Environmental Contamination as an Important Route for the Transmission of the Hospital Pathogen VRE: Modeling and Prediction of Classical Interventions

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Abstract

Background: In addition to the close contact between patients and medical staff, the contamination of surfaces plays an important role in the transmission of pathogens such as *vancomycin-resistant enterococci* (VRE). Mathematical modeling is a very convenient tool for hospital infection control as it allows the quantitative prediction of the effects of special hygiene and control interventions.

Methods: We present a compartmental model which describes the dynamics of transmission from patient to patient, also taking into account the interaction with medical staff and environmental contamination. Empirical data from a VRE outbreak in the onco-haematological unit at the University Medical Center Freiburg (Germany) were collected with 100 consecutive admissions being followed up for 90 days. Stochastical simulations were used to predict the prevalence of patients colonised with VRE at the time when at least one of the following interventions were introduced: hand hygiene, disinfection of surfaces, cohorting, screening and antibiotic reduction.

Results: Graphical figures show the temporal dynamics of several simulation scenarios. If no prevention or intervention is present, simulations based on transmission models predict an expected endemic prevalence per ward of 0.83 (95% CI:0.66, 1.00) after the first infected person enters the unit. Interventions may reduce this prevalence, but only the combination of several interventions can control a VRE outbreak.

Conclusions: The model predicts that only the combination of several interventions can control an VRE outbreak in this setting. The inclusion of environmental contamination improves the compartmental model and allows a prediction of the efficacy of the disinfection of surfaces. These results can be applied to other settings and will therefore help to understand and control the spread of nosocomial pathogens.

Keywords: infection control, stochastic model, poisson process, epidemiological modeling, monte carlo simulation

Introduction

Nosocomial infections due to multi-resistant pathogens like *vancomycin-resistant enterococci* (VRE) are a major infection control problem, especially in intensive-care and haematology units. Several outbreaks of VRE have occurred in hospitals in the United States and in Europe, especially affecting severely ill patients whose immune system is compromised. They play an important role in prolonging the length of stay in hospital and thus further increasing costs [1]. Targeted intervention strategies are essential to control outbreaks and reduce transmisson of multi-resistant pathogens.

Mathematical modeling is increasingly used to describe the temporal transmission dynamics of infections in general (e.g. SARS) [2] and hospital infections in particular [3–7]. It has been shown that modeling is an adequate tool for predicting the impact of interventions on the endemic prevalence [8]. Deterministic as well as stochastic models are used for hospital infection control, but stochastic models are more suitable for single wards because of the usually small number of patients. Most models assume that pathogens are transmitted via the hands of medical staff. Austin et al. [9, 10] applied the deterministic Ross-Macdonald model to VRE which was originally used to model vector-borne malaria transmission,

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but which is also valid for other pathogens like MRSA [11]. This model was used to analyse the VRE transmission exclusively via the hands of medical staff. This mode of transmission is primarily responsible for infection in intensive-care units. Environmental contamination (such as door handles), however, also plays an important role, [12] especially in onco-haematological units and other hospital services with patients that are mobile and not strictly confined to the bed. Recently, Kramer et al. [13] published a systematic review showing that nosocomial pathogens can persist on surfaces for several days and can therefore be a continuous source of transmission. McBryde and McElwain [14] describe this additional environmental route with a system of ordinary differential equations (ODE) in a deterministic model. In their paper, the model accounts for the contamination of medical staff by contaminated environment which indirectly leads to patient colonisation. McBryde and McElwain show that the mean endemic prevalence of colonised patients is higher if environmental contamination is taken into account. To predict the impact of interventions, especially regular surface disinfection, the inclusion of this route of transmission is essential. Since it is based on a deterministic model, the solution of ODE's only yields the mean prevalence, but it does not account for random fluctuations [7].

In the present paper, we present a stochastic model for VRE-transmission that may be more typical for units (i.e. onco-haemotological) where patients are more active than patients in intensive-care units, and where therefore not only medical staff but also the contaminated environment might play an important role. We included the environment as well as possible transmission via the hands of medical staff as additional parameters. Since patients can also acquire the pathogen directly from the contaminated environment, it differs from the model by McBryde and McElwain [14]. Hypothetical parameters were taken from the literature. Monte-Carlo simulations were used in order to show the impact of the following classical infection control interventions: increased hand hygiene, cohorting, screening on admission, reduction of antibiotic usage and regular preventive surface disinfection. These results can be applied to other settings and will therefore help us to understand and control epidemic spread of nosocomial pathogens.

Motivating example of an VRE outbreak

All patients (100 consecutive admissions) in an onco-haematological unit (19 beds) at the University Medical Center Freiburg in Germany were followed from November 2004 until January 2005 (90 days). Screening and regular surveillance cultures (rectal/skin swabs, urine/blood culture) were used to determine the colonisation/infection status of each patient. For the purpose of the study, the focus was set on colonisation rather than infection, so the data of patients who were colonised or infected by VRE were treated in the same manner. Figure 1 shows the prevalence of VRE-colonisation depending on time.

Methods

Modeling

The compartmental model which describes VRE-transmission in a hospital unit is displayed in Figure 2. A colonised patient might become contaminated from close contact with environmental surfaces and/or the hands of health-care workers.

For the mathematical description of the transmission dynamics from Figure 2 the following assumptions are made: the number of beds in the unit is fixed, and the unit is fully occupied, i.e. every discharged patient is replaced by a new admission (first row in Table 1). We assume that

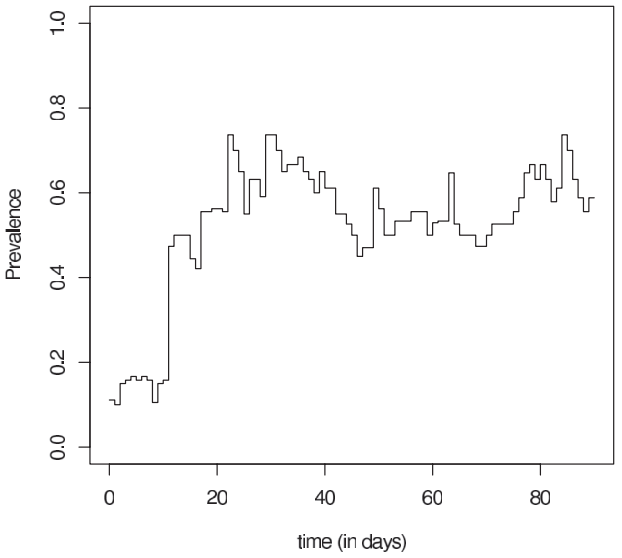

Figure 1. Prevalence of colonised/infected VRE-positive patients on the onco-haemotological unit at the University Medical Center Freiburg, Germany (11/2004–01/2005).

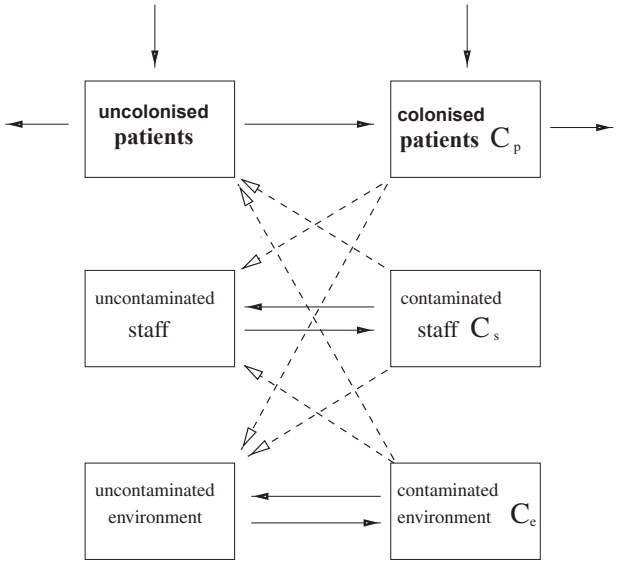

Figure 2. Compartmental model of the VRE-transmission dynamics of two routes of colonisation/infection: through hand to hand contact and via environmental contamination. Solid arrows stand for admission, discharge, colonisation or (de) contamination. Dashed arrows stand for close contacts where pathogens can be transmitted. C_p is the number of colonised patients, C_s the number of contaminated staff and C_e the number of surfaces that are contaminated.

medical staff as well as patients themselves can be contaminated with VRE-pathogens via surfaces. While there is migration among patients due to admission and discharge (or death), we assume that the number of medical staff and environmental surfaces is constant. We prefer the Reed-Frost to the Greenwood assumption (see Becker [15] or Anderson [16] for details), i.e. each person among the contaminated staff independently creates infectious contacts. This means we use the term $C_s(t)(N_p - C_p(t))$, e.g. the number of possible contact-pairs between contaminated staff and susceptible patients at time t (Table 1), instead of just $(N_p - C_p(t))$. The term $1/N_p$, $1/N_s$ and $1/N_e$ appears, since for a contact-transmitted pathogen we do not expect the total transmission rate to increase with N_p, N_s or N_e (true mass action).

Intervention strategies

A unit with the parameters described in Table 2 without any of the interventions discussed below is used as the starting point. In general, to control outbreaks of infections each intervention will primarily affect rates, e.g. colonisation or contamination rates. However, if rates are changed, this will also have an impact on the temporal dynamics and therefore reduce/increase the (endemic) prevalence of colonised patients.

The following interventions are discussed here:

1. *Hand hygiene and usageof gloves for staff.* This method of intervention or prevention is very important since it is, in principle, 100% effective, but there are numerous studies showing that there is a lack of compliance. Eckmanns et al. [17] demonstrated that behavioral attitudes were responsible for low compliance. Frequent

Table 1. Mathematical model describing the compartmental model.

Event	Increase/decrease	Rate
colonised admission	$C_p \to C_p + 1$	$(\gamma N_p + (\gamma' - \gamma)C_p(t))\phi$
VRE-transmission	$C_p \to C_p + 1$	$\left(\beta_{sp}\frac{C_s(t)}{N_s} + \beta_{ep}\frac{C_e(t)}{N_e}\right)(N_p - C_p(t))$
colonised removal	$C_p \to C_p - 1$	$\gamma' C_p(t)$
med. staff contamination	$C_s \to C_s + 1$	$\left(\beta_{ps}\frac{C_p(t)}{N_p} + \beta_{es}\frac{C_e(t)}{N_e}\right)(N_s - C_s(t))$
med. staff decontamination	$C_s \to C_s - 1$	$\mu C_s(t)$
environmental contamination	$C_e \to C_e + 1$	$\left(\beta_{se}\frac{C_s(t)}{N_s} + \beta_{pe}\frac{C_p(t)}{N_p}\right)(N_e - C_e(t))$
environmental decontamination	$C_e \to C_e - 1$	$\kappa C_e(t)$

Table 2. Default parameters for the VRE-transmission in a hypothetical hospital unit.

Parameter	Interpretation	Value	Reference
N_p	number of beds	20	
N_s	number of medical staff	5	
N_e	number of contact surfaces	100	
$C_p(t=0)$	number of colonised patients at time 0	1	
$C_s(t=0)$	number of contaminated staff at time 0	0	
$C_e(t=0)$	number of contaminated surfaces at time 0	0	
ϕ	admission colonisation prevalence	0.10	[3, 10]
γ	uncolonised discharge rate	0.10/day	[4–7, 10]
γ'	colonised discharge rate	0.05/day	[4–6, 10]
μ	staff decontamination rate	24/day	[10, 11]
$1/\mu$	duration of staff contamination	1 h	[10, 11]
κ	environmental cleaning rate	1/day	
β_{sp}	transmission rate from staff to patient*	0.3/day	[4, 5, 7]
β_{se}	transmission rate from staff to environment*	2/day	[14]
β_{ps}	transmission rate from patient to staff*	2/day	[4, 5, 7, 10]
β_{pe}	transmission rate from patient to environment*	2/day	[14]
β_{es}	transmission rate from environment to staff*	2/day	[14]
β_{ep}	transmission rate from environment to patient*	0.3/day	

*In general, the transmission rate is a product of the contact rate and colonisation/contamination probability. Here, we assume a contact rate of 5 and colonisation (contamination) probability of 0.06 (or 0.4).

visits of infection control teams might improve the compliance, since the Hawthorne effect is likely to influence hand hygiene. Here, we assume a compliance rate of 50%, and the intervention will therefore reduce the contamination rate by 50%. This intervention directly affects the rates β_{sp}, β_{se}, β_{ps} and β_{es} with factor 0.5.

2. *More frequent disinfection of surfaces.* It has frequently been shown that contaminated environment might be responsible for outbreaks of hospital-acquired infection [18]. Several bacteria and viruses might survive for weeks and even months on dry surfaces. Studies show that Enterococcus (including VRE) might persist from 5 days up to 4 months. Here, we assume the rate of environmental decontamination to increase from normal cleaning (once per day) up to 3 times per day.
3. *Cohorting of colonised patients*. One-to-one nursing is among the most expensive interventions. To describe cohorting, it is necessary to know the nursing-staff proportion and the probability of having cohorted contacts. In our simulations, we assumed a nursing-staff proportion of 70% and a cohorting probability of 80%. Therefore, the colonisation rate is decreased by a factor of $1–0.8*0.7 = 0.44$. This factor is multiplied with the rates β_{sp}, β_{ps}, β_{pe} and β_{ep}.
4. *Screening and isolation*. Although the microbiological methods of detecting VRE have been improved in recent years, this strategy is expensive. Every new admission is screened for VRE and is isolated if the result is positive. This means that no more colonised patients enter the unit ($\phi = 0$).
5. *Reduction of antibiotic usage*. Frequent usage of antibiotics, especially Vancomycin, is known to increase the risk of colonisation and infection with VRE [19]. We assume that the risk for acquiring VRE is 3 times increased for patients undergoing antibiotic therapy compared to those who do not. Reduction of antibiotic usage by 50% will reduce the colonisation rate by a factor of 0.25 [10]. This means that this factor directly affects the rates β_{sp} and β_{ep}.

The simulation study is explained in detail in the appendix. For our simulations, we assume that

one VRE-positive patient enters the unit on day 0. During the first 20 days, there are none of the intervention programs mentioned above. After 20 days, we study the following scenarios: only one intervention of the interventions mentioned above; the combination of intervention 1 and 2 with one or two of the remaining ones; and the combination of all interventions. This means that the rates have changed for each scenario, respectively. The reduction of the endemic prevalence to 10% is defined as "clinically controlled".

Results

If there were no prevention and intervention programs in place on the unit, a VRE outbreak would probably occur after one patient entered the unit. According to our model, after about 30 days, the expected prevalence of colonised patients would reach the endemic equilibrium of a mean equal to 83% ('no intervention'). This corresponds approximately to the initially observed situation of the VRE outbreak at the onco-haemotological ward at the University Medical Center Freiburg, Germany. The prevalence depending on time is displayed in Figure 3 with a 95% pointwise confidence band for each of the interventions. Only cohorting and an antibiotic reduction of 50% significantly could reduce the endemic prevalence (both from ~80% up to ~55%). Interestingly, improved hand hygiene alone could not affect the endemic prevalence at all (Fig. 3), although it directly changed several rates (β_{sp}, β_{se}, β_{ps} and β_{es}). Together with intervention 1 (hand hygiene) and 2 (increased disinfection), the prevalence could be reduced by up to ~35% (Fig. 4). Only the combination of several intervention programs would effect a dramatic reduction in the prevalence. Finally, there is a high probability that a VRE outbreak would be clinically controlled when all interventions are combined: the expected endemic prevalence is 0.06 (95% CI:0.01, 0.11).

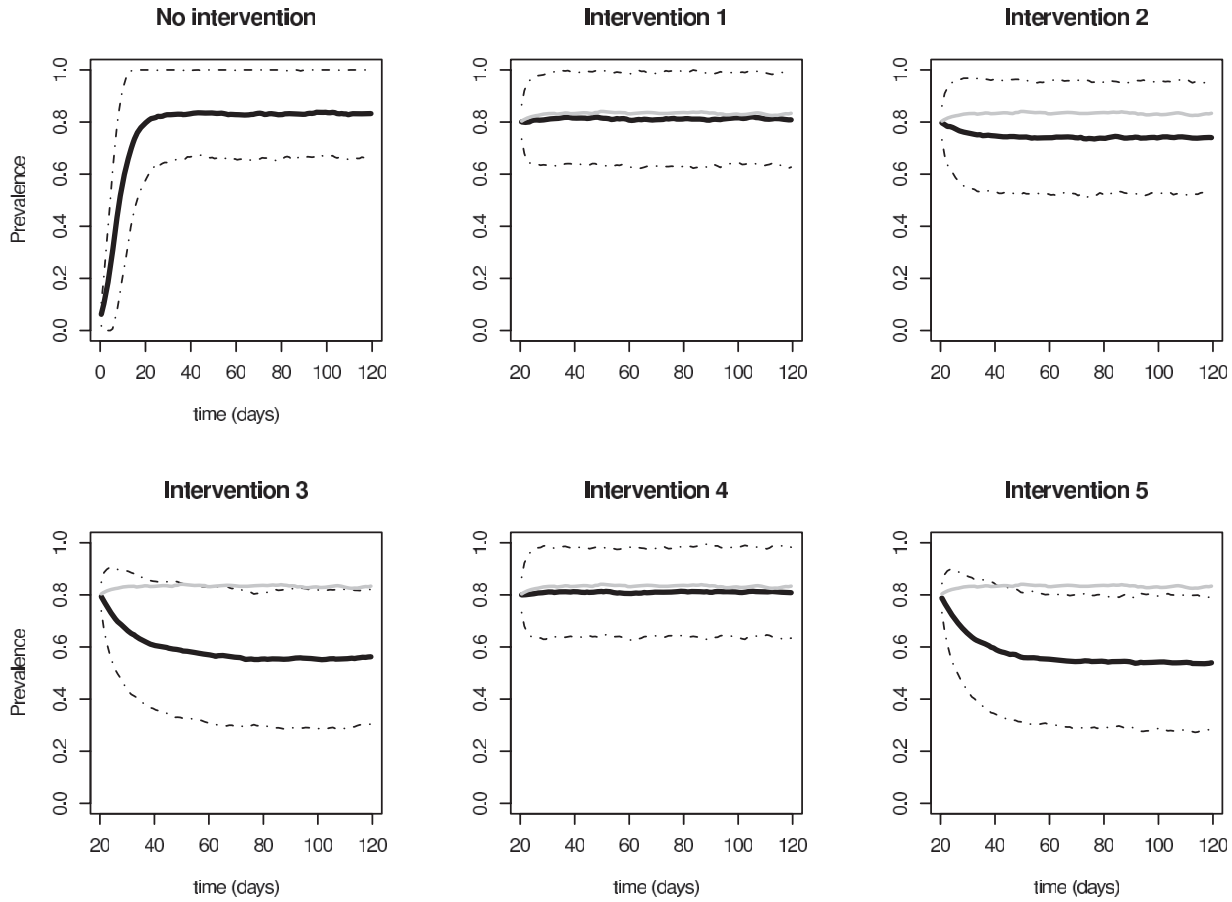

Figure 3. Results of simulation scenarios. Expected prevalence is displayed with 95% pointwise confidence band 20 days after the first colonised/infected person entered the unit. The gray line in the pictures, except in the first one, shows the mean prevalence when there is no intervention.

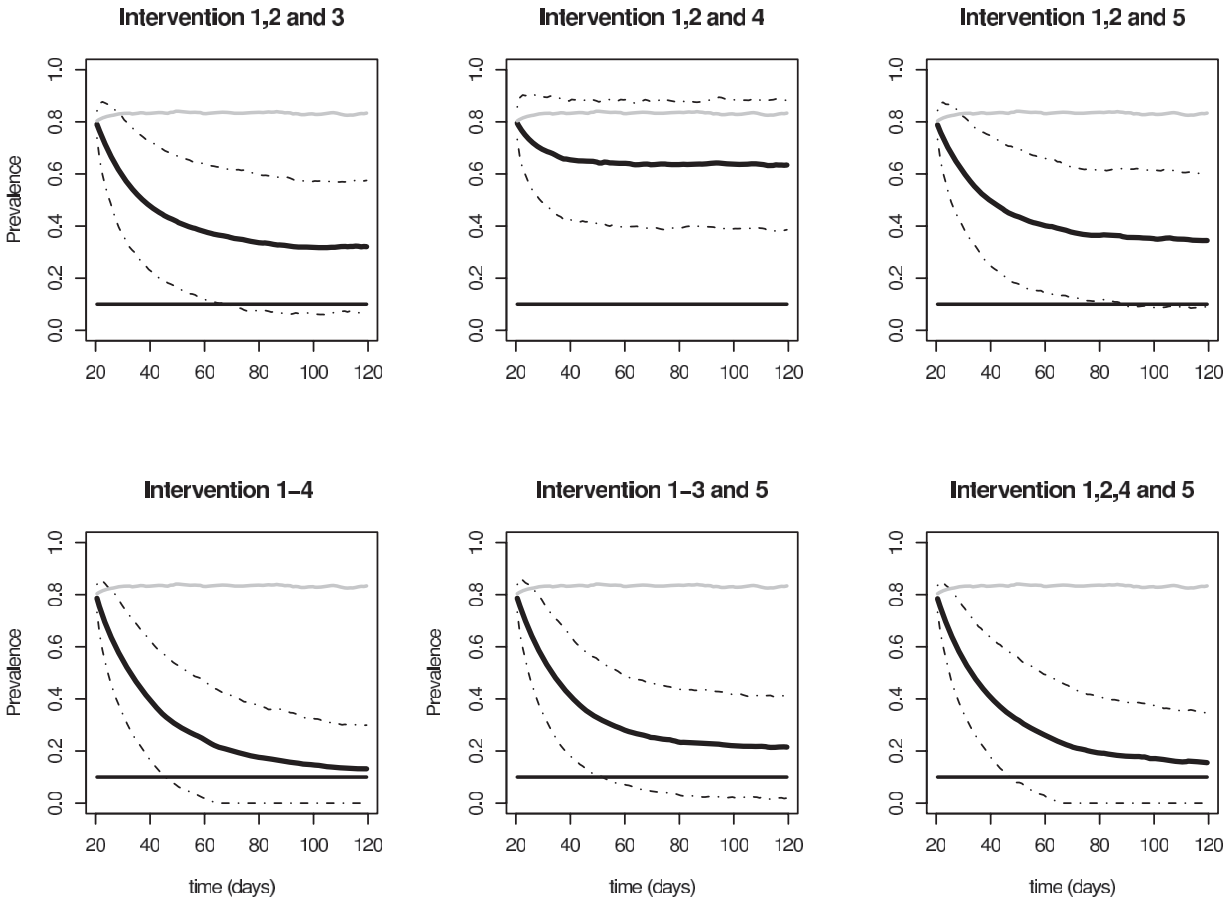

Figure 4. Results of simulation scenarios. Expected prevalence is displayed with 95% pointwise confidence band. The gray line in the pictures, other than the first one, shows the mean prevalence when there is no intervention. The straight line at 10% marks the line which is defined as "clinically controlled".

Discussion

Several groups have recently developed mathematical models to describe nosocomial outbreak situations and evaluate different intervention strategies [5, 10, 11]. Most of these models are designed for intensive care units where patients are immobilized and transmission occurs via hospital personnel. This mode of transmission may be predominant for certain pathogens (e.g. gram-negative *bacilli, S. aureus*). However, bacteria that are carried in the gastrointestinal tract (such as *enterococci* or *Clostridium diffcile*) are probably spread more easily directly from patient to patient through inanimate surfaces [13]. This may also be the reason why these pathogens are common among hospitalised patients who are not in intensive care units. Outbreaks of VRE have been described in various hospital settings such as dialysis units, [20] oncology wards, [21] and long-term care facilities [22]. Recent infection control research [13, 23] has shown that environmental contamination can not be neglected when studying the effect of interventions, especially the disinfection of surfaces where pathogens like VRE can persist and contaminate the hands of medical personnel. Vigorous enforcement of routine cleaning measures has been shown to significantly reduce the transmission of VRE in an intensive care unit [23]. In order to effectively account for the influence of environmental surfaces as vehicles for the transmission of VRE in settings other than intensive care units, we tried to modify existing approaches.

Some of the strategies suggested to reduce or eliminate VRE from hospitals are quite expensive, and a careful evaluation of the cost-effectiveness of these methods is therefore necessary. D'Agata and colleagues described a model for the interactions involved in the transmission of VRE in the hospital setting and were able to quantify the effect of several interventions on the prevalence of VRE [4].

In the present study, several clinically relevant intervention strategies for controlling nosocomial VRE infections (i.e. emphasis of hand hygiene, more rigorous surface disinfection, screening and cohorting of colonised patients, and reduction of antibiotic usage) were analysed and compared. Using our model predictions of the effect of these interventions on the endemic prevalence could be made. Our main finding is that the improvement of hand hygiene as a commonly used intervention has no effect on the endemic prevalence when used without any other interventions.

An explanation could be that most colonisations were transmitted from the contaminated environment, since usually a pathogen persists on surfaces much longer than on the hands of health-care workers. A further major finding is that only a combination of interventions might control an outbreak.

McBryde and McElwain [14] extended the patient-staff-patient model used by D'Agata et al. [4] to include the role of environment, but there are two limitations to their approach: Firstly, only medical staff but not patients can acquire the pathogen directly from contaminated surfaces. In a clinical setting such as an oncology ward or a dialysis unit, patients are often very mobile and share equipment (e.g. home trainer, coffee makers, games etc.). We therefore believe that this important route should be taken into account. Secondly, the deterministic model used by McBryde and McElwain does not show variation which is necessary for small populations (e.g. limited number of beds in the unit). Therefore, we used Monte-Carlo simulations in order to take random fluctuations into account and report 95% pointwise confidence bands covering the expected prevalences.

Our approach suffers from limitations which need to be discussed: modeling in general depends largely on the plausibility of the underlying assumptions. Realistic models are often very complex and include a multitude of parameters (overfitting), whereas simple models depend on a number of assumptions and are less realistic. In this paper, we used several parameters based on previous studies and for others assumed values that seemed plausible.

We would like to emphasize that predictions of the endemic prevalence look different if other default values are assumed. However, each ward is different with regard to hygiene, contact behaviour, shifts of health-care workers and infection control policy. We tried to consider a hypothetical and *standard* ward with values given from the literature. Although these values were aligned by clinical experts, we advise caution when directly applying our results to wards with different parameter values. Nevertheless the trend concerning the impact of interventions should be similar.

A much simpler patient-to-patient transmission model would need to be used [15, 24–28] for the development of a model that uses a strictly data-based empiric estimation of parameters (e.g. the direct transmission rate). The application of appropriate statistical models is necessary to estimate data-based rates which depend on time, since the transmission rate probably changes with time after the interventions. Then, it will be possible to obtain empirical evidence about the effectiveness of these programs, i.e. if the transmission rate decreases after specific interventions are introduces.

In conclusion, for the evaluation of infection control procedures in hospitals, it is essential to describe at least the dynamic interaction of the factors that are involved in the interventions to reduce transmission. To achieve this aim, simulations remain a substantial tool for the prediction of interventions and yield fundamental insights into the epidemic nature.

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References

[1] Beyersmann, J., Gastmeier, P., Grundmann, H., Barwolff, S., Geffers, C., Behnke, M. et al. 2006 May. Use of multistate models to assess prolongation of intensive care unit stay due to nosocomial infection. *Infect. Control Hosp. Epidemiol.*, 27(5):493–9.

[2] Prince, A., Chen, X. and Lun, K.C. 2005. Containing acute disease outbreak. *Methods Inf. Med.*, 44(5):603–8.

[3] Perencevich, E.N., Fisman, D.N., Lipsitch, M., Harris, A.D., Morris, JGJ. and Smith, D.L. 2004 Apr. Projected benefits of active surveillance for vancomycin-resistant enterococci in intensive care units. *Clin. Infect. Dis.*, 38(8):1108–15.

[4] D'Agata, EMC., Webb, G. and Horn, M. 2005 Dec. A mathematical model quantifying the impact of antibiotic exposure and other interventions on the endemic prevalence of vancomycin-resistant enterococci. *J. Infect. Dis.*, 192(11):2004–11.

[5] D'Agata, EMC., Horn, M.A. and Webb, G.F. 2002 Mar. The impact of persistent gastrointestinal colonisation on the transmission dynamics of vancomycin-resistant enterococci. *J. Infect. Dis.*, 185(6):766–73.

[6] Bootsma, MCJ., Diekmann, O. and Bonten, MJM. 2006 Apr. Controlling methicillin-resistant Staphylococcus aureus: quantifying the effects of interventions and rapid diagnostic testing. *Proc. Natl. Acad. Sci.* U.S.A., 103(14):5620–5.

[7] Cooper, B.S., Medley, G.F. and Scott, G.M. 1999 Oct. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J. Hosp. Infect.*, 43(2):131–47.

[8] Grundmann, H. and Hellriegel, B. 2006 Jan. Mathematical modelling: a tool for hospital infection control. *Lancet. Infect. Dis.*, 6(1):39–45.

[9] Austin, D.J. and Bonten, M.J. 1998 Sep. Vancomycin-resistant enterococci in intensive care hospital settings. *Mem. Inst. Oswaldo Cruz.*, 93(5):587–8.

[10] Austin, D.J., Bonten, M.J., Weinstein, R.A., Slaughter, S. and Anderson, R.M. 1999 Jun. Vancomycin-resistant enterococci in intensive-care hospital settings: transmission dynamics, persistence, and the impact of infection control programs. *Proc. Natl. Acad. Sci.* U.S.A., 96(12):6908–13.

[11] Grundmann, H., Hori, S., Winter, B., Tami, A. and Austin, D.J. 2002 Feb. Risk factors for the transmission of methicillin-resistant Staphylococcus aureus in an adult intensive care unit: fitting a model to the data. *J. Infect. Dis.*, 185(4):481–8.

[12] Bonten, M.J., Hayden, M.K., Nathan, C., van Voorhis, J., Matushek, M., Slaughter, S. et al. 1996 Dec. Epidemiology of colonisation of patients and environment with vancomycin-resistant entero-cocci. *Lancet.*, 348(9042):1615–9.

[13] Kramer, A., Schwebke, I. and Kampf, G. 2006. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infect. Dis.*, 6:130.

[14] McBryde, E. and McElwain, D. 2006. A mathematical model investigating the impact of an environmental reservoir on the prevalence and control of vancomycin-resistent enterococci. *J. Infect. Dis.*, 193:1473–4. Comment.

[15] Becker, N.G. Analysis of infectious disease data. 1st ed. New York: Chapman and Hall Ltd, 1989.

[16] Anderson, R.M. and May, R.M. Infectious diseases of humans. 1st ed. New York: Oxford University press, 1991.

[17] Eckmanns, T., Bessert, J., Behnke, M., Gastmeier, P. and Ruden, H. 2006 Sep. Compliance with antiseptic hand rub use in intensive care units: the hawthorne effect. *Infect. Control. Hosp. Epidemiol.*, 27(9):931–4.

[18] Rutala, W. and Weber, D. 2001. Surface disinfection: should we do it? *J. Hosp. Infect.*, 48:S64–S8.

[19] Murray, B. 2000 Mar. Vancomycin-resistant enterococcal infections. *N. Engl. J. Med.*, 342(10):710–21.

[20] Humphreys, H., Dolan, V., Sexton, T., Conlon, P., Rajan, L., Creamer, E. et al. 2004 Sep. Implications of colonisation of vancomycin-resistant enterococci (VRE) in renal dialysis patients. Learning to live with it? *J. Hosp. Infect.*, 58(1):28–33.

[21] Hachem, R., Graviss, L., Hanna, H., Arbuckle, R., Dvorak, T., Hackett, B. et al. 2004 May. Impact of surveillance for vancomycin-resistant enterococci on controlling a bloodstream outbreak among patients with hematologic malignancy. *Infect. Control. Hosp. Epidemiol.*, 25(5):391–4.

[22] Padiglione, A.A., Grabsch, E., Wolfe, R., Gibson, K. and Grayson, M.L. 2001 Sep. The prevalence of fecal colonisation with VRE among residents of long-term-care facilities in Melbourne, Australia. *Infect. Control. Hosp. Epidemiol.*, 22(9):576–8.

[23] Hayden, M.K., Bonten, MJM., Blom, D.W., Lyle, E.A., van de Vijver, DAMC and Weinstein, R.A. 2006 Jun. Reduction in acquisition of vancomycin-resistant enterococcus after enforcement of routine environmental cleaning measures. *Clin. Infect. Dis.*, 42(11):1552–60.

[24] Pelupessy, I., Bonten, MJM. and Diekmann, O. 2002 Apr. How to assess the relative importance of different colonisation routes of pathogens within hospital settings. *Proc. Natl. Acad. Sci.* U.S.A., 99(8):5601–5.

[25] Cooper, B. and Lipsitch, M. 2004 Apr. The analysis of hospital infection data using hidden Markov models. *Biostatistics*, 5(2):223–37.

[26] Andersson, H. and Britton, T. Stochastic epidemic models and their statistical analysis. 1st ed. New York: Springer, 2000.

[27] Becker, N.G. and Britton, T. 1999. Statistical Studies of Infectious Disease Incidence. *Journal of the Royal Statistical Society, Series B*: *Statistical Methodology*, 61:287–307.

[28] Forrester, M. and Pettitt, A.N. 2005 Jul. Use of stochastic epidemic modeling to quantify transmission rates of colonisation with methicillin-resistant Staphylococcus aureus in an intensive care unit. *Infect. Control. Hosp. Epidemiol.*, 26(7):598–606.

[29] Renshaw, E. Modelling biological populations in space and time. 1st ed. Cambridge: Cambridge University press, 1991.

Appendix

Stochastic variant of the deterministic model

The number of colonised patients, contaminated staff, and surfaces in stochastic model described in Table 1 are now represented as discrete random variables $C_p(t)$, $C_s(t)$, $C_e(t)$. Following transition probabilities can be deduced:

$$\begin{aligned}&P([C_p(t+\Delta t), C_s(t+\Delta t), C_e(t+\Delta t)]\\&\quad=[i+1, j, k]\,|\,[C_p(t), C_s(t), C_e(t)]=[i, j, k])\\&\quad=((\gamma N_p+(\gamma'-\gamma)i)\phi\\&\qquad+\left(\beta_{sp}\frac{j}{N_s}+\beta_{ep}\frac{k}{N_e}\right)(N_p-i))\Delta t+o(\Delta t)\end{aligned}$$

$$\begin{aligned}&P([C_p(t+\Delta t), C_s(t+\Delta t), C_e(t+\Delta t)]\\&\quad=[i, j+1, k]\,|\,[C_p(t), C_s(t), C_e(t)]=[i, j, k])\\&\quad=\left(\beta_{ps}\frac{i}{N_p}+\beta_{es}\frac{k}{N_e}\right)(N_s-j)\Delta t+o(\Delta t)\end{aligned}$$

$$\begin{aligned}&P([C_p(t+\Delta t), C_s(t+\Delta t), C_e(t+\Delta t)]\\&\quad=[i, j, k+1]\,|\,[C_p(t), C_s(t), C_e(t)]=[i, j, k])\\&\quad=\left(\beta_{se}\frac{j}{N_s}+\beta_{pe}\frac{i}{N_p}\right)(N_e-k)\Delta t+o(\Delta t)\end{aligned}$$

$$P(C_p(t+\Delta t)=i-1\,|\,C_p(t)=i)=(\gamma' i)\Delta t+o(\Delta t)$$

$$P(C_s(t+\Delta t)=j-1\,|\,[C_s(t)=j)=(\mu j)\Delta t+o(\Delta t)$$

$$P(C_e(t+\Delta t)=k-1\,|\,[C_e(t)=k)=(\kappa k)\Delta t+o(\Delta t)$$

all other transitions have probability $o(\Delta t)$.

Simulation study

For the Monte-Carlo simulations, the parameters from Table 2 and initial values have been used. The time to an event is assumed to be exponentially distributed. The occurrence of events is defined to be independent of the other events. The following procedure generates data samples which have these properties: all seven rates from Table 1 are added ($=\Sigma(t)$). The time to the next event is sampled as exponentially distributed time with parameter $\Sigma(t)$. The conditional probability that single event i ($i \in \{1, ..., 7\}$) happens is proportional to the corresponding rate of change, e.g. at T a colonised admission happens with probability equals (rate of event 1)/Σ (T–). After calculating the new $\Sigma(T)$ (with new $C_p(T)$), the iteration starts again up to a fixed time point (i.e. 120 days); see Renshaw[29] for details. For each scenario, 1000 simulations were performed and, after smoothing the 95% pointwise confidence bands, calculated.