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Modeling of the transmission dynamics of carbapenem resistant *Klebsiella pneumoniae* in hospitals and design of control strategies

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Abstract

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) has emerged as a major threat to global public health. Epidemiological and infection controls associated with CRKP are very challenging owing to several potential elements involved in a complicated cycle of transmission. Here, we proposed a comprehensive mathematical model to investigate the transmission dynamics of CRKP, determine factors affecting the prevalence, and evaluate the impact of interventions on the transmission. The model includes the essential compartments, which are uncolonized, asymptomatic colonized, symptomatic colonized, and relapsed patients. Moreover, the symptomatic colonized and relapsed patients are further classified into subpopulations according to their number of treatment failures or relapses. We found that the admission of colonized patients and the use of antibiotics have a significant influence on the endemic transmission. The proposed treatment efficacy, which is defined as a combination of the treatment duration and the probability of successful treatment, could also describe the effects of antibiotic treatment on the transmission. A high efficacy of the antibiotic treatment could significantly reduce the likelihood of readmission of a patient in the health care unit. In addition, our findings demonstrate that the CRKP transmission with different epidemiological characteristics needs to be controlled with distinct interventions.

Introduction

Klebsiella pneumoniae (KP), a gram-negative bacterium, is a member of the *Klebsiella* genus of *Enterobacteriaceae*. It is one of the most relevant opportunistic pathogen causing a variety of nosocomial infections such as bacteremia, pneumonia, wound infection, intra-abdominal and urinary tract infection [1]. In health care settings, the transmission of KP can occur through direct person-to-person contacts such as contaminated hands of staff, contamination of the environment, or the use of contaminated medical equipment. Beta-lactams are first-line treatment of KP infections. However, in recent years, KP have developed resistances to these antibiotics, including to the last-resort carbapenems. Overuse and/or misuse of such antibiotics has contributed to the emergence of carbapenems-resistant *Klebsiella pneumoniae* (CRKP) [2]. CRKP infections are associated with high morbidity and mortality [2-4]. Indeed, the mortality of patients infected with CRKP, ranging from 30 % to 44% and strikingly reaching 70% in the case of bacteremia, is three times higher than the one of the patients infected with susceptible KP strains [1, 5-8].

Carbapenems-resistant *Klebsiella pneumoniae* was originally reported in the United States during the late 1990s [9, 10]. Since then, it has rapidly disseminated across countries and continents such as Canada, UK, Spain, France, India, etc. [4]. The incidence of CRKP has been markedly increasing at an alarming rate for recent decades. China Antimicrobial Resistance Surveillance Trial Program showed that the prevalence of CRKP escalated from 0.9% in 2007 to 19.9% in 2018 [11]. In 2019, the European Centre for Disease Prevention and Control reported that trends in a population-weighted mean percentage for resistance to carbapenems had significantly increased in European Union and European Economic Area countries over the last five years, with the three highest resistance percentages reported from Greece (58.3%), Romania (32.3%) and Italy (28.5%) [12].

Controlling the spread of CRKP in health care units is very challenging because the acquisition and transmission of CRKP is a convoluted process governed by several components. The admission of CRKP carriers is one of the most significant factors directly causing an increase in the prevalence of CRKP in hospitals. The carriage rate of CRKP on admission can possibly reach 37.9 % depending on the settings [13-16]. Furthermore, most CRKP carriers are asymptomatic and can serve as the main reservoir of CRKP in hospitals [17-19], causing the ongoing spread in health care settings [20]. A number of studies additionally showed that the

prevalence of asymptomatic carriers could vary over a considerable range, from 0.3% to 69.5% [16, 21-23]. Therefore, without active surveillance of CRKP prevalence, we cannot timely establish contact precautions among the carriers to contain the transmission of CRKP.

Treatment of infections associated with CRKP is evidently problematic with extremely high failure rates, resulting in an increase in hospital length of stay [24-27]. Moreover, in spite of receiving appropriate antibiotic therapy, patients occasionally have a relapse with the same strain of CRKP [28-33]. Indeed, it was found that among patients with no clinical signs of symptoms after the treatment, more than 40% of them had still clinical urine cultures positive for CRKP [34]. Accordingly, re-hospitalization of these relapsed patients is another integral part that seriously contributes to acceleration of the transmission of this pathogen [24, 35, 36]. Mathematical models have been extensively employed to examine the spread of nosocomial pathogens and to estimate the impact of intervention [37-44]. One of the basic and popular modeling frameworks is the compartmental model in which the population of interest is divided into separated compartments based on their infection status [43]. In the past few years, the models were extended to incorporate contact precautions [44], environment [40, 43], or antibiotic use [39] to gain insight into the spread of pathogens, such as Methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii* and Vancomycin-resistant *Enterococci* (VRE). However, very few works have focused on the transmission of CRKP [45, 46]. In those studies, patients are merely categorized into uncolonized and colonized patients. Only isolation of colonized patients, hand hygiene compliance and contact precautions were interventions concerned in their models to assess the impact of measures to control the spread. Moreover, none of those studies took into account the effect of antibiotic treatment on the epidemics. To scrutinize the sophisticated mechanism behind the transmission of CRKP, the attributable components corresponding to the dissemination of CRKP need to be incorporated into the model.

In this work, we constructed a comprehensive model to investigate the mechanisms by which these pathogens spread within health care settings and to evaluate the extent to which infection control measures contribute to CPKP confinement. Unlike previous models on KP, our analysis includes the essential components, which are uncolonized, asymptomatic colonized, symptomatic colonized, and relapsed patients. The symptomatic colonized and relapsed patients were further differentiated into different classes according to the number of times that a patient has experienced treatment failure in the hospital.

We fundamentally examined the impact of admission of colonized patients on the endemic prevalence of CRKP and assessed the effect of antibiotic treatment on the transmission. In this study, we defined the treatment efficacy which takes into account the treatment duration and the probability of successful treatment, both of which could affect the prevalence of CRKP in hospitals [39]. In addition, we calculated the probability distribution of patients experiencing a different number of times of treatment failure or relapse in the hospital. Finally, this study was the first attempt that obtained a disease control guideline under different treatment scenarios. This guideline should be beneficial for treatment decision design that could effectively prevent or reduce the spread of CRKP in hospitals.

Results

The CRKP model formulation

The transmission dynamics of carbapenem-resistant *Klebsiella Pneumonia* (CRKP) within a health care unit (HCU) involves the transmission of the pathogen between two distinct groups of the population, namely, patients and staff. Patients are usually considered as hosts, whereas staff acts as vector transmitting CRKP from patients to patients. In the proposed model (Figure 1), patients are classified into four epidemiological classes based on their CRKP infection status; namely, uncolonized (S), asymptomatic colonized (C), symptomatic colonized (I), and relapsed (R) patients. Asymptomatic colonized patients cannot be identified without active surveillance. They are, therefore, treated as ordinary patients as if they were not colonized by CRKP. In contrast, symptomatic patients are easier to be identified and will be treated under contact precautions such as the use of gloves, gowns, private rooms, or cohort rooms housing only symptomatic colonized patients with the same strain. Relapsed patients are those who had previously received successful treatment but are readmitted to the hospital due to a relapse of the infection. Here, successful treatment refers to a treatment in which a patient is cured and do no exhibit any more clinical signs of symptoms after the treatment. In addition, the staff is divided into two classes; uncontaminated (S_S) and contaminated staff (C_S) who have not been and have been contaminated with CRKP, respectively. For the sake of simplicity and because the diseased staff are assumed to be self-isolated, the staff compartments are not explicitly shown in the kinetic scheme in Figure 1.

In the kinetic transmission model of CRKP, uncolonized patients acquire CRKP following contacts with contaminated staff at a rate λ (Eq.(9)). A fraction x of those new colonized patients progresses into the symptomatic colonized class and the remaining fraction becomes asymptomatic colonized [13, 16, 17, 19, 23, 47-50]. Symptomatic colonized patients are then treated with antibiotics at a rate φ which treatment either succeeds with probability, z, in curing the patients, or fails with probability, $1 - z$. Among cured patients discharged from the hospital, a fraction e of them subsequently develops a relapse of infection and will be re-hospitalized at a relapsing rate r [51, 52]. Symptomatic colonized, I_k, and relapsed patients, R_k, are distinguished and kept track by the history index k counting the number of times a patient has already experienced failure treatments or relapses. For example, I_0 and I_1 represent the number of symptomatic colonized patients who have received none and one time of the antibiotic treatment, respectively. Natural decolonization of CRKP is not included in the model because the duration of natural decolonization is much longer than the other time scales (e.g., length of stay in the hospital) [53-55]. In the absence of treatment, symptomatic colonized patients die from the infection at a rate μ. The total admission rate of patients is Λ among which fractions u and y are symptomatic and asymptomatic colonized patients ($k = 0$), respectively. Discharge of uncolonized patients and asymptomatic colonized patients occurs at the same rate γ as they are indistinguishable.

Similarly, uncontaminated staff becomes contaminated with CRKP after having contacts with asymptomatic or symptomatic colonized patients at a rate λ_S (Eq.(8)). However, staff engaged in the treatment or care of symptomatic colonized patients need to follow the contact precautions to prevent or reduce the transmission of pathogens. The probability of transmitting the pathogen from the symptomatic colonized patients to staff is controlled by the effectiveness of contact precautions (p): $0 \leq p \leq 1$. For instance, $p = 0$ and $p = 1$ indicate that the contact precaution, e.g., using gloves, absolutely can and cannot protect transmitting pathogens between patients and staff, respectively. On the other hand, contaminated staff can be decontaminated at a rate $(1 - \delta)\alpha_{min} + \delta\alpha_{max}$, where α_{min} and α_{max} are the minimum and maximum of the decontamination rate, respectively, and δ is the precaution compliance.

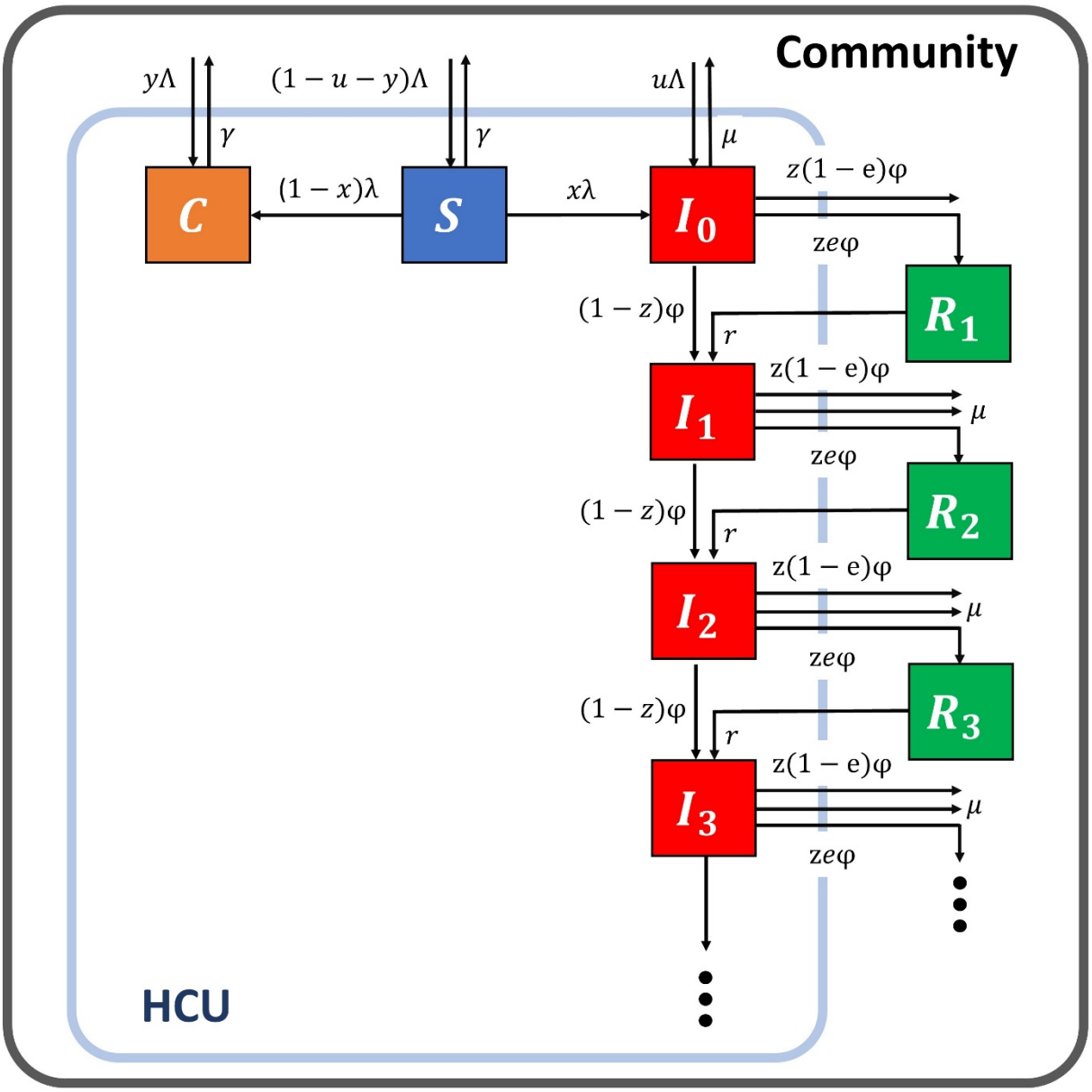

Figure 1. Schematic of the kinetic transmission model of carbapenem-resistant *klebsiella pneumoniae* (CRKP) in a health care unit (HCU).

Prevalence Drivers

Admission of colonized patients from the community or from other healthcare establishments has a direct impact on the incidence and prevalence of CRKP carriage and infections within the considered hospital [33, 56]. In this section, we simulated the model regardless of antibiotic use to investigate the impacts of the exogenous patients. Their effects on

the epidemics were represented by the total prevalence (P) and the fraction of infectious (q) (Eq.(26)). In this study, the incoming prevalence (P_{in}) was defined as the combination of a fraction of symptomatic colonized (u) and of asymptomatic colonized patients (y) admitted into the hospital: $P_{in} = u + y$. For example, $P_{in} = 0$ and $P_{in} = 1$ represent no and only colonized patients being hospitalized, respectively.

Because the transmission is driven by both endogenous and exogeneous patients, the total prevalence is expressed as a function of the hospital prevalence with no incoming prevalence (P_0) and the standardized prevalence (θ_1) (Eq.(27)). The P_0 was used to represent the intrinsic spread in the hospital. Obviously, P_0 is zero for $R_0 < 1$ and it continuously increases for $R_0 > 1$ (Figure 2a) with the expression of P_0 as a function of R_0 is given in Table 2. The calculation for the basic reproduction number (R_0) is described in the subsection of Basic Reproduction Number in the Method section. To demonstrate to what extent the incoming prevalence affects the total prevalence, θ_1 was calculated as given in Eq.(28), which turns out to be independent of R_0. Figure 2b shows that θ_1 increases from zero at $P_{in} = 0$ to one at $P_{in} = 1$ and it is slightly higher for a larger proportion of the symptomatic colonized patients admitted to the hospital (or higher u/y) (see Table 2 for the expression θ_1 of as function of P_{in}). Indeed, in the absence of treatment, the symptomatic colonized patients stay longer in the hospital than asymptomatic colonized patients. Therefore, an increase in the admission of symptomatic colonized patients affect more the total prevalence than that of asymptomatic colonized patients. In conclusion, both the basic reproduction number (R_0) and the incoming prevalence (P_{in}) are the main drivers of the total prevalence of the infection in the hospital.

Like for the prevalence, the fraction of colonized patients q is expressed in terms of the fraction of infectious when there is no incoming prevalence (q_0) and the standardized fraction of infectious (θ_2) in Eq.(27). As expected, q_0 is constant and independent of R_0 (Figure 2c, see Table 2 for the analytical expression of q_0). The behavior of θ_2 as a function of with P_{in} and u/y is quite similar to that of θ_1 (Figure 2d and Table 2). It is consistent with the fact that the ratio of symptomatic colonized patients to colonized patients in the hospital increases with incoming symptomatic colonized patients. In conclusion, the incoming prevalence (P_{in}) is the driver of the fraction of colonized patients for a given setting infection parameters.

The relationships among those parameters were investigated by fitting the simulated curves with mathematical expressions. For each graph the formulas and r-squares obtained from the best fit to simulations data are all summarized in Table 2.

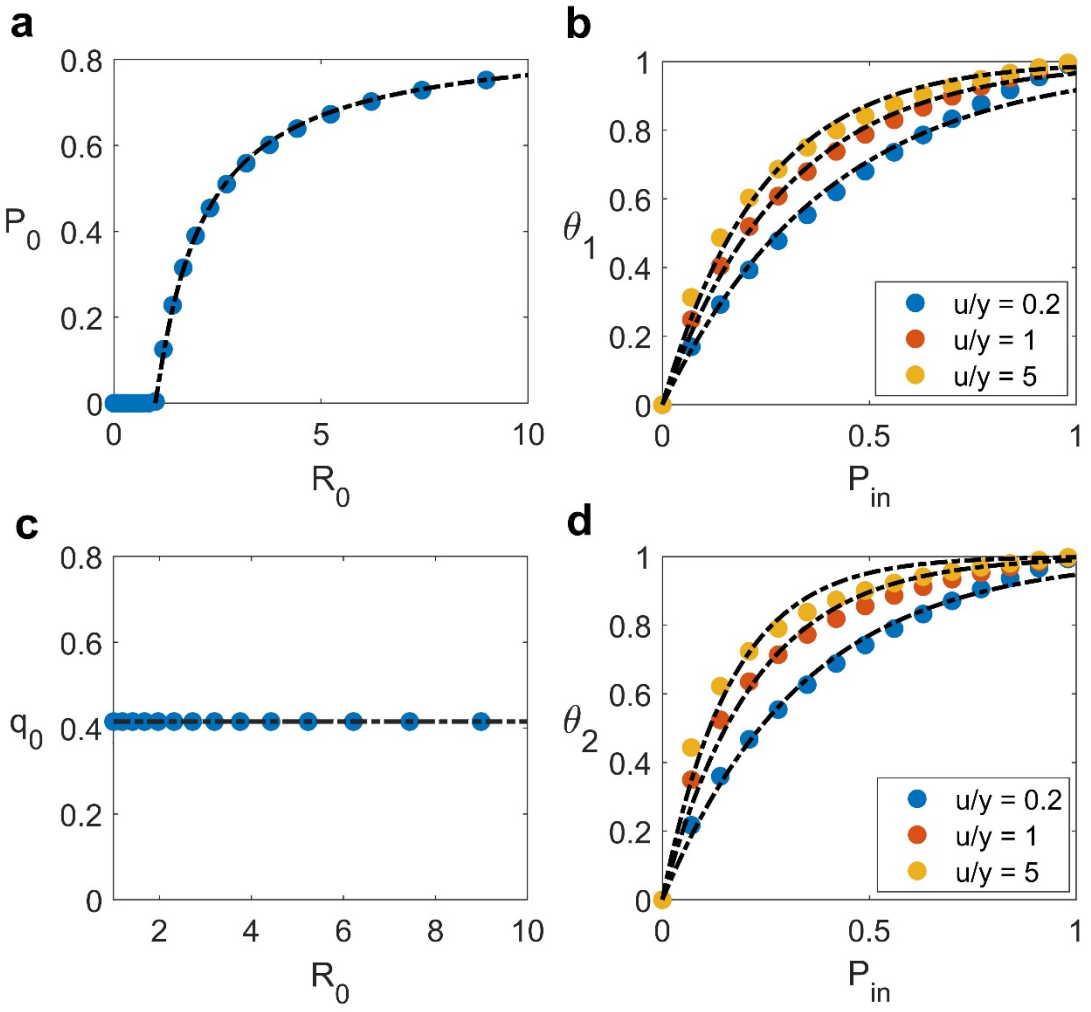

Figure 2. Prevalence and fraction of colonized patients. **(a)** the hospital prevalence and **(c)** the fraction of colonized patients as a function of R_0 with no incoming prevalence, $P_{in} = 0$**. (b)** The standardized prevalence and **(d)** the standardized fraction of colonized patients as a function of P_{in}. The disease is assumed to spread with $R_0 = 1.5$. Different colors represent different ratios of fractions of symptomatic colonized to that of asymptomatic colonized patients admitted into the hospital. Black-dash lines are best fit to simulation data.

Treatment Efficacy

To estimate the impact of a treatment on the progression and prevalence of infection, it is important to first understand how the effectiveness of this treatment is assessed. The length of hospital stay is one of the risk factors facilitating the spread of CRKP in hospital. Patients with prolonged hospital duration are more likely to transmit the pathogens to uncolonized patients and vice versa. In addition, the probability of successful treatment is another undeniable factor controlling the number of symptomatic colonized patients in the hospital. The lower is the successful treatment probability the more unfavorable outcomes are, e.g., a relapse of infection and treatment failure. The patients with those adverse outcomes can subsequently become reservoirs of CRKP in the hospital setting. In this work, the treatment is applied only on symptomatic colonized patients. And to investigate the effects of the treatment on the transmission, we introduced the treatment efficacy (TE) indicator, given in Eq.(10), defined as the ratio of the rate of successful treatment without relapse to the total removal rate of patients including death mortality. The indicator $TE = TE(z, f|, e_m, \nu)$ is a two-dimensional function of z (indicating the effectiveness in curing patients) and f (measuring the probability of leaving the hospital alive, defined in Eq.(11)) with two parameters (e_m and ν, in Eq.(12)) characterizing the antibiotic related patient response. By construction, $0 \leq TE \leq f$, thus $TE = 0$ when either $z = 0$ or $f = 0$ and $TE \to 1$ when $f \to 1$ (i.e., almost all treated patients leave the hospital alive) whereas $TE = f$ when $z = 1$ indicating that the treatment efficacy is not maximal even when the treatment has a curing efficiency of 100% but over a treatment duration of order of the patient lifetime in the hospital. The contours plots of TE in (z, f) space are displayed in Figure 3. Each section represents the different treatment efficacies (TE) with different colors. High TE, especially $TE > 0.9$ (small red area) requires high value of f, i.e., a high fraction of treated patients leaving the hospital alive (see Figure 3). Different values of ν in Fig. 3 is to illustrate the effect of using different antibiotic kinds.

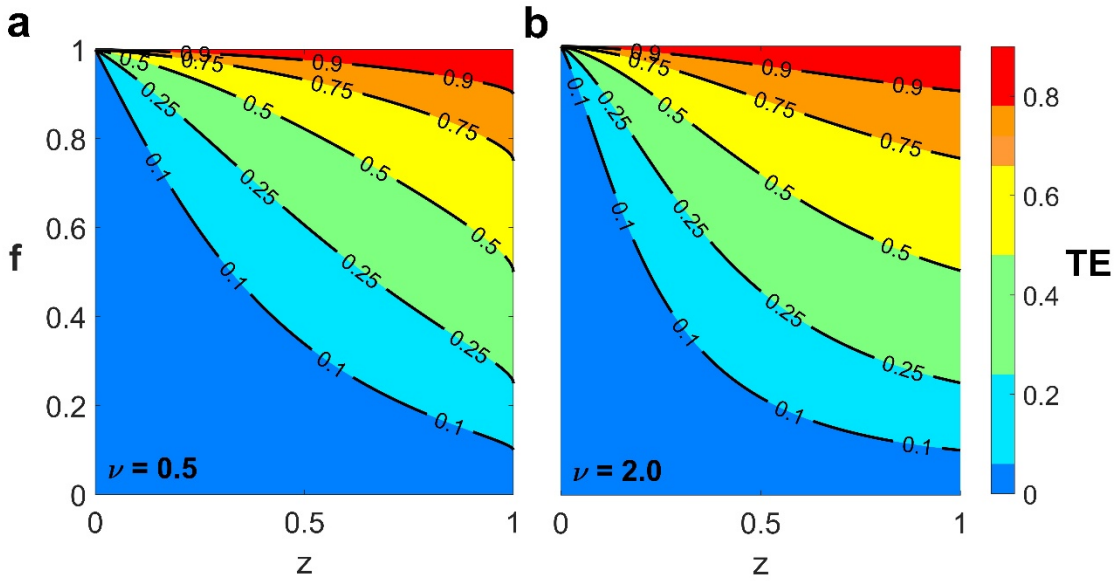

Figure 3. Contours of treatment efficacy. The treatment efficacy (TE) is plotted in (z, f) space with ν = 0.5 **(a)** and 2.0 **(b)** with $e_m = 0.8$ (see Table 1). Each section represents the different TE with different colors.

Transmission-Controllable Areas

Precaution compliance and antibiotic treatment are basic interventions used to prevent disease transmission in hospitals. However, controlling the spread of CRKP is still crucial owing to a myriad of important factors associated with CRKP infection and the limited understandings of the mechanisms behind the transmission. To construct effective control measures, we need to profoundly understand how fast the disease initially spreads and what components contribute to the transmission before implementing the interventions. In this study, two parameters were introduced to describe the epidemiological characteristics of the disease transmission. First is the basic reproduction number in the absence of interventions (R_{00}) was used to delineate how the disease originally spreads. As R_{00} consists of the summation of partial basic reproduction numbers from an asymptomatic (R_{0C}) and symptomatic (R_{0I}) colonized patient (see, Eq.(15)), we introduced a second parameter ε, defined by the ratio of R_{0I} to R_{00} (see, Eq.(16)), that measures the relative contribution of symptomatic colonized patients in the transmission of the infection with respect to all colonized patients. Furthermore, ε can be adjusted by tuning the precaution contact effectiveness (p) so that lowing p results in reducing the impact of symptomatic colonized

patients in the transmission of infection in the hospital. This aspect must be taken into account together with the treatments when designing the disease control strategies.

To determine sets of parameters for combination of interventions, we constructed transmission-controllable areas of parameters based on R_0. The reasoning is that as the spread of infection is controlled for $R_0 < 1$, the transmission-controllable area defines an ensemble of parameters such that $R_0 < 1$. The details of calculations are explained at the end of the subsection of Basic Reproduction Number in the Method section. Four parameters, which are R_{00}, ε, the precaution compliance (δ), and the treatment efficacy (TE), are used to determine the transmission-controllable area (Figure 4). The $R_0 = 1$ lines (see Eq.(17)) is calculated to separate sets of such parameters corresponding to $R_0 < 1$ (transmission-controllable area) from $R_0 > 1$ (uncontrollable area). In Figure 4, the transmission-controllable areas are illustrated by the hatched areas above the $R_0 = 1$ lines and different treatment efficacies (TE) are represented by different colors.

As shown in Figure 4, in general, when the infection spreads with $R_{00} > 1$, the minimum of precaution compliance (δ) needs to be increased to keep the spread controllable. In addition, when the antibiotic treatment is implemented, the disease spread is more effortlessly to be controlled because enhancing the treatment efficacy enlarges the sizes of transmission-controllable areas. Interestingly, for the transmission with $\varepsilon = 0.1$ (Figure 4a), the sizes of transmission-controllable areas are almost the same from $TE = 0$ to 1, indicating that the antibiotic treatment has no significant impact in reducing the transmission with low ε. In contrast, the transmission-controllable areas are broader for the transmission with higher ε, especially, $\varepsilon = 0.9$ (Figure 4c). This indicates that when the transmission is dominantly driven by symptomatic colonized patients or high ε, the antibiotic treatment with a bit higher TE can considerably control the spread of disease. Therefore, the epidemiological characteristics of the transmission are unavoidable factors for designing intervention strategies. Within this framework, the transmission-controllable area provides penitential control measures to combat the spread of and manage the patients infected with CRKP in the hospital.

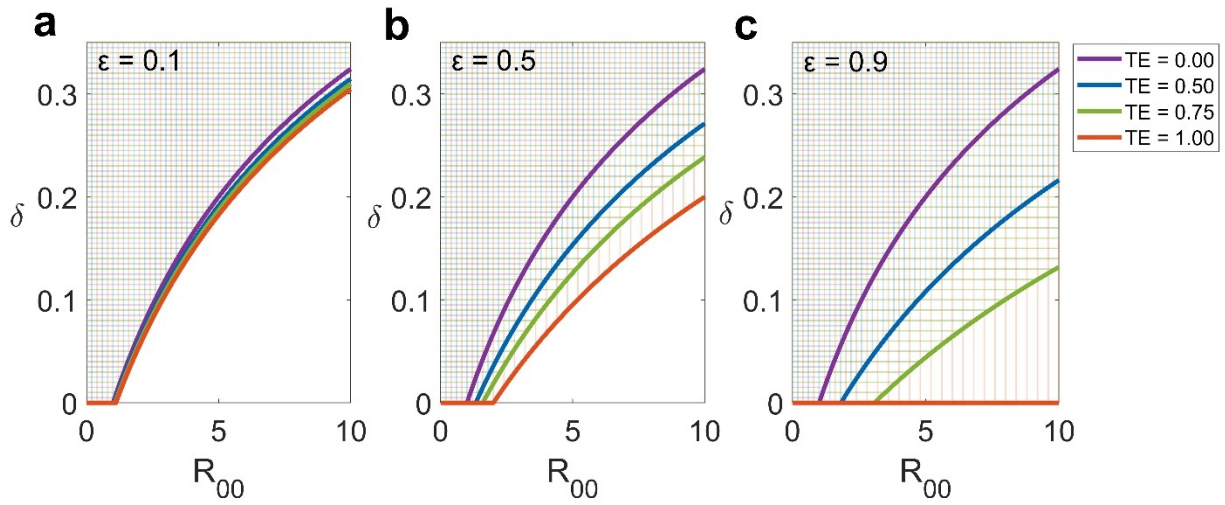

Figure 4. Transmission-controllable area. The transmission-controllable area (hatched areas above the lines) illustrates sets of parameters corresponding to the control of transmission with $R_0 < 1$. Solid line represents the $R_0 = 1$ line separating the controlled (above) from the uncontrolled (below) areas. Different treatment efficacies (TE) are shown with different colors. Transmissions with $\varepsilon = 0.1$, 0.5, and 0.9 are depicted in **a**, **b**, and **c**, respectively.

Probability Distribution of Relapses

The treatment failure and re-hospitalization due to a relapse of infection are significant factors contributing to the continuing disease transmission in the hospital. In this section, the probability distribution, G_k, that a symptomatic colonized patients has experienced k treatments failures or relapses is simulated. As shown in Figure 5 for different treatment efficacies, G_k versus k follows a geometric distribution (see, Eq.(22)) with the probability of relapse, $g = (f - TE)/(1 - TE)$, decreasing with treatment efficacy.

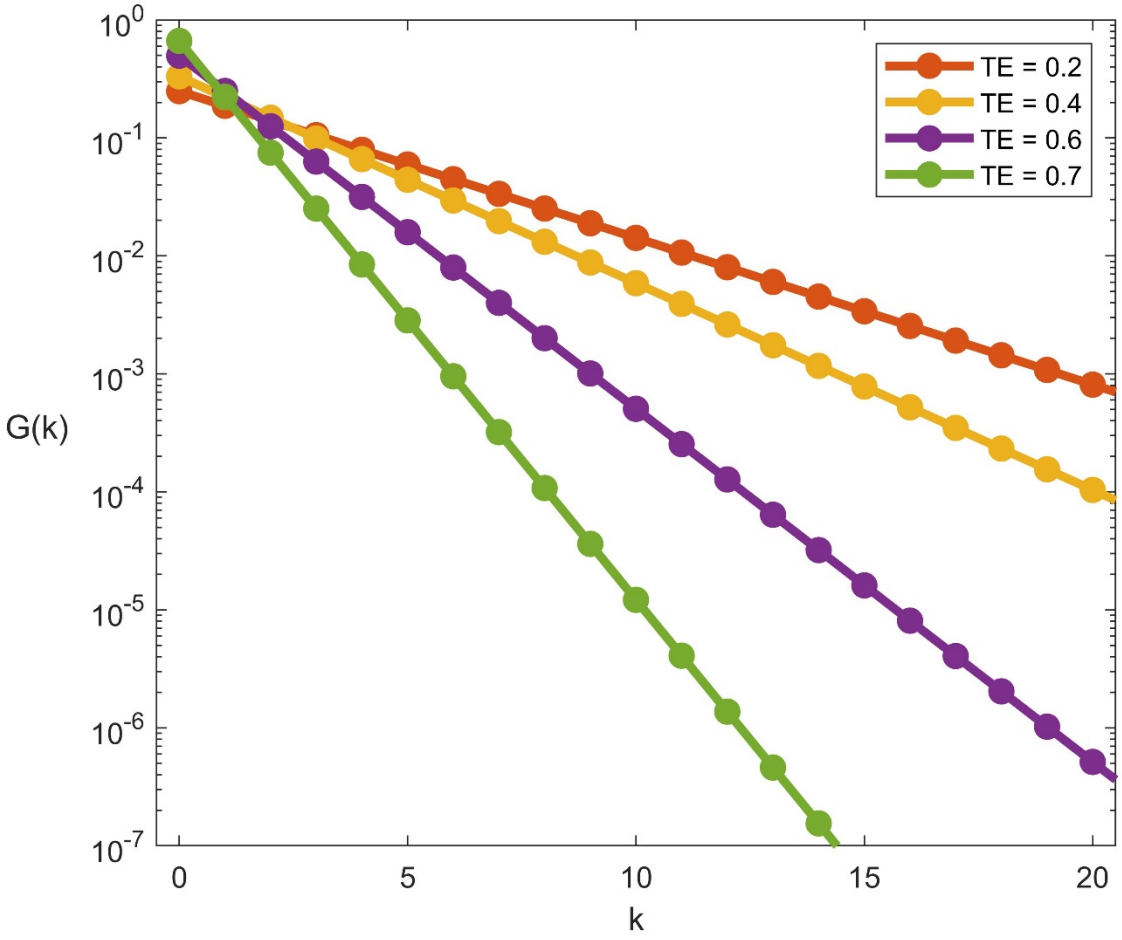

Figure 5. Probability distribution of relapses. k represents the number of times that a patient has experienced treatment failures or relapses. Different treatment efficacies (TE) are shown by different colors.

Impact of Successive Interventions

Finally, we simulated a scenario of successive interventions on the time course of the infection progression (Figure 6). For the sake of illustration, the simulation starts with a single symptomatic colonized patient in the hospital, while all other patients are not colonized and susceptible to the infection and no colonized patients from outside of the hospital are admitted. In

the absence treatment, the infection is assumed to spread with $R_0 = 1.93$ (Figure 6, panel a) and the total prevalence and numbers of asymptomatic and symptomatic colonized patients continuously increase in the course of time up to the plateau steady state. The precaution compliance (δ) is then increased from 0.1 to 0.13 to mitigate the transmission (panel b) by lowering R_0 to 1.56. Subsequently, the antibiotic treatment with the treatment efficacy (TE) of 0.5 is set on. This drastically diminishes the total prevalence and the numbers of asymptomatic and symptomatic colonized patients in the hospital (panel c). As TE is not high enough, the number of relapsed patients in the hospital increases. As a final intervention, TE is upgraded to 0.75 at which point all parameters are under the transmission-controllable area corresponding to $R_0 < 1$. As a result, the infection in the hospital is completely eradicated (panel d). Values of all parameters used in the simulation are summarized in Table 1.

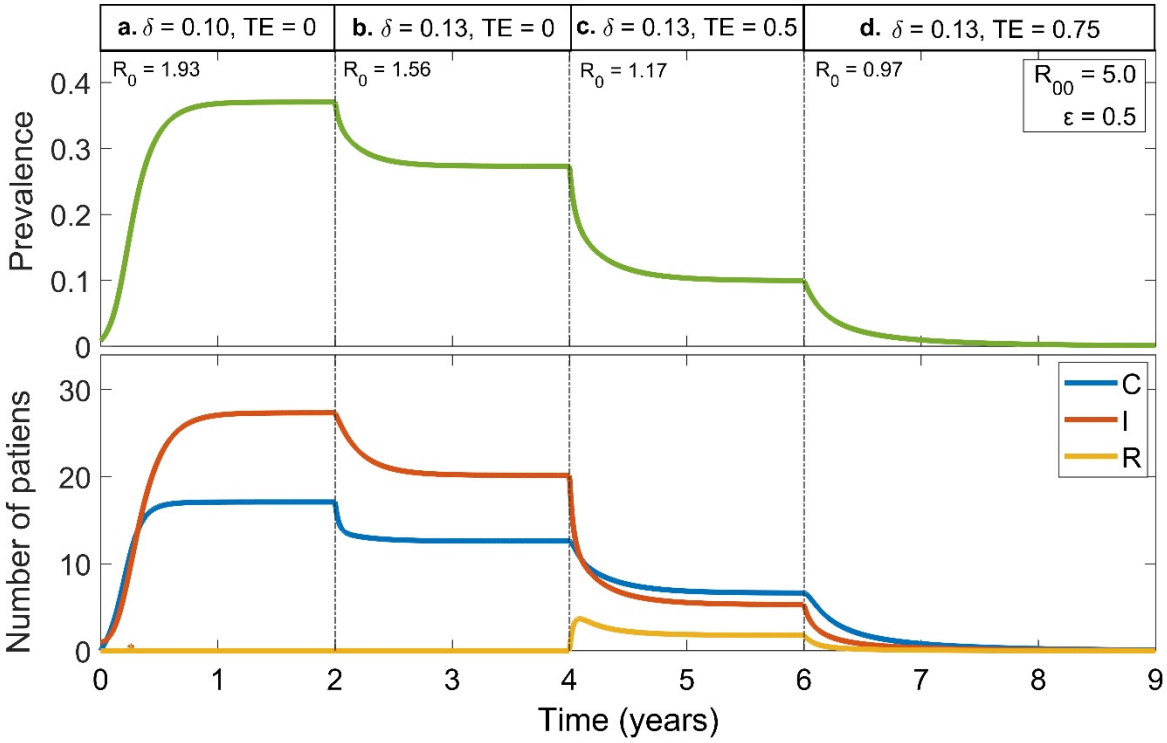

Figure 6. Impact of successive interventions on the time course of the infection progression. The epidemic with no intervention (panel **a**) is controlled by increasing precaution compliance (panel **b**), then using the treatment on symptomatic colonized patients (panel **c**), and finally

enhancing the treatment efficacy (panel **d**). The impact of successive interventions on the epidemics time course is represented by the prevalence (above) and the number of patients (below).

Discussions and conclusions

Carbapenems-resistant *Klebsiella pneumoniae* (CRKP) is one of the main culprits of hospital-acquired infections. Controlling the CRKP spread is highly demanding owing to a majority of risk factors associated with infections and a complicated mechanism hidden in the transmission. In the present study, we proposed the comprehensive transmission dynamics model for CRKP. Unlike previous studies [45, 46], our model includes various compartments based on clinical characteristics; namely, uncolonized, asymptomatic colonized, symptomatic colonized and relapsed patients. The proposed model was then employed to gain a better understanding of how an incoming prevalence and antibiotic treatment shapes the transmission in a hospital. Moreover, to our knowledge, this is the first study to provide the transmission-controllable area allowing to improve decision support for disease prevention and control.

The impacts of incoming prevalence on the CRKP transmission in the hospital were first investigated. We found that the total prevalence consists of the hospital prevalence in the absence of admitted colonized patients and the standardized prevalence. Clearly, the hospital prevalence is zero when the basic reproduction number (R_0) is less than one while it progressively increases for $R_0 > 1$. Moreover, when more colonized patients are admitted, the total prevalence increases regardless R_0 and leading to a larger proportion of hospitalized symptomatic colonized patients. Likewise, we found that the fraction of symptomatic among colonized patients is independent of R_0 but depends on the incoming prevalence and the proportion of admitted symptomatic colonized patients, as the standardized prevalence does.

Our findings indicate that the admission of patients has a direct influence on the transmission in the hospital [47, 57]. Although R_0 can be reduced below unity using contact precautions, precautions compliance, or other interventions, the disease always persists in the hospital when colonized patients are constantly admitted into the hospital. Moreover, when R_0 is greater than one, the disease inevitably spreads in the hospital regardless of the admission of colonized patients, which agrees with previous modeling studies of the transmission dynamics of

Acinetobacter baumannii [40] and vancomycin-resistant Enterococcus [58]. Furthermore, this information may help support decision making for the implementation of active surveillance for CRKP carriers on admission, leading to early identification and isolation of colonized patients in control measure for disease prevention [59-62].

In addition, we introduced the treatment efficacy representing the effect of treatment applied on symptomatic colonized patients, including both the treatment duration and the probability of successful treatment. Our results show that although when the probability of treating patients successfully is high, the disease can remain in the hospital if the treatment duration is too long compared to the time scale of transmission. This is because the symptomatic colonized patients treated with prolonged duration will stay longer in the hospital, leading to a high probability of transmitting pathogens to uncolonized patients [58, 63]. However, they can still serve as a main source of CRKP in a hospital setting if they are treated with a short treatment duration but without effectiveness [64]. Therefore, patients with CRKP infection need to be treated as swiftly and efficaciously as possible [43]. To attain a high treatment efficacy requires both high probability of successful treatment and high probability of leaving the hospital alive, i.e., short treatment duration (Figure 3). Such a limitation can be broken by changing to antibiotics capable of a more efficient reduction in the probability of patients becoming relapsed [32, 65, 66].

Preventing the transmission of and managing infections associated with CRKP is challenging [67-69]. In our study, the transmission-controllable area was first proposed to provide criteria for designing potential control measures. The disease will be eliminated in the hospital when values of parameters related to both intervention and transmission fall into the transmission-controllable area. We demonstrated that the transmission with distinct epidemiological characteristics required different interventions. For example, the transmission dominantly driven by symptomatic colonized patients should be controlled with antibiotic treatment. The reason is that the impact of treatment increases when the disease is more transmissible, partly caused by the low effectiveness of contact precautions between staff and symptomatic colonized patients [57]. In addition, the effectiveness of the intervention can be more enhanced by improving precaution compliance. Although the minimum compliance rate must be increased if the disease originally spreads faster, this threshold can be reduced by increasing the treatment efficacy. In our simulation, we found that treatment with higher efficacy can significantly enlarge the transmission-

controllable area (Figure 4), which results in a larger number of possible combinations of interventions that can control the transmission.

In contrast, to combat the transmission in which symptomatic colonized patients are not main drivers, it is necessary to focus on precaution compliance instead of antibiotic treatment. This is because the impact of antibiotic treatment is less effective on such transmission that even treatment with high efficacy cannot noticeably increase the size of the transmission-controllable area. Many researches have repeatedly demonstrated that precaution compliance is an important control strategy that substantially affects the endemic prevalence of nosocomial infections [45, 46, 58, 70-72]. For example, the endemic transmission could not be contained by compliance with hand hygiene only ranging between 10% and 20%, but it could be eradicated when the compliance was ameliorated to be approximately at least 50% [73]. Therefore, the transmission-controllable area is beneficial for designing intervention strategies in which different combinations of antibiotic treatment and precaution compliance are effective for certain specific transmissions.

Treatment of infections associated with CRKP is very complicated, leading to various possible poor outcomes, e.g., a relapse, persistence, or deterioration of symptoms [33, 74]. Therefore, repeatedly retreatment of patients due to those unpleasant outcomes is ineluctable. In this model, we can generate the probability distribution of symptomatic colonized patients with the history of the number of times a patient has experienced treatment failures or relapses (Figure 5). We found that the distribution is directly governed by the treatment efficacy. Antibiotic treatment with higher efficacy lower the probability that a patient will be retreated, leading to a decrease in the prevalence of CRKP in the hospital. In contrast, the patients will have a greater probability of retreatment when receiving an inefficacy and an inappropriate duration of antibiotic treatment [35, 75]. Unfortunately, the supporting empirical data is still inadequate to construct the frequency of retreated patients attributed to antibiotic therapy failure. Only a few researches provided details of case reports of patients who were retreated over one time [76-78]. Another group of patients who need retreatment is relapsing patients. The percentages of patients who subsequently become relapsing may vary in a substantial range, 0 - 65%, depending on several factors such as antibiotics, duration of therapy, etc. [24, 30, 75, 79-82]. Such a high rate of relapsing could cause the patients to suffer from the repeated infection, which can reach four episodes of infections [35, 76]. However, similar to the retreatment associated with failure of

antibiotic therapy, the information containing the number of times of re-hospitalized patients due to relapse is not sufficient for the model validation. Fortunately, there are a few researches investigating the recurrence of CRKP infections [64, 80]. The number of episodes due to recurrent infections was counted using retrospective observational data. Interestingly, we found that the frequency of the infection episodes is consistent with the exponential behavior as described in our model. Note that the recurrence was characterized as reinfection or relapse. The reinfection was defined as in patients for whom the recurrent isolates differed from the original genotype, whereas the relapse means recurrence of infection with the same genotype.

In the present research, the proposed comprehensive model can describe the transmission of CRKP and assess the impact of disease control strategies on the transmission dynamics. However, the findings of this study are subject to several limitations. First, the model does not take into account the transmission through the hospital environment, which may act as a disease reservoir [83]. Nevertheless, some empirical data demonstrated that the hospital environment contamination marginally affects the spread of Gram-negative bacteria [84]. Patient-to-patient transmission was also neglect in the model. Although this transmission route may occur when patients stay in the same unit, it is rare comparing with staff-to-patients transmission [85]. Second, it was assumed that all patients admitted into the hospital have no history of the use of antibiotics. It is known that the disruption of the normal human gastrointestinal microbiota ecosystem due to antibiotics exposure predisposes to CRKP infections or colonization [86, 87]. Therefore, this assumption might affect the transmission dynamics in the hospital setting. Finally, it should be noted that antibiotics used for all treatments were assumed to be the same, as well as the treatment duration. In reality, the antibiotic treatment course should be adjusted according to the medical conditions of patients; this may also affect the prevalence of CPKP in the hospital [35, 76].

In conclusion, the understanding presented herein is valuable for describing the sophisticated mechanism of CRKP transmission and for designing more effective disease control programs. The influx of colonized patients, treatment efficacy of antibiotics, and characteristics of the transmission are integral parts of the disease control. The application of the proposed disease-controllable area is a novel strategy that may help us attain the maximum prevention and containment for CKRP transmission in the hospital setting.

Methods

The Mathematical Model for CRKP Transmission

To describe the dynamics of CPKP transmission, we exploited the structure of mathematical models for vector-borne diseases [42, 88]. In this model, patients are considered as target hosts whereas staff as vectors transmitting CRKP from patients to patients. Patients are categorized into four different groups, namely, uncolonized (S), asymptomatic colonized (C), symptomatic colonized (I), and relapsed (R) patients. Staff are classified into two groups, uncontaminated (S_S) and contaminated (C_S). The change in the number of individuals in each subpopulation is calculated using the ordinary differential equations. For patients, the dynamics of the transmission as shown in Figure 1 is described as follows:

$$\frac{dS}{dt} = (1-u-y)\Lambda - \lambda S - \gamma S, \tag{1}$$

$$\frac{dC}{dt} = y\Lambda + (1-x)\lambda S - \gamma C, \tag{2}$$

$$\frac{dI_0}{dt} = u\Lambda + x\lambda S - (\varphi + \mu)I_0, \tag{3}$$

$$\frac{dI_k}{dt} = (1-z)\varphi I_{k-1} + rR_k - (\varphi + \mu)I_k, \tag{4}$$

$$\frac{dR_k}{dt} = ze\varphi I_{k-1} - rR_k, \tag{5}$$

where k counts the number of times a patient has experienced treatment failure or relapses. For staff, the rates of changes of individuals in each compartment are described by,

$$\frac{dS_S}{dt} = -\lambda_S S_s + [(1-\delta)\alpha_{min} + \delta\alpha_{max}]C_s, \tag{6}$$

$$\frac{dC_S}{dt} = \lambda_S S_s - [(1-\delta)\alpha_{min} + \delta\alpha_{max}]C_s. \tag{7}$$

After contacts with colonized patients, the uncontaminated staff becomes contaminated with a force of infection,

$$\lambda_s = amb_s(1-\delta)\frac{(C+pI)}{N}, \tag{8}$$

where $I = \sum_{k=0} I_k$ is the total number of symptomatic colonized patients, N is the total number of patients in the hospital, $N = S + C + I$, a is the daily number of contacts for a patient, m is the patient density, i.e., the ratio of the total number of patients to that of staff in the hospital and b_s is the probability that an uncontaminated staff becomes contaminated after contact with colonized patients. Similarly, the force of infection (λ) for uncolonized patients acquiring CRKP after having contacts with contaminated staff is given by,

$$\lambda = ab(1-\delta)\frac{C_s}{N_s}, \tag{9}$$

where b is the probability that a uncolonized patient acquires CRKP after contact with contaminated staffs and N_S is the total number of staffs.

Treatment Characterization

In the model described above, the treatment of symptomatic colonized patients is included in Eqs.(3) and (4). Treatment of symptomatic colonized patients associated with CRKP is very challenging because of various possible outcomes so that even patients receiving successful treatment could be re-hospitalized due to a relapse. A treatment is characterized by its effectiveness in curing the patient without relapse and after how long. The treatment duration and unfavorable outcomes, namely, a relapse of patients or failure of treatment, are significant factors contributing to the spread of disease in hospitals. To quantify the impacts of the treatment on the transmission, we have defined an indicator, the treatment efficacy (TE), that takes into account all those treatment aspects as follows,

$$TE = \frac{(1-e)z\varphi}{(1-e)z\varphi + \mu} = \frac{(1-e)zf}{(1-e)zf + (1-f)} \tag{10}$$

where $(1-e)z\varphi$ is the rate of successful treatment without relapse (in which z is the probability of successful treatment and e the probability that a cured patient has a relapse) and $(1-e)z\varphi + \mu$ represents the total removal rate of patients including death mortality. TE is rewritten in terms of f, the fraction of symptomatic colonized patients who escape the death thanks to treatment, given by,

$$f = \frac{\varphi}{\varphi + \mu}. \tag{11}$$

As the probabilities z and e are not independent, we assumed that the relationships between z and e can be described by the relation:

$$e = e_m(1 - z)^{\nu}, \tag{12}$$

where e_m is the maximum value of e and ν the shape parameter. Eq.(12) can be regarded as the characteristic patient response to an antibiotic kind. Profiles of the treatment efficacy are displayed in Figure 3.

Basic Reproduction Number

The basic reproduction number (R_0) is an important epidemiologic metric used to describe the transmissibility of infectious disease. It provides the number of secondary cases generated by a colonized individual during his or her infectious period. In our study, the next generation method was employed to calculate R_0 [89]. For simplicity, we assumed that only uncolonized patients are admitted into the hospital. Thus, the R_0 can be computed as follows:

$$R_0 = \left[\frac{mbb_s a^2(1-\delta)^2}{(1-\delta)\alpha_{min} + \delta\alpha_{max}}\right]\left[\frac{1-x}{\gamma} + \frac{px}{(1-e)z\varphi + \mu}\right]. \tag{13}$$

To investigate the impacts of interventions on the epidemics in hospitals, we need to understand how the disease spreads before implementation of interventions. Two indicators were calculated to describe the epidemiological characteristics of the transmission. First is the basic reproduction number in the case of no intervention (R_{00}), which can be written in terms of the basic reproduction number for asymptomatic colonized patients (R_{0c}) and that for symptomatic colonized patients (R_{0I}). The second is ε, defined as the ratio of R_{0I} to R_{00}. Consequently, R_0 can be rewritten as a function of R_{00} and ε as,

$$R_0 = \left[\frac{\alpha_{min}(1-\delta)^2}{(1-\delta)\alpha_{min} + \delta\alpha_{max}}\right][1 - \varepsilon + \varepsilon(1 - \boldsymbol{TE})]R_{00}, \tag{14}$$

where

$$R_{00} = \left[\frac{mbb_s a^2}{\alpha_{min}}\right]\left[\frac{1-x}{\gamma} + \frac{px}{\mu}\right] = R_{0C} + R_{0I} \tag{15}$$

and

$$\varepsilon = \frac{R_{0I}}{R_{00}} = \frac{px\gamma}{(1-x)\mu + px\gamma}. \tag{16}$$

By definition of R_0, the disease will be under control when $R_0 < 1$. Therefore, to determine the boundary separating regions of sets of parameters that correspond to controllable and non-controllable areas, we set $R_0 = 1$ and solve the resulting equation for δ to obtain:

$$\delta = \frac{(2r-1)\alpha_{min} + \alpha_{max} - \sqrt{[(2r-1)\alpha_{min} + \alpha_{max}]^2 - 4r(r-1){\alpha_{min}}^2}}{2r\alpha_{min}}, \tag{17}$$

where $r = [1 - \varepsilon + \varepsilon(1-TE)]R_{00}$.

The steady state of the model

For $R_0 > 1$, the set of equations (1) – (5) admit steady states for each class of patients that can be derived after calculations as,

$$\begin{cases} C^* = s_0 + s_1 I^* \\ C^* = c_0 + c_1 I^* \\ I^* = \left[-i_1 + \sqrt{i_1^2 + 4i_0 i_2}\right]/2i_2\,, \\ R^* = \dfrac{ze\varphi I^*}{r} \end{cases} \tag{18}$$

where,

$$\begin{cases} s_0 = \left[(1-u-y)+\frac{1}{x}u\right]N \\ s_1 = \frac{1}{\gamma}[(1-e)z\varphi+\mu]\left[(1-u-y)-\frac{1}{x}(1-u)\right]-\left[(1-u-y)+\frac{1}{x}u\right] \\ c_0 = \left[y-\frac{(1-x)}{x}u\right]N \\ c_1 = \frac{1}{\gamma}\left[\frac{(1-x)}{x}(1-u)+y\right][(1-e)z\varphi+\mu]+\left[\frac{(1-x)}{x}u-y\right] \\ i_0 = \frac{u\gamma N}{x}\left[\frac{amb_s(1-\delta)}{N}c_0+[(1-\delta)\alpha_{min}+\delta\alpha_{max}]\right]+\frac{mbb_s a^2(1-\delta)^2}{N}c_0 s_0 \\ i_1 = \frac{1}{x}\left[(1-u)\big((1-e)z\varphi+\mu\big)+u\gamma\right]\left[\frac{amb_s(1-\delta)}{N}c_0+[(1-\delta)\alpha_{min}+\delta\alpha_{max}]\right] \\ \quad -\frac{amb_s(1-\delta)}{N}(c_1+p)\,\frac{u\gamma N}{x}-\frac{mbb_s a^2(1-\delta)^2}{N}\big(c_0 s_1+s_0(c_1+p)\big) \\ i_2 = \frac{amb_s(1-\delta)}{N}\,\frac{1}{x}(c_1+p)\big[(1-u)\big((1-e)z\varphi+\mu\big)+u\gamma\big]-\frac{mbb_s a^2(1-\delta)^2}{N}s_1(c_1+p) \end{cases} . \quad (19)$$

Moreover, symptomatic colonized patients (I) and relapsed patients (R) are classified into subpopulations corresponding to the number of times, *k,* that a patient has experienced treatment failure or relapses. Therefore, the steady states I_k^* and R_k^* (such that, $I^* = \sum_{k=0} I_k^*$ and $R^* = \sum_{k=0} R_k^*$) are computed as follows:

$$\begin{cases} I_k = \left[\frac{f-TE}{1-TE}\right]^k I_0 \\ R_k = \frac{ze\varphi}{r} I_{k-1} \end{cases} \quad (20)$$

Finally, using the relation, $I^* = \sum_{k=0}^{\infty} I_k^*$, we obtain,

$$I_0 = \left(\frac{1-f}{1-TE}\right) I^* \quad (21)$$

Now, plugging back Eq.(21) into Eq.(20), we obtain,

$$I_k = I^* G_k \implies G_k = (1-g)g^k \;;\; g = \left(\frac{f-TE}{1-TE}\right) \quad (22)$$

where G_k is the normalized (i.e., $\sum_{k=0}^{\infty} G_k = 1$) probability distribution that a symptomatic colonized patient has experienced *k* relapses, and g is the probability of relapse.

Simulations

In this study, patient-to-patient and staff-to-staff transmissions is not considered, and the patient and staff populations is assumed homogeneous. In addition, the number of patients in the hospital is kept constant such that the total number of admissions equals that of discharge from the hospital:

$$\Lambda + rR = \gamma S + \gamma C + (z\varphi + \mu)I. \tag{23}$$

Moreover, we assume that the dynamics of contamination in staffs is fast compared to that in the patient population. Therefore, we consider the dynamics of contamination in staffs at the steady state with the number of contaminated staffs given by:

$$C_S = \frac{\lambda_S N_S}{\lambda_S + [(1-\delta)\alpha_{min} + \delta\alpha_{max}]}. \tag{24}$$

to be used in Eq.(9). In the simulation, the Euler method was used to deterministically solve the sets of ordinary equations. All figures and calculation were generated using MATLAB software (version R2020b, The MathWorks, Inc). The descriptions and values of all parameters used in the model are summarized in Table 1.

Table 1. Variables and Parameters of the Model

Symbol	Definition	Value [range]	Unit	References
u	Fraction of symptomatic colonized patients at admission	0 [0-1]	-	Assumed
y	Fraction of colonized patient at admission	0 [0-1]	-	Assumed

γ	Discharge rate of patients	1/8.8 [1/18-1/4.4]	/day	[19, 46, 47, 90-95]
a	Total number of contacts that a patient acquires per day	8 [8-13.8]	/patient /day	[42, 58]
m	Patient density (ratio of no. patients to no. staffs)	4 [1-8]	-	[39, 42, 45, 58, 72, 96, 97]
b	Probability of a patient acquiring CRKP after having contact with a contaminated staff	0.025 [0.01-0.42]	-	[42, 43, 58, 88]
b_S	Probability of an uncontaminated staff becoming contaminated after having contact with a colonized or a symptomatic colonized patient	0.11 [0.1-0.45]	-	[41-43, 45, 46, 58, 88]
p	Contact precaution effectiveness	0.63 [0-1]	-	Assumed
α_{min}	Minimum of decontamination rate	2	/day	Assumed
α_{max}	Minimum of decontamination rate	24		
δ	Precautions compliance	0-1	-	Assumed
x	Fraction of uncolonized patients becoming symptomatic colonized patients	0.2 [0.09-0.56]	-	[13, 17, 19, 23, 47-49, 61, 90, 98, 99]
z	Probability of successful treatment	0-1	-	Assumed

e	Probability of a patient subsequently having a relapse of infection	eq. 19	-	-
e_{max}	The maximum value of e	0.8	-	Assumed
φ	Treatment rate	1/14 [1/28-1/7]	/day	[35, 76, 79, 81, 100-104]
r	Readmission rate due to a relapse of infection	1/16 [1/84-1/8.5]	/day	[30, 35, 36, 51, 52, 76, 81, 102, 105]
μ	Death rate associated with CRKP	0.0178 [0.014-0.073]	/day	[5, 6, 8, 106-110]

Note: Determining the death rate (μ) is a bit challenging because reported deaths include several cases in which the patients have severe underlying disease or comorbidity. Hence, the attributable mortality rate was used to reduce this ambiguity [5, 111]. Because the attributable mortality rate provides the percentage of infection-related deaths during a length of hospital stay. Therefore, the μ was calculated as,

$$\mu = \frac{-\ln\left(1 - 0.01 \times \text{attributable mortality (\%)}\right)}{1/\varphi}. \quad (25)$$

In this study, the length of hospital stay was assumed to be equal to the treatment duration ($1/\varphi$).

Prevalence and Fraction of Colonized Patients

As indicators of the disease progression in the hospital, we used the total prevalence (P) of colonized patients and, among them, the fraction of symptomatic colonized (q):

$$\begin{cases} P = \dfrac{C+I}{N}, \\ q = \dfrac{I}{C+I}. \end{cases} \tag{26}$$

such that qP provides the fraction of symptomatic colonized among all patients. The disease transmission is governed by not only the in-hospital patients but also by the incoming prevalence, $P_{in} = u + y$, where u and y are the fractions of symptomatic and asymptomatic colonized patients, respectively, admitted into the hospital. To investigate how P_{in} shapes the disease extension, P and q are written as:

$$\begin{cases} P = (1-\theta_1)P_0 + \theta_1 P_1, \\ q = (1-\theta_2)q_0 + \theta_2 q_1. \end{cases} \tag{27}$$

where P_0 and P_1 are the within-hospital prevalence of colonized and q_0 and q_1 the fractions of symptomatic colonized with $P_{in} = 0$ and $P_{in} = 1$, respectively. θ_1 and θ_2 are the standardized prevalence and the standardized fraction of colonized, respectively:

$$\begin{cases} \theta_1 = \dfrac{P - P_0}{P_1 - P_0}, \\ \theta_2 = \dfrac{q - q_0}{q_1 - q_0}, \end{cases} \tag{28}$$

Note that $P_1 = 1$.

Table 2. The formulas and the R-squares from curve fittings

Fitting equations		**R-square**
$P_0 = 0.8495\left(1 - \dfrac{1}{R_0}\right)^{1.095}$ for $u = y = 0$		0.9996
$q_0 = \dfrac{1}{1 + \left(\dfrac{1-x}{x}\right)\left(\dfrac{\mu}{\gamma}\right)} = 0.4154$ for $u = y = 0$		1.0000
	$1 - \exp(-2.484P_{in})$ for $u/y = 0.2$	0.9866

$\theta_1 =$	$1 - \exp(-3.365P_{in})$	for $u/y = 1.0$	0.9940
	$1 - \exp(-4.157P_{in})$	for $u/y = 5.0$	0.9870
$\theta_2 =$	$1 - \exp(-2.943P_{in})$	for $u/y = 0.2$	0.9927
	$1 - \exp(-4.538P_{in})$	for $u/y = 1.0$	0.9776
	$1 - \exp(-6.080P_{in})$	for $u/y = 5.0$	0.9559

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Data availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Author contributions

DJB: designed the research and supervised the work.
SC: data curation and performed all calculations.
SC, CM and DJB: analysed the results, edited and draft the manuscript. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional Information

NA

Figures

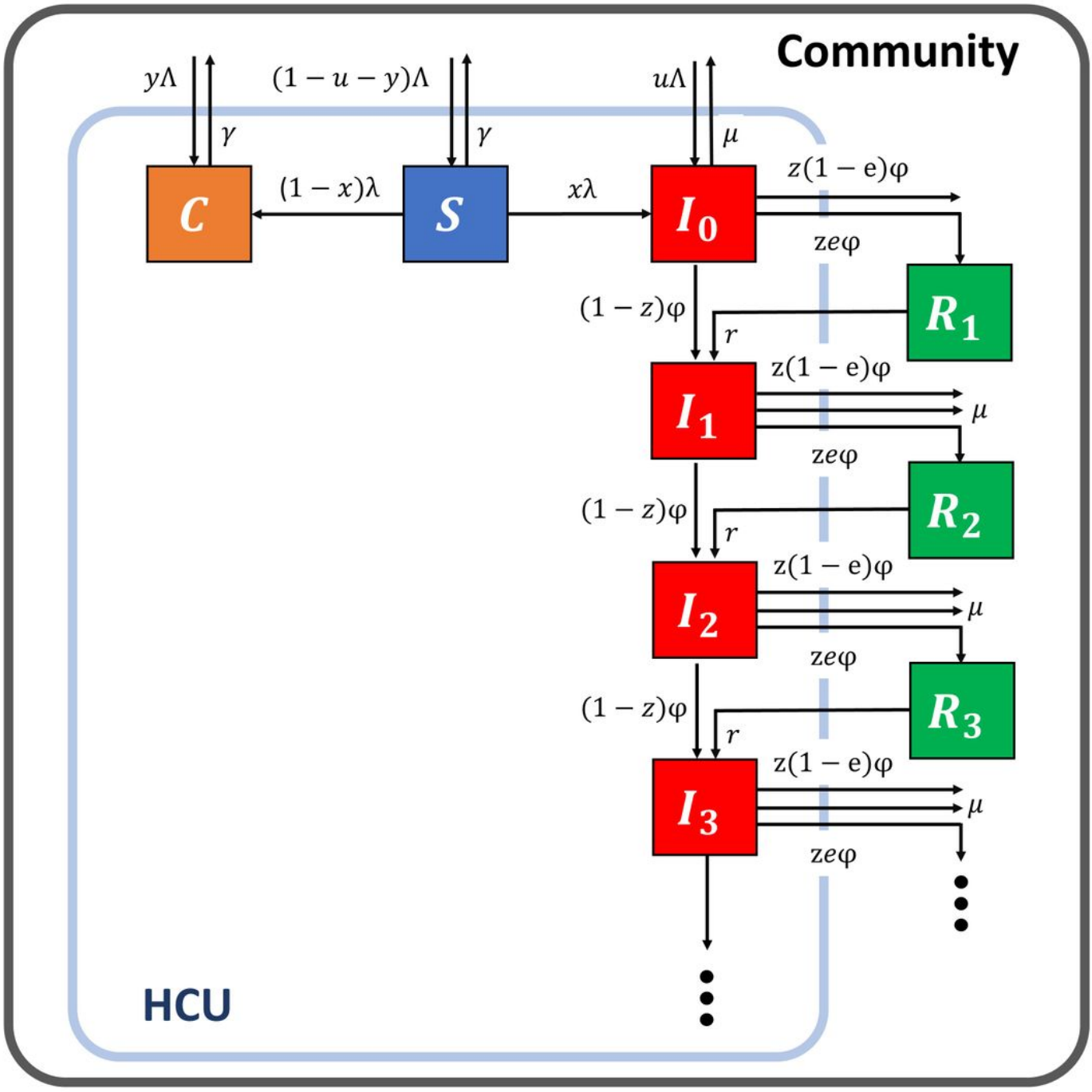

Figure 1

Schematic of the kinetic transmission model of carbapenem-resistant klebsiella pneumoniae (CRKP) in a health care unit (HCU).

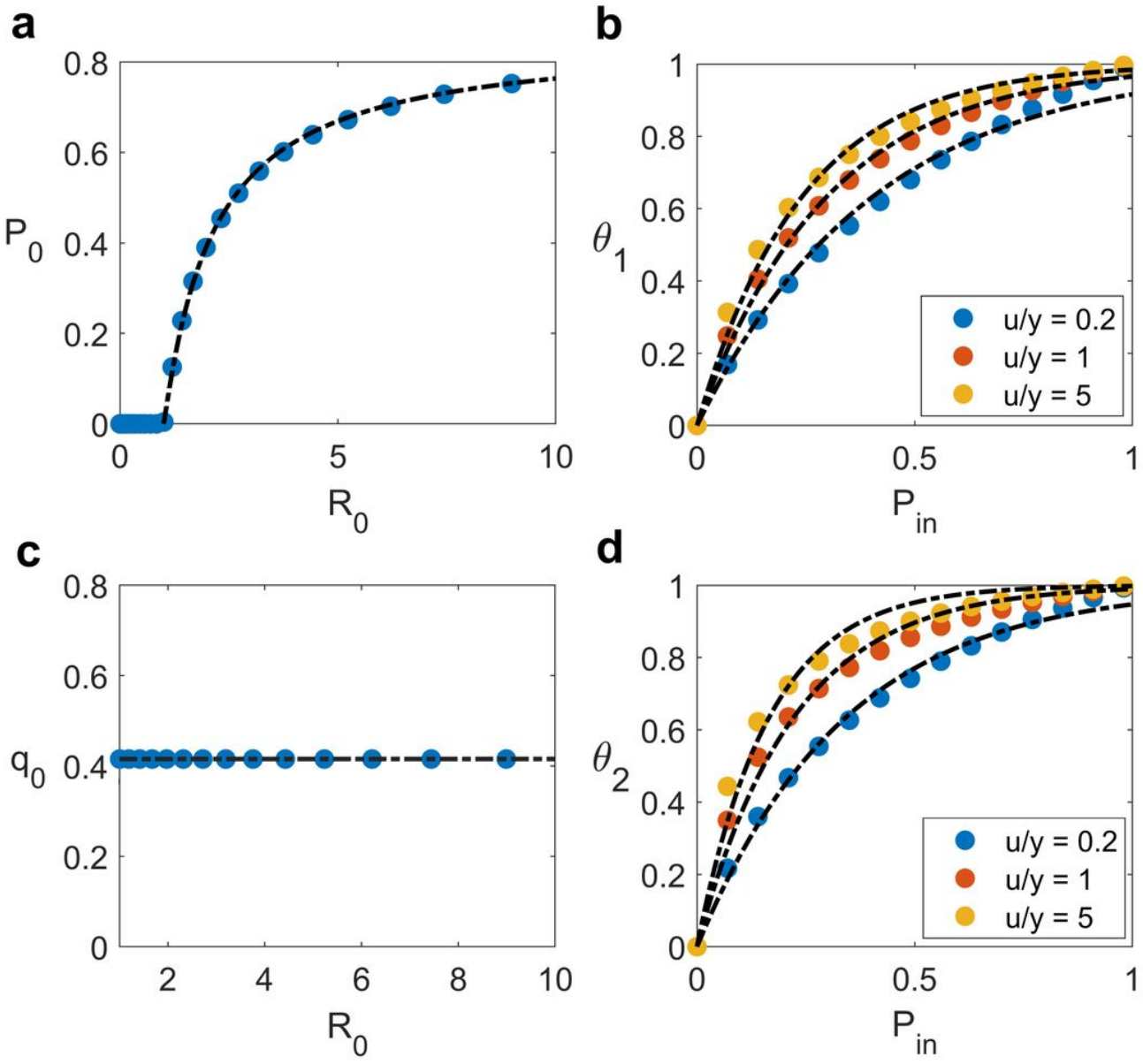

Figure 2

Prevalence and fraction of colonized patients. (a) the hospital prevalence and (c) the fraction of colonized patients as a function of R_0 with no incoming prevalence, P_in=0. (b) The standardized prevalence and (d) the standardized fraction of colonized patients as a function of P_in. The disease is assumed to spread with R_0=1.5. Different colors represent different ratios of fractions of symptomatic colonized to that of asymptomatic colonized patients admitted into the hospital. Black-dash lines are best fit to simulation data.

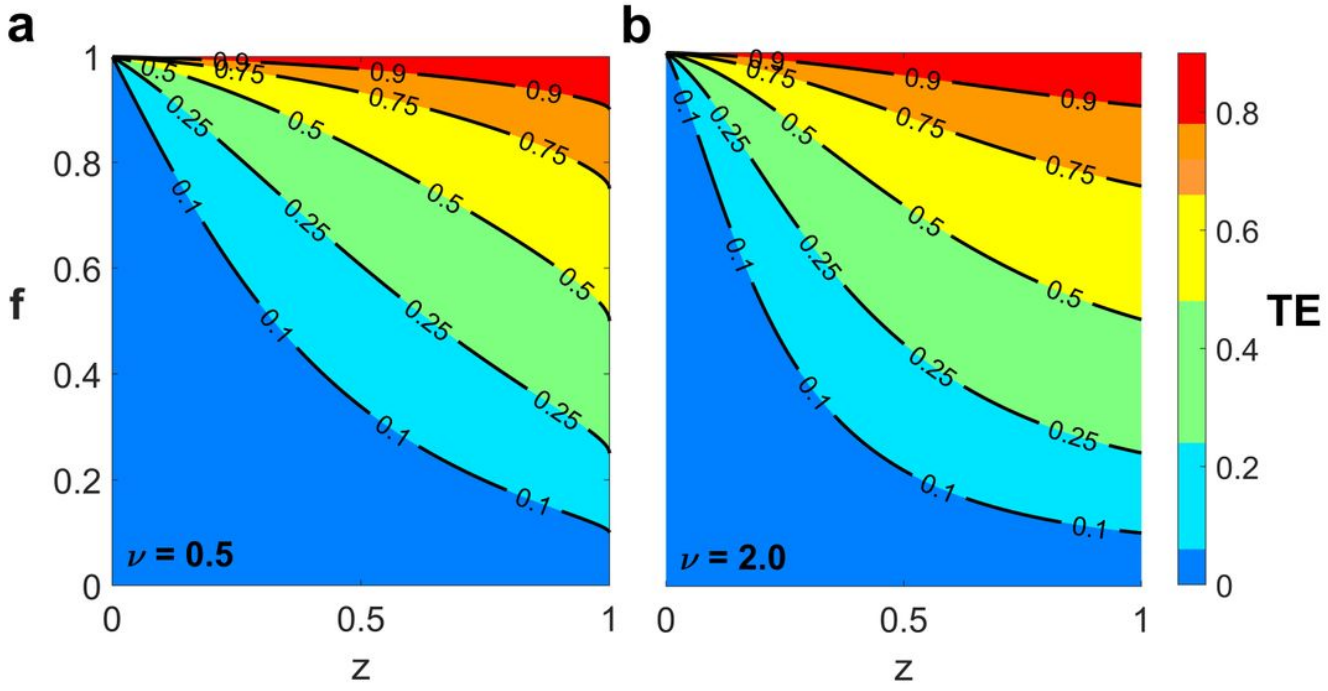

Figure 3

Contours of treatment efficacy. The treatment efficacy (TE) is plotted in (z, f) space with v = 0.5 (a) and 2.0 (b) with e_m=0.8 (see Table 1). Each section represents the different TE with different colors.

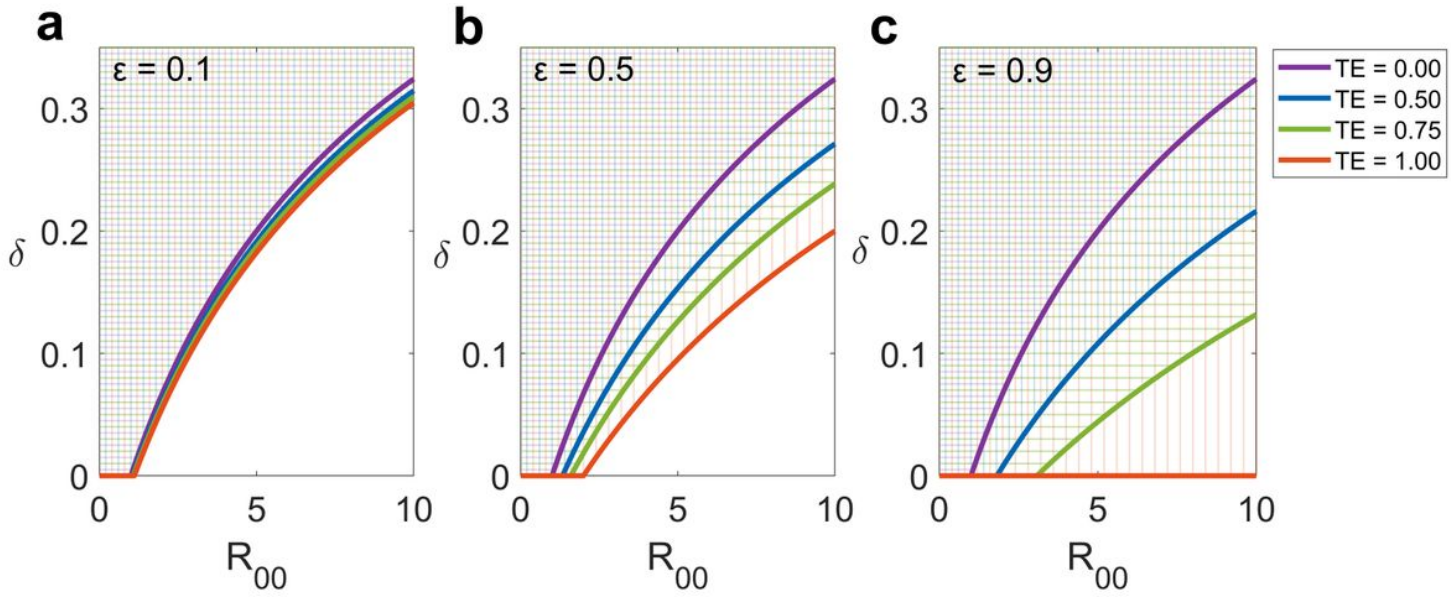

Figure 4

Transmission-controllable area. The transmission-controllable area (hatched areas above the lines) illustrates sets of parameters corresponding to the control of transmission with R_0<1. Solid line represents the R_0 = 1 line separating the controlled (above) from the uncontrolled (below) areas. Different treatment efficacies (TE) are shown with different colors. Transmissions with ε=0.1, 0.5, and 0.9 are depicted in a, b, and c, respectively.

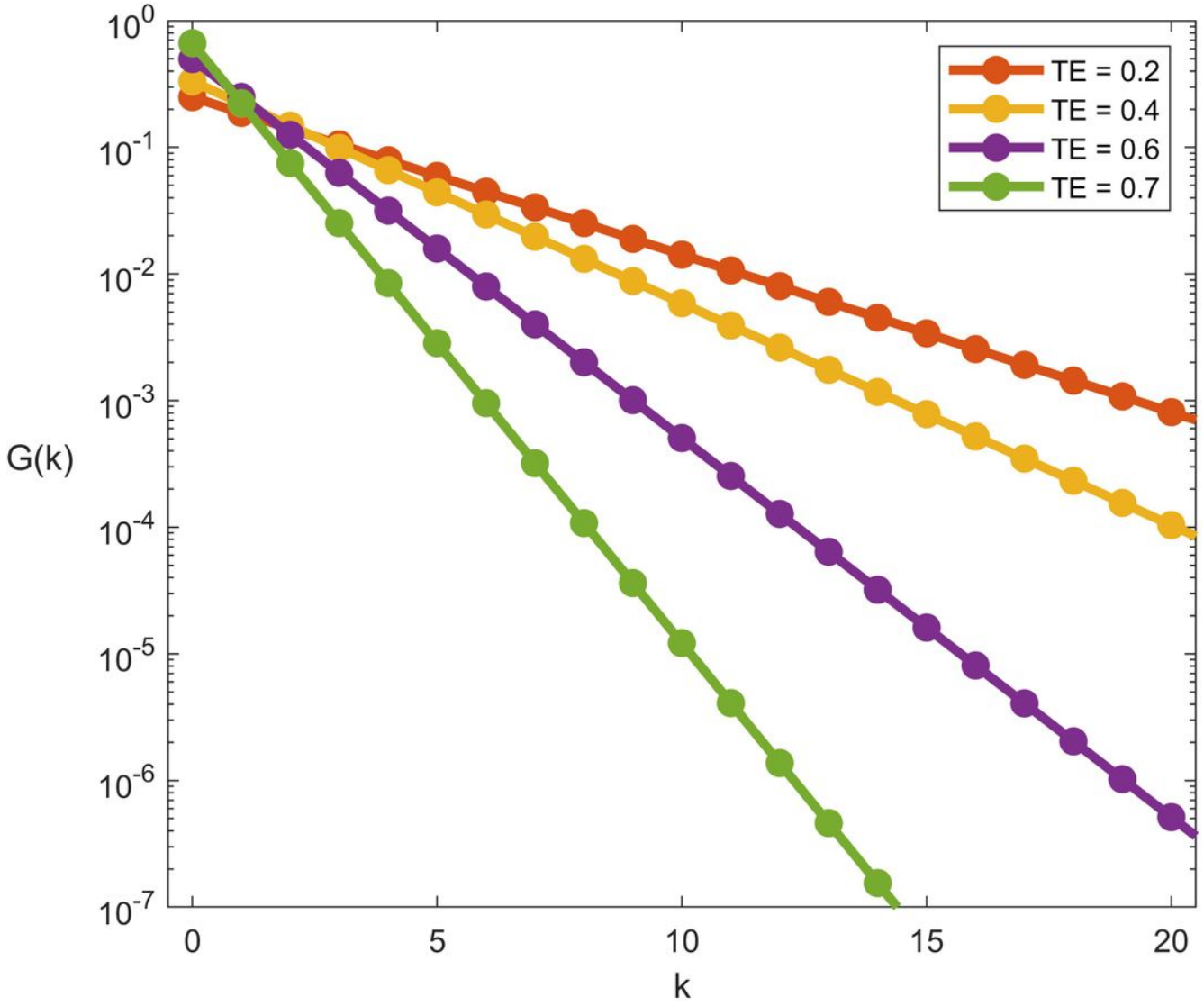

Figure 5

Probability distribution of relapses. k represents the number of times that a patient has experienced treatment failures or relapses. Different treatment efficacies (TE) are shown by different colors.

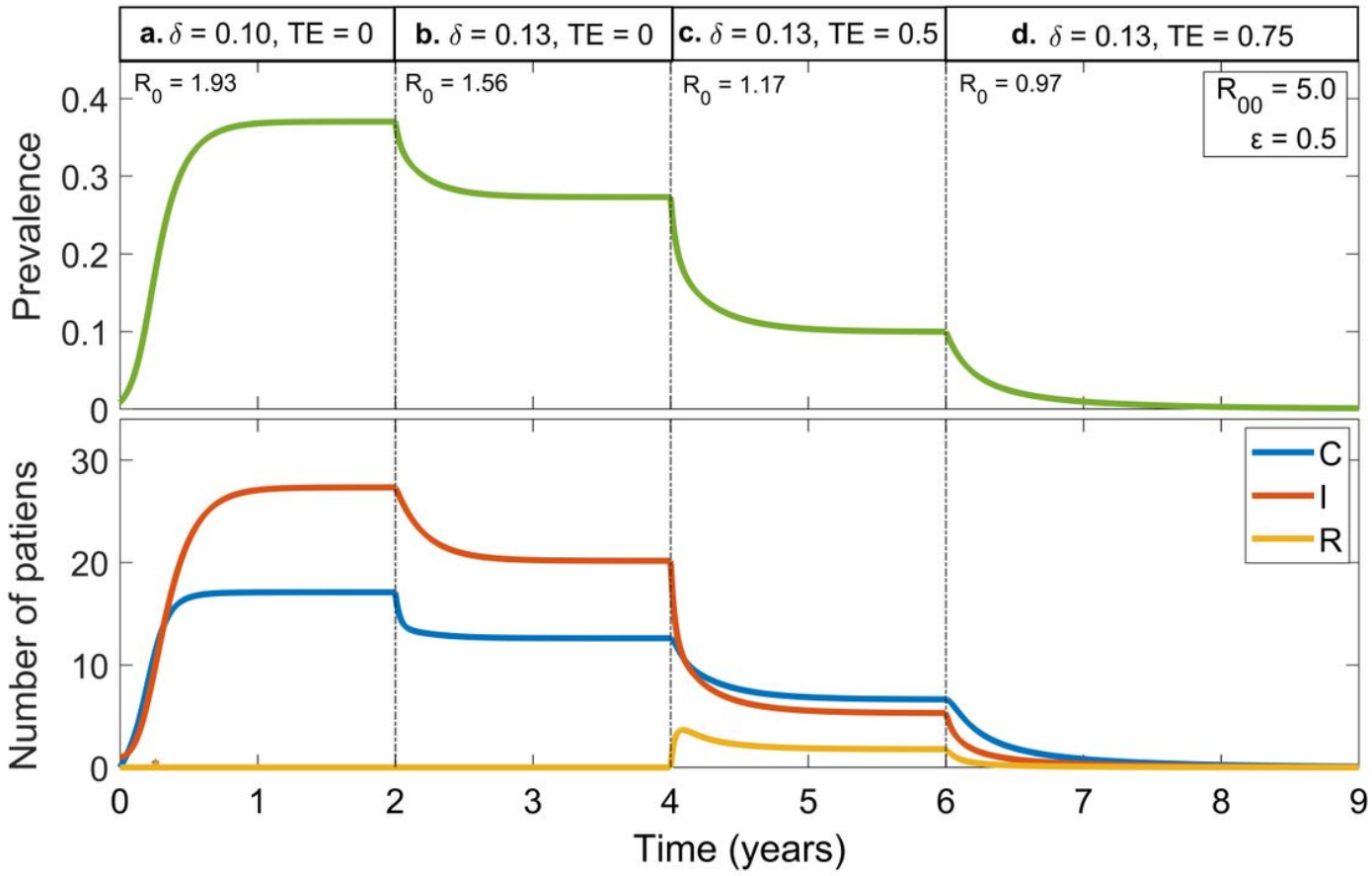

Figure 6

Impact of successive interventions on the time course of the infection progression. The epidemic with no intervention (panel a) is controlled by increasing precaution compliance (panel b), then using the treatment on symptomatic colonized patients (panel c), and finally enhancing the treatment efficacy (panel d). The impact of successive interventions on the epidemics time course is represented by the prevalence (above) and the number of patients (below).