таких заболеваний, во многих странах она остается высокой. Контроль инфекционных заболеваний осложняется наличием асимптомных носителей, которые, не страдая от инфекциионной болезни сами, тем не менее могут распространять бактерии среди других пациентов, часто посредством временно инфицированных рук медицинского персонала. В данной диссертации при помощи математических методов рассматриваются несколько актуальных вопросов контроля антибиотико-резистентных инфекций в больницах.

Прежде всего, асимптоматические носители бактерий должны быть обнаружены, что может быть осуществлено посредством традиционных или быстрых молекулярных методов. При этом тестирование при приеме в больницу может быть нацелено на различные группы пациентов. Когда носители выявлены, они могут быть изолированы и/или им могут быть назначены антибиотики и/или могут быть приняты другие меры для уменьшения шанса заражения других пациентов.

В главе 2 были оценены эффективность и стоимость четырех стратегий тестирования различных групп пациентов при приеме в больницу с последующей изоляцией выявленных носителей (с эффективностью 100%, 50%, 25% и 10%). Как и ожидалось, наиболее дорогостоящей, но и наиболее эффективной в уменьшении количества метициллин-резистентного золотистого стафилококка (methicillin-resistant *Staphylococcus aureus,* MRSA) оказалась стратегия тестирования всех пациентов при приеме в больницу. Две других стратегии *i)* тестирование пациентов имевших MRSA в истории предыдущих госпитализаций и всех пациентов при приеме в палаты интенсивной терапии и *ii*) тестирование при приеме в больницу только пациентов имевших MRSA в истории предыдущих госпитализаций, оказались существенно дешевле, но при этом, тем не менее, существенно снижающими количество MRSA инфекций. Более того, данные две стратегии экономически оправдывают себя за менее чем 10 лет даже при невысокой эффективности изоляции и, таким образом, являются привлекательными для контроля MRSA в больницах.

Носителями бактерий могут быть не только пациенты, но и медицинский персонал, который может оказаться персистентными носителями бактерий (например в носовой полости). Так как медицинские работники многократно контактируют с различными пациентами, то, будучи носителями бактерий, они могут передавать их незараженным пациентам. В главе 3 изучен вклад персистентных носителей среди медицинского персонала в процесс распространения бактерии в эндемических условиях. Было показано, что в эндемических условиях тестирование пациентов

при госпитализации с последующей изоляцией / лечением выявленных носителей, даже при относительно невысокой эффективности изоляции, является более эффективной мерой, чем тестирование медицинского персонала с последующим замещением / лечением зараженных медицинских работников. Исключение составляет случай, когда малое количество медицинских работников ответственны за большое количество случаев заражения. Таким образом, были выявлены два параметра являющиеся ключевыми для выбора эффективной стратегии: доля инфицированных медицинских работников и частота заражения ими пациентов. Доля инфицированных медицинских работников была ранее экспериментально оценена в немногочисленных исследованиях. Частоту же заражения от персистентных носителей среди медицинского персонала измерить сложнее, в то время как этот параметр может оказаться очень важным при принятии решения о тестировании медицинского персонала.

В больницах по всему миру было проведено огромное количество клинических исследований с целью уменьшения количества MRSA. Некоторые из них рапортовали о положительном результате от принятых мер, другие же не обнаружили уменьшения количества MRSA инфекций. В американском исследовании Jain с соавторами. уменьшение инфекционных заболеваний с MRSA составило почти 70%. Такое феноменальное уменьшение инфекций было приписано тестированию и изоляции пациентов, несмотря на то, что в исследовании был применен целый комплекс различных мер. Для того, чтобы предотвратить возможность неоправданных ожиданий от единичных мер лицами определяющими регламент функционирования больниц, в главе 4 был оценен максимально возможный эффект от тестирования и изолирования пациентов. При помощи математической модели было показано, что лишь небольшая доля того огромного уменьшения количества инфекционных заболеваний в статье Jain и соавторов может быть объяснена мерами по предотвращению распространения бактерии в больнице. Эти меры не могли иметь такой огромный эффект в силу того, что случаи инфицирования MRSA в больницах были достаточно редки ещё до начала исследования. Большее количество носителей MRSA были уже инфицированны на момент их приема в больницу. Таким образом это впечатляющее уменьшение количества MRSA в больницах было результатом других мер, принятых во время исследования (например улучшение в процедурах установки внутривенных капельниц.

Грамотрицательные бактерии, такие как *Enterobacteriaceae*, резистентные к 3му поколению цефалоспоринов, являются еще одной обострившейся в последние годы проблемой. Распространение таких бактерий от пациента к пациенту – это лишь один из возможных путей распространения резистентных к цефалпспоринам 3-его поколения генам. Однако этот путь распространения можно контролировать стандартными мерами, такими как изолирование пациентов, гигиена рук, минимизирование контактов, антибактериальное лечение, группирование пациентов и

медицинских работников и т.д. В главе 5 были оцененены инфекционность (заразность?) *Enterobacteriaceae: E. coli* и *Klebsiella*. ((Или?)) В главе 5 были оцененены инфекционные способности *Enterobacteriaceae: E. coli* и *Klebsiella*.Основываясь на данных 24х месячного микробиологического исследования в 13 европейских больницах, было показано, что в одних и тех же условиях *Enterobacteriacea*е вида *Klebsiella* в 3,7 раза более инфекционны (заразны?), чем вид *E. coli.* При этом оцененный индекс репродукции обеих видов был существенно ниже единицы, что означает, что распространение этих бактерий в современных больницах существенно затруднено. В таком случае, маловероятно, что дополнительные меры по предотвращению распространения этих бактерий в больницах покажут заметную эффективность в снижении данных инфекций.

Acknowledgments

First of all I want to thank my supervisors Prof. Marc Bonten and Dr. Martin Bootsma. Thank you for the opportunity to get involved in these interesting projects and bring them to completion. I am very grateful to you for your patience and for always being very supportive during the whole duration of my PhD journey! I learned to be critical about data and results interpretation, which is an important skill for any scientist. Martin, thank you for your attention to the details that was instrumental for correction of many mistakes I made on this long way – I value that very much. I have learned a lot from you! Marc, I am especially grateful for all wise supervising, scientific ideas and excellent working atmosphere in your group. I will keep many good memories from being part of such a great team!

I want to thank the members of the reading committee: Prof. M.E.E. Kretzschmar, Prof. J.A.P. Heesterbeek, Prof. O. Diekmann, Prof. J.A.J.W. Kluijtmans, Prof. A. Voss for your willingness to invest time in reading end evaluating my thesis.

I would like to thank Prof. Odo Diekmann for all seminars, courses, journal clubs and discussions you organised. They were extremely useful and educative and helped me to understand topics that were totally new to me at the time I started my PhD.

I want to thank everybody who participated in WMMs (Wednesday morning meeting); the time on WMM always was very enlightening. It is certainly one of the things I am missing a lot already.

I would like to thank everyone with whom I have enjoyed working in Institute of Mathematics and Utrecht University Medical Centre. Slavik, Pieter, Sasha, Lennie, Sebastian, Irene, Mirjam many others with whom I regularly discussed scientific and non-scientific subjects. It was a lot of fun to be working with you!

I am thankful to my friends Aleksandra Babenko and Ekaterina Anissimova-Israel for acting as my paranimphs, for all their support and help. Aleksandra, during these years you always was the example for me and, hereby, motivated. Katya, thank you for being around in good and bad times and being ready to support me in any circumstances. You always understand me like no other.

I want to thank all my friends who have been around me during this period Tanya Berezikova and Marjana Bevova, thank you for being such a great company. Special thanks to Zhenya Berezikov, the person whom I know from school times and whose comments have always been very motivating to me.

I want to thank my parents and relatives. Я благодарна моим родным и близким за их моральную поддержку и веру в меня. Спасибо моим сестрам Александре

и Ксении за моральную поддержку. Ксюша, твой вопрос о «не распылении интересов» заставил меня всерьез задуматься. Мама, спасибо за неизменную моральную поддержку во время моих поисков себя. И, конечно, спасибо за помощь в оформлении книги. Папа, спасибо тебе за то, что периодически напоминал мне кем я была, чего хотела и чего могу достичь.

Big thanks to my husband and my son, who have been of tremendous support to me during all this time. I am very grateful for your support, your believing in me, your encouragement and stimulating me along the way.