ANALYSIS

Modelling an outbreak of an emerging pathogen

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Abstract | To illustrate the usefulness of mathematical models to the microbiology and medical communities, we explain how to construct and apply a simple transmission model of an emerging pathogen. We chose to model, as a case study, a large (>8,000 reported cases) on-going outbreak of community-acquired meticillin-resistant *Staphylococcus aureus* (CA-MRSA) in the Los Angeles County Jail. A major risk factor for CA-MRSA infection is incarceration. Here, we show how to design a within-jail transmission model of CA-MRSA, parameterize the model and reconstruct the outbreak. The model is then used to assess the severity of the outbreak, predict the epidemiological consequences of a catastrophic outbreak and design effective interventions for outbreak control.

Catastrophic outbreak
An extremely large outbreak in a confined population that may be caused by the synergistic interaction of two processes: a high level of transmission and a large inflow of infectious individuals into the transmission site.

Prevalence
The number of infected individuals at a specific time.

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doi:10.1038/nrmicro1660

Mathematical models of infectious disease dynamics — transmission models — have become valuable tools for understanding the dynamics of outbreaks and epidemics, designing effective interventions and making informed health policy decisions[1]. The first mathematical model was published in 1766 by Daniel Bernoulli[2]. The main purpose of Bernoulli's mathematical analysis was to influence public health policy by quantifying the population-level benefits of universal inoculation against smallpox[2,3]. Since then, the analysis of simple transmission models has often been shown to provide important and non-intuitive insights into the dynamics of infectious diseases. Simple models have been used as 'building blocks' to develop more elaborate complex models that have been analysed using sophisticated mathematical and computational techniques. In this Review, we show how to construct and analyse a simple transmission model of the outbreak dynamics of an emerging pathogen. We use, as an illustrative example, an outbreak of community-acquired meticillin-resistant *Staphylococcus aureus* (CA-MRSA). Strains of CA-MRSA have recently emerged, and one of the major risk factors for CA-MRSA that has been identified is incarceration[4]. Here, we demonstrate how to use modelling to understand a large (8,448 cases were reported between 2002 and 2005 (REF. 5)) on-going outbreak of CA-MRSA in the Los Angeles County Jail (LACJ). We show how to design a within-jail transmission model, parameterize the model and use it to reconstruct the outbreak. We also show how to use the model to: first, assess the severity of the outbreak; second, predict the epidemiological consequences of a catastrophic outbreak; and, third, design effective interventions for outbreak control.

The epidemiology of CA-MRSA

CA-MRSA is an emerging pathogen that is currently a great public health concern, as the prevalence of CA-MRSA infection is increasing in many communities[6]. Until the mid-1990s, MRSA was primarily linked to hospitals and nursing homes and was termed hospital-acquired MRSA (HA-MRSA)[6–7]. However, over the past decade new strains of MRSA have evolved in the community; these CA-MRSA strains have substantial genetic, microbiological and clinical differences compared with the HA-MRSA strains[8–18]. Whereas HA-MRSA strains cause morbidity and mortality primarily in hospitalized patients, infection with CA-MRSA strains has caused the deaths of otherwise healthy individuals[16,19,20]. Outbreaks of CA-MRSA have occurred in communities of men who have sex with men, homeless populations, inmates in correctional facilities, military recruits, competitive sports teams and children in day-care centres[4,11]. Outbreaks of CA-MRSA have also recently been reported in hospitals[4,11].

Over the past decade, many mathematical models of the transmission of HA-MRSA in hospitals have been developed[21–34], beginning with the first model by Sebille and colleagues[31,32]. Strains of HA-MRSA are transmitted between patients, between healthcare personnel and between healthcare personnel and patients. Therefore, some of the HA-MRSA models that have been developed are complex, as they model specific mixing interactions between patients and healthcare personnel. In general, these transmission models have been formulated and analysed in order to understand the transmission dynamics of HA-MRSA within a hospital or within an intensive care unit (ICU); these models have generally been theoretical

Nurse cohorting
Reducing the contact of nurses with a large group of patients by assigning specific groups of nurses to the care of only a subset of patients. This intervention reduces the interaction of nurses with patients and is therefore expected to reduce nurse–patient transmission.

Title 15
Title 15 deals with "Miscellaneous Crimes" and is part of the California Penal Code.

Incidence
The number of newly infected individuals per unit of time.

and not based on data. The results of these studies have been used to suggest theoretical intervention strategies for reducing HA-MRSA in hospitals or ICUs[21,22,24,25,27,28,31]. Suggested intervention strategies have been in the form of recommendations for healthcare personnel and have mainly focused on suggesting increases in the levels of both nurse cohorting and hand washing[27,28]. Transmission models have also been linked with economic analyses to determine the cost-effectiveness of specific interventions in hospitals[33].

Hospitals and long-term-care facilities are obviously the foci for the transmission of HA-MRSA but not for CA-MRSA; it is currently unknown which locations are high-transmission sites for CA-MRSA. Recently it has been proposed that correctional facilities might be important sites for the transmission of CA-MRSA[4,35–39] as inmates have poor access to medical care, crowded living conditions and suboptimal hygiene[40–42]. Furthermore, it has been suggested that these facilities could be accelerating the progression rate of CA-MRSA by limiting access to soap, showers and clean clothes[7]. According to Title 15 requirements in California, it is only required that inmates be offered showers three times a week and be given two pairs of underwear and one jumpsuit per week. Approximately two million adults in the United States are currently confined in correctional facilities. Large outbreaks of CA-MRSA have been reported in prisons and jails in California, Texas, Missouri, Georgia and Mississippi[8,35,40,41,43]. The 3,365 jails in the United States house fewer inmates than do prisons, but jails have a higher turnover rate and receive the majority of the admissions to correctional facilities (approximately ten million adults per year). Thus, it has been suggested that jails could be an extremely important contributing factor to the rising number of CA-MRSA infections in certain communities[4,35]. The transmission of CA-MRSA between jails might also be occurring[38]. It is also possible that, in certain locations, the rising epidemic of CA-MRSA in the community is an important contributor to jail outbreaks.

Modelling an outbreak of CA-MRSA

Transmission models can be used to analyse an outbreak in a specific location to: identify whether the outbreak site is a transmission 'hot spot'; to predict if the outbreak is likely to develop into an epidemic; and to design effective outbreak-control strategies. To illustrate and apply these modelling concepts, we will show how to use a model to analyse an ongoing outbreak of CA-MRSA in the LACJ, which is the largest jail in the world. The LACJ houses ~165,000 inmates per year and contains ~20,000 inmates at any given time. This jail is currently experiencing one of the largest outbreaks of CA-MRSA seen so far in any correctional facility[37]. The outbreak began in 2001 when inmates began to complain of skin lesions caused by 'spider bites'; starting in September 2001, all reported bites were cultured. In subsequent months the jail screened the facilities, ensured that pest-control measures were in place, fumigated many facilities and tested spiders. The spiders were found to be harmless, yet the number of infections continued to increase and the jail subsequently reported the outbreak to the Los Angeles County Department of Health Services (LACDHS)[37]. In August 2002, the LACDHS recommended standardizing surveillance, treatment and infection-control protocols. At the beginning of October in the same year physicians at the LACJ began to take cultures from all inmates with skin lesions.

The outbreak in the LACJ grew exponentially during the initial stage of the outbreak, from January 2002 to September 2002; over this time period 628 clinical infections from skin lesions and the bloodstream were found (565 in male inmates (FIG. 1) and 63 in female inmates). During this period of exponential growth the incidence in the women's facility increased almost twice as fast — with a doubling time of 6.5 months (95% confidence interval (CI): 5.1–7.9 months) — as the incidence in the men's facility. In the men's facility there was a doubling time of 11.6 months (95% CI: 8.0–15.2 months)[36]. The outbreak continues and, to date, more than 8,000 infections have been reported.

Constructing a transmission model of a CA-MRSA outbreak. Transmission models can be constructed to be either deterministic or stochastic. Deterministic models adequately predict epidemic dynamics in large populations, where the effect of chance events is small. Stochastic models, however, can be used to predict the dynamics of outbreaks in small populations, where chance events can have major effects. Both deterministic and stochastic models are reasonably straightforward to analyse numerically. However, simple deterministic models are much easier to analyse mathematically than their stochastic counterparts. Therefore, we will first construct a deterministic transmission model, and then use a stochastic version of the same model to reconstruct the temporal dynamics of the outbreak in the LACJ.

To construct a simple deterministic model that describes the dynamics of an infectious disease it is necessary to first understand the dynamics of the host population, the important transmission processes that are driving the outbreak and the biology of the pathogen. This information can be determined by studying the demography of the system (for example, the correctional facility

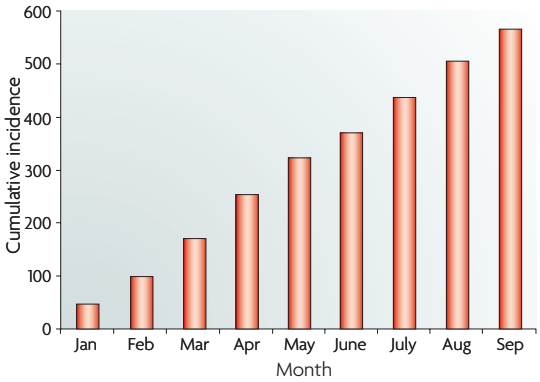

Figure 1 | **Cumulative incidence of community-acquired meticillin-resistant *Staphylococcus aureus* in males in the Los Angeles County Jail from January 2002 to September 2002.**

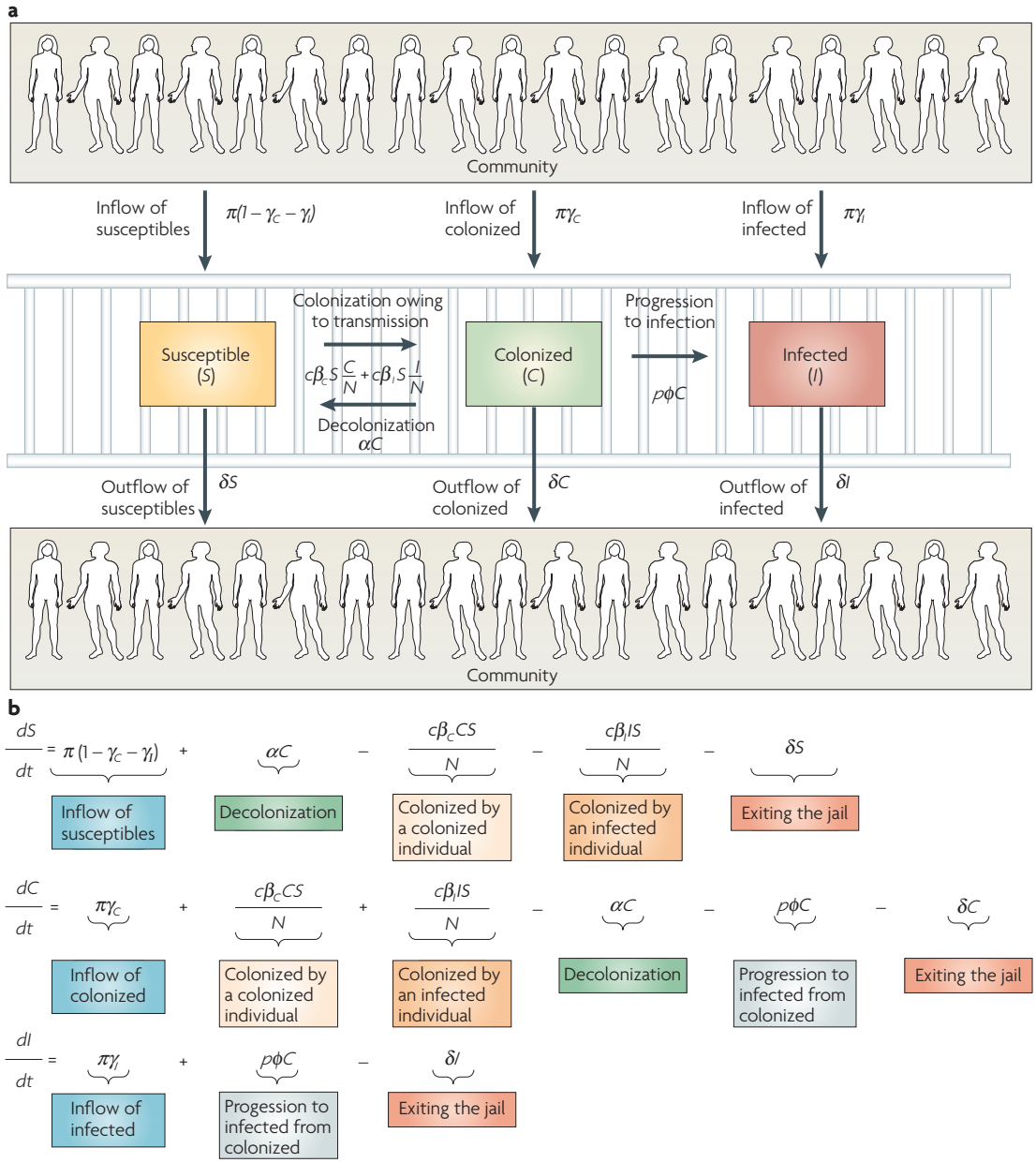

Figure 2 | **Graphical depiction, and equations for, the within-jail community-acquired meticillin-resistant *Staphylococcus aureus* transmission model.** Panel **a** shows the inflow into the jail and the outflow from the jail of susceptible non-carrier (*S*), asymptomatically colonized (*C*) and infected (*I*) individuals. The arrow pointing from the *S* to the *C* state shows that non-carrier individuals can become colonized (that is, individuals can move from the *S* to the *C* state). The arrow pointing from the *C* to the *S* state shows that colonized individuals can become decolonized (that is, individuals can move from the *C* to the *S* state). The arrow pointing from the *C* to the *I* state shows that colonized individuals can become infected (that is, individuals can move from the C to the *I* state). The three equations that correspond to this diagram and that specify this simple transmission model are shown in panel **b**. Parameter definitions (and values) are shown in TABLE 1. This model is deterministic but can be simply transformed into a stochastic model by the addition of probabilities.

or hospital) that is being studied and by working with infectious disease experts during the model construction phase to ensure that the model is simple but realistic. To model the transmission of HA-MRSA in hospitals it is sometimes necessary to model transmission among patients and medical workers, because medical workers can act as vectors to transmit HA-MRSA from patient to patient[45]. In correctional facilities there is almost no direct contact between staff and inmates, so, it is only necessary to model transmission among inmates.

To define a model that can be applied to the transmission of CA-MRSA in a small population that has both immigration and emigration of the host (such as the LACJ), we begin by specifying that inmates are always in

one of three mutually exclusive states: susceptible (non-carrier) (*S*); asymptomatically colonized with CA-MRSA and infectious (*C*); or infected with CA-MRSA and infectious (*I*). Therefore, the model is constructed as a three-state model that is mathematically specified in terms of three equations. A graphic representation of the model, including parameters, is shown in FIG. 2a. The equations that specify the model are shown in FIG. 2b and the parameters are defined in TABLE 1. The model tracks the flow, over time, of inmates into and out of the three states, and also the flow of inmates into and out of the jail. It includes the three important processes that drive the jail outbreak: within-jail transmission; the inflow of infected cases; and the inflow of asymptomatic colonized individuals that progress to infection while they are incarcerated. The model that we constructed is designed to track the dynamics of CA-MRSA over the first 9 months of the outbreak, from the beginning of the outbreak in January 2002 to September 2002, and therefore it does not include the potential effects of any interventions, such as treatment. To construct the model, we make eight assumptions.

Assumption 1. Inmates enter the jail at rate π, and the average incarceration time ($1/\delta$) during the initial stage of the outbreak is constant. Thus, during the outbreak, the number of inmates in the jail (*N*) remains constant and is specified by the relationship $N = \pi/\delta$.

Assumption 2. Inmates enter the jail in one of three mutually exclusive states: asymptomatically colonized with CA-MRSA with a probability of γ_C; infected with CA-MRSA, with a probability of γ_I; or a non-carrier, with a probability of $1-\gamma_C-\gamma_I$ (FIG. 2a).

Assumption 3. Both asymptomatically colonized (*C*) and infected (*I*) inmates are infectious.

Assumption 4. Within the jail, non-carrier inmates (*S*) can become colonized upon contact with either asymptomatically colonized (*C*) or infected (*I*) inmates, with a probability of β_C or β_I, and a rate of *c* (owing to direct and indirect contacts as a result of sharing towels or other personal items), or be released from the jail as a non-carrier at rate δ (FIG. 2a). The model also allows for the possibility that some non-carrier inmates might directly move to the infected state (*I*) without spending time in the colonized state.

Assumption 5. Within the jail, asymptomatically colonized inmates (*C*) can: remain colonized and transmit CA-MRSA while incarcerated with a probability of β_C and at a rate of *c*; become decolonized during incarceration (in $1/\alpha$ days on average); be released from the facility while still colonized at a rate of δ; or progress to the infected state while incarcerated, with a probability of *p* and at a rate of φ (FIG. 2a).

Assumption 6. Within the jail, infected (*I*) patients can transmit CA-MRSA while incarcerated, with a probability of β_I and at a rate of *c*, and be released from the facility while still infected, at a rate of δ (FIG. 2a).

Assumption 7. The majority of infected inmates do not clear their infection or colonization while in jail without treatment, as the average incarceration time is short (approximately 1 month; FIG. 3a).

Assumption 8. We assume homogeneous (that is, random) mixing, as: inmates were often moved to minimize

Table 1 | **Parameter ranges used in the multivariate uncertainty analysis to calculate R_0**

Parameters[36]	Symbol	Males	Females
Total number of inmates	*N*	16,956	2,200
Number of individuals booked per day	π	341–407	64–81
Average incarceration time (days)	$1/\delta$	42–50	27–34
Probability that an inmate enters the jail colonized with CA-MRSA	γ_c	$8.8\times10^{-5}-4.923\times10^{-3}$	$4.43\times10^{-4}-7.77\times10^{-3}$
Probability that an inmate enters the jail infected with CA-MRSA	γ_I	$8.8\times10^{-5}-4.923\times10^{-3}$	$4.43\times10^{-4}-7.77\times10^{-3}$
Average decolonization time (days)	$1/\alpha$	30–120	30–120
Proportion of colonized individuals who progress to infection	*p*	0.10–0.30	0.10–0.30
Average time for colonized individuals to progress to infection (days)	$1/\phi$	4–15	4–15
Probability that a non-carrier individual would become colonized with CA-MRSA upon contact with a colonized individual	β_c	$1\times10^{-5}-1.5\times10^{-3}$	$1\times10^{-5}-2\times10^{-3}$
Probability that a non-carrier individual would become colonized with CA-MRSA upon contact with an infected individual	β_I	$1\times10^{-5}-1.5\times10^{-3}$	$1\times10^{-5}-2\times10^{-3}$
Average number of contacts per day	*c*	5–50	5–50

See REF. 44 for more information on multivariate uncertainty analysis. See the main text for other references. CA-MRSA, community-acquired meticillin-resistant *Staphylococcus aureus*; R_0, basic reproduction number.

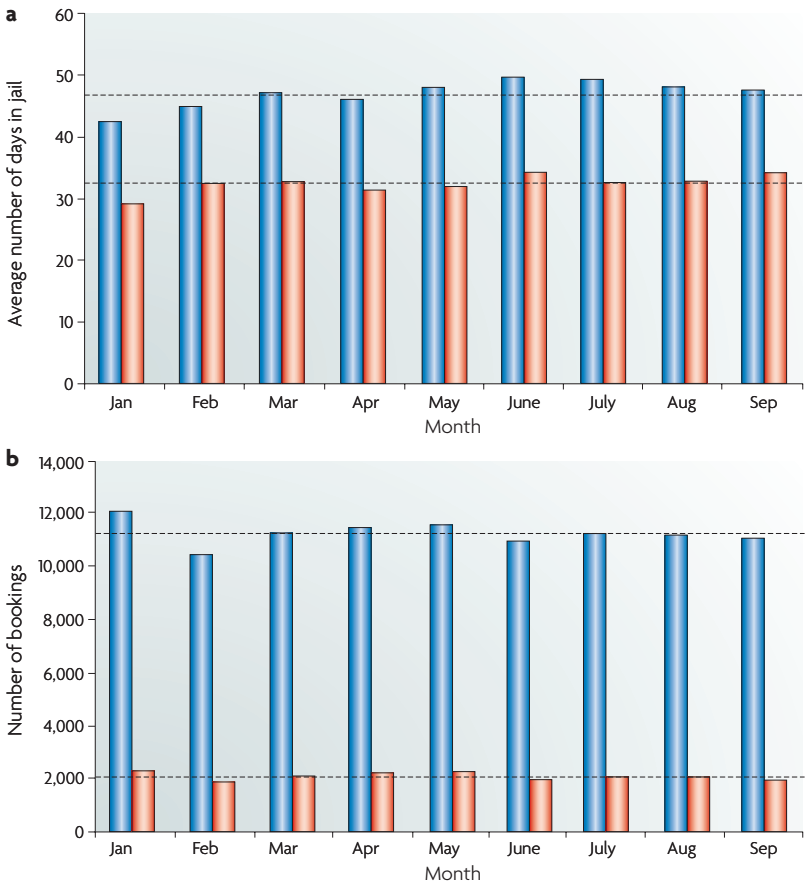

Figure 3 | **Model Parameters.** The average incarceration time in days (**a**) and number of inmates booked per month (**b**) from January 2002 to September 2002 for males (blue bars) and females (red bars). The dashed lines indicate the averages over the 9 months of the initial stage of the outbreak.

the build-up of gang factions; infected inmates were not segregated in the early stage of the outbreak; and inmates congregated during meal and recreation times.

Parameter estimation. As parameter values are never precisely known, the best approach for analysing transmission models is to estimate ranges for each parameter and conduct an uncertainty analysis[44–49]. Parameter ranges can be estimated from various sources including empirical data, expert opinion and/or best estimates from the literature. We have used all three approaches to parameterize the CA-MRSA model; parameter ranges are shown in TABLE 1.

Data from the LACJ were used to estimate ranges for most of the parameters in the model. Inmate population size, incarceration times (FIG. 3a) and booking rates (FIG. 3b) were calculated from gender-specific data. The probability that an inmate entered the jail already infected was calculated from surveillance data combined with data on gender, culture date and booking date. A case of CA-MRSA was defined as an inmate with a positive culture of MRSA from a wound or sterile site. The LACDHS assumed that inmates incarcerated for 5 days or less had been infected before booking and inmates incarcerated for 15 days or more had been infected within the jail[37]. These data were used to calculate the probability that an individual who entered the jail was already infected with CA-MRSA. Using these probabilities and booking data, we estimated that the number of infected male inmates entering the LACJ varied from ~1 to 60 per month, and the number of infected female inmates that entered the LACJ varied from ~1 to 19 per month. Assuming that, as with infection, colonization rates were low, we modelled the same variability for colonization as for infection. Strain transmissibility was estimated by fitting the model predictions to incidence data (FIG. 4). Infected individuals might be more infectious than colonized individuals as their bacterial load is higher. However, currently there are no data that quantify any differences in infectivity. Thus, we made the parsimonious assumption that transmissibility was similar for both infected and colonized individuals.

Expert opinion was used to estimate ranges for three parameters: the average time to decolonization; the proportion of colonized individuals who progress to infection; and the average number of contacts per day. Best estimates from the literature were used to estimate the range for the average time taken for colonized individuals to progress to

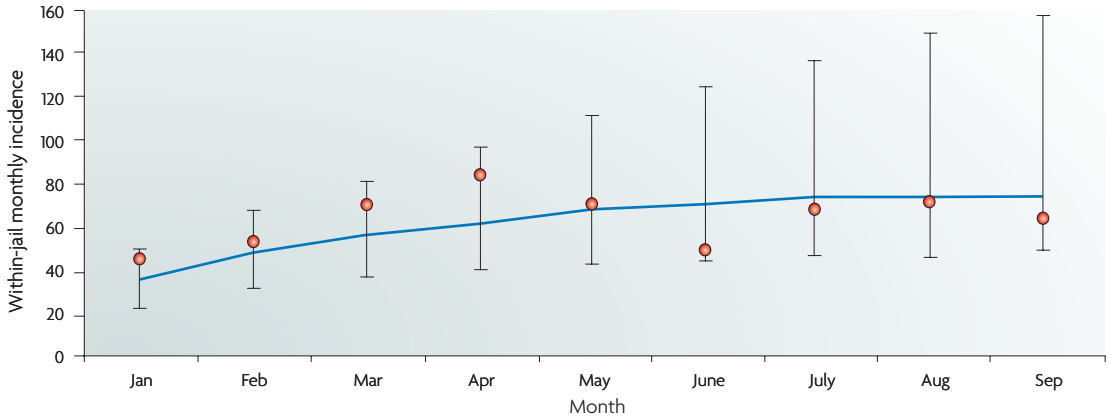

Figure 4 | **Results from the stochastic within-jail transmission model.** One thousand second-order Monte Carlo simulations were used to show the temporal evolution of the number of new community-acquired meticillin-resistant *Staphylococcus aureus* infections per month in the Los Angeles County Jail (male data only). Red spheres are the observed (that is, empirical) infection incidence data in 2002.

Uncertainty analysis
An analysis in which the variation in the value of an outcome variable is determined. The variability that is observed in the outcome variable is due to the uncertainty in estimating the exact value of each parameter in the model.

Box 1 | **Calculating the R_0**

Here, we show how to derive the mathematical expression for the basic reproduction number (R_0) and understand the formula that was derived in biological terms. To mathematically calculate an analytical expression for the R_0, we used a method that was developed by van den Driessche and Watmough[50]. Using the series of ordinary differential equations that define the model (FIG. 2b), we first created two 2×1 vectors, F and V, that represent the new and transported infections, respectively, into the two infected states.

$$\mathbf{F} = \begin{bmatrix} \frac{cS}{N}(\beta_C C + \beta_I I) \\ 0 \end{bmatrix} \quad \mathbf{V} = \begin{bmatrix} -C(\alpha + p\phi + \delta) \\ p\phi C - \delta I \end{bmatrix} \tag{1}$$

Next, we computed the Jacobian matrices of F and V at a disease-free equilibrium. These are denoted **F** and **V**, respectively.

$$\mathbf{F} = \begin{bmatrix} c\beta_C & c\beta_I \\ 0 & 0 \end{bmatrix} \quad \mathbf{V} = \begin{bmatrix} -(\alpha + p\phi + \delta) & 0 \\ p\phi & -\delta \end{bmatrix} \tag{2}$$

Finally, we calculated R_0 as the maximum eigenvalue of $\mathbf{F}(-\mathbf{V})^{-1}$:

$$\mathbf{F} \cdot (-\mathbf{V})^{-1} = \begin{bmatrix} \frac{c(\beta_C \delta + \beta_I p\phi)}{\delta(\alpha + p\phi + \delta)} & \frac{c\beta_I}{\delta} \\ 0 & 0 \end{bmatrix} \tag{3}$$

Thus:

$$R_0 = \frac{c\beta_C + p\phi c\frac{\beta_I}{\delta}}{\alpha + p\phi + \delta} \tag{4}$$

Next, we provide a biological interpretation of R_0. As shown in the flow diagram in FIG. 2a, a colonized individual can take three routes: decolonize; leave the jail colonized; or progress to the disease state. R_0 (see equation 4) is derived as a weighted average of the R_0s that occur if each of the different routes is taken.

$$R_0 = q_1 R_0^1 + q_2 R_0^2 + q_3 R_0^3 \tag{5}$$

Using the symbols from the ordinary differential equations that specify the model (FIG 2b), we can calculate: the fraction of colonized individuals that decolonize before they leave the jail;

$$q_1 = \frac{\alpha}{\alpha + p\phi + \delta} \tag{6}$$

the fraction of colonized individuals that leave the jail still colonized;

$$q_2 = \frac{\delta}{\alpha + p\phi + \delta} \tag{7}$$

and the fraction of colonized individuals that progress to infection while in the jail.

$$q_3 = \frac{p\phi}{\alpha + p\phi + \delta} \tag{8}$$

The number of new infections that are caused by individuals who take the first two routes is

$$R_0^1 = R_0^2 = \frac{c\beta_C}{\alpha + p\phi + \delta} \tag{9}$$

whereas the number of new infections that are caused by individuals that progress to disease is

$$R_0^3 = \frac{c\beta_C}{\alpha + p\phi + \delta} + \frac{c\beta_I}{\delta} \tag{10}$$

which is the sum of the number of new infections they cause from the colonized and infected states. Thus, the weighted average of the three R_0s is

$$R_0 = \left(\frac{\alpha}{\alpha + p\phi + \delta}\right)\left(\frac{c\beta_C}{\alpha + p\phi + \delta}\right) + \left(\frac{\delta}{\alpha + p\phi + \delta}\right)\left(\frac{c\beta_C}{\alpha + p\phi + \delta}\right) + \left(\frac{p\phi}{\alpha + p\phi + \delta}\right)\left(\frac{c\beta_C}{\alpha + p\phi + \delta} + \frac{c\beta_I}{\delta}\right) \tag{11}$$

which reduces to

$$R_0 = \frac{c\beta_C + p\phi c\frac{\beta_I}{\delta}}{\alpha + p\phi + \delta} \tag{12}$$

infection[7,20,38,40]. Notably, strains of CA-MRSA have been found to have more rapid doubling times and increased virulence in comparison with strains of HA-MRSA.

Temporal transmission dynamics of the CA-MRSA outbreak. We sampled ranges of all of the parameters using a statistical technique called Latin Hypercube Sampling[44] and then simulated a stochastic version of the deterministic transmission model to predict and reconstruct the incidence rates for the first 9 months of the outbreak (that is, we conducted a multivariate uncertainty analysis[44]). A stochastic model was used to incorporate the effect of chance events into the determination of incidence rates. Multivariate uncertainty analysis was used to determine the expected variability (that is, uncertainty) in the predicted incidence that was due to the uncertainty in estimating the values of the model's parameters. To conduct a multivariate uncertainty analysis, we first assigned a range of values to each parameter in the model (TABLE 1). These parameter ranges were then sampled 1,000 times and used to generate 1,000 scenarios of the model[44–49]. For a simple transmission model, a sample size of 1,000 is sufficient for sampling the entire parameter space[44]. The resulting predicted (that is, reconstructed) incidence for the first 9 months of the outbreak in 2002 had a high degree of variability (FIG. 4). The variability in the incidence is due both to chance effects and to the uncertainty in estimating parameter values. Interestingly, the reconstructed incidence data that were generated by the model quickly stabilized, even though inmates with CA-MRSA continued to enter the jail (FIG. 4). Mathematically, the level at which the incidence stabilized is described as the endemic equilibrium.

Estimating the severity of an outbreak

Transmission models can be used to calculate the basic reproduction number (R_0)[1]; R_0 specifies the average number of secondary infections that are generated by one infectious case at the beginning of the outbreak, when every person is susceptible. R_0 can be used to quantify the probability that an outbreak will develop into an epidemic, and also provide an indication of the expected severity of the outbreak or epidemic. R_0 has different interpretations if infected individuals can enter the population. If there is no immigration of infected patients, the interpretation of R_0 is simple. The value of R_0 indicates whether the outbreak will die out (this occurs if R_0 is less than 1) or become an epidemic (this occurs if R_0 is greater than 1). Incidence and prevalence increase as the value of R_0 increases. In a population in which there is immigration of infectious individuals (such as a jail or a hospital population), assessing the significance of the value of R_0 is more complex. In this case, even if R_0 is less than 1, the outbreak will not die out as long as the inflow of infectious or colonized individuals continues. If R_0 is greater than 1, the outbreak in the enclosed population can develop into a catastrophic outbreak.

An analytical formula for R_0 can be derived by a simple analytical solution of the three equations that specify the within-jail simple CA-MRSA transmission model[1]; see BOX 1 for the mathematical derivation of R_0 and a biological interpretation of this formula. The analytical expression is shown in equation 4 of BOX 1. The definitions of the parameters that are represented as symbols in the R_0 equation are shown in TABLE 1. R_0 is a threshold parameter that provides an estimate of within-jail transmission. By conducting a multivariate uncertainty analysis of R_0 (using equation 4, BOX 1, Latin Hypercube Sampling[44], a sample size of 1,000 and the parameter ranges given in TABLE 1), 1,000 values of R_0 were calculated. The calculated frequency distribution of the 1,000 R_0 values for the men's facility in the LACJ is shown in FIG. 5a; the median value of R_0 from this distribution is 0.60 (interquartile range (IQR) of 0.34–0.97). R_0 was 0.55 (IQR of 0.30–0.90) in the women's facility.

By using the frequency distribution shown in FIG. 5a, the probability that the within-jail transmission was not high enough to sustain the outbreak could be determined. This probability was calculated by dividing the number of R_0 values that were less than one by the sample size. This probability was 0.78 (FIG. 5a) in the men's facility and 0.80 (data not shown) in the women's facility in the LACJ. As there was a high probability that R_0 was less than 1 in both facilities, it was concluded that within-jail transmission of CA-MRSA was not high enough to sustain the outbreak. Therefore, the on-going outbreak was maintained because of the continuous inflow into the jail of colonized and infected individuals from the community.

Catastrophic outbreaks: conditions and effects

Transmission models can be used to determine the conditions that will change an outbreak in a closed population into a catastrophic outbreak. If the value of R_0 is less than 1 an outbreak can be large, but it is not catastrophic. For example, although there have been more than 8,000 CA-MRSA infections in the LACJ this outbreak is not catastrophic, as the value of R_0 in both the men's and women's facilities was less than one. The critical parameter values (at which R_0 becomes equal to 1) can be determined by changing the values of the parameters in the R_0 formula. The outbreak has the potential to become catastrophic when these critical parameter values are exceeded, as at these parameter values the value of R_0 will increase to become greater than 1. A stochastic version of the deterministic transmission model can then be simulated, using a series of parameter values that are greater than their critical values, to predict the potential incidence and prevalence levels of catastrophic outbreaks.

As the outbreak in the LACJ was not catastrophic, the model predicts that the within-jail prevalence of infection was probably low (significantly less than 5%; FIG. 5b) and that only a few infected inmates were released per month: there were a median of 72 (IQR of 46–150) infected men (FIG. 5c) and 21 (IQR of 13–44) infected women (data not shown). At the beginning of the outbreak, male and female inmates were incarcerated for 47 and 33 days on average, respectively (TABLE 1), and these parameter values were used in the model. If the model is used to calculate the incarceration times that are required so that R_0 is equal to 1, then

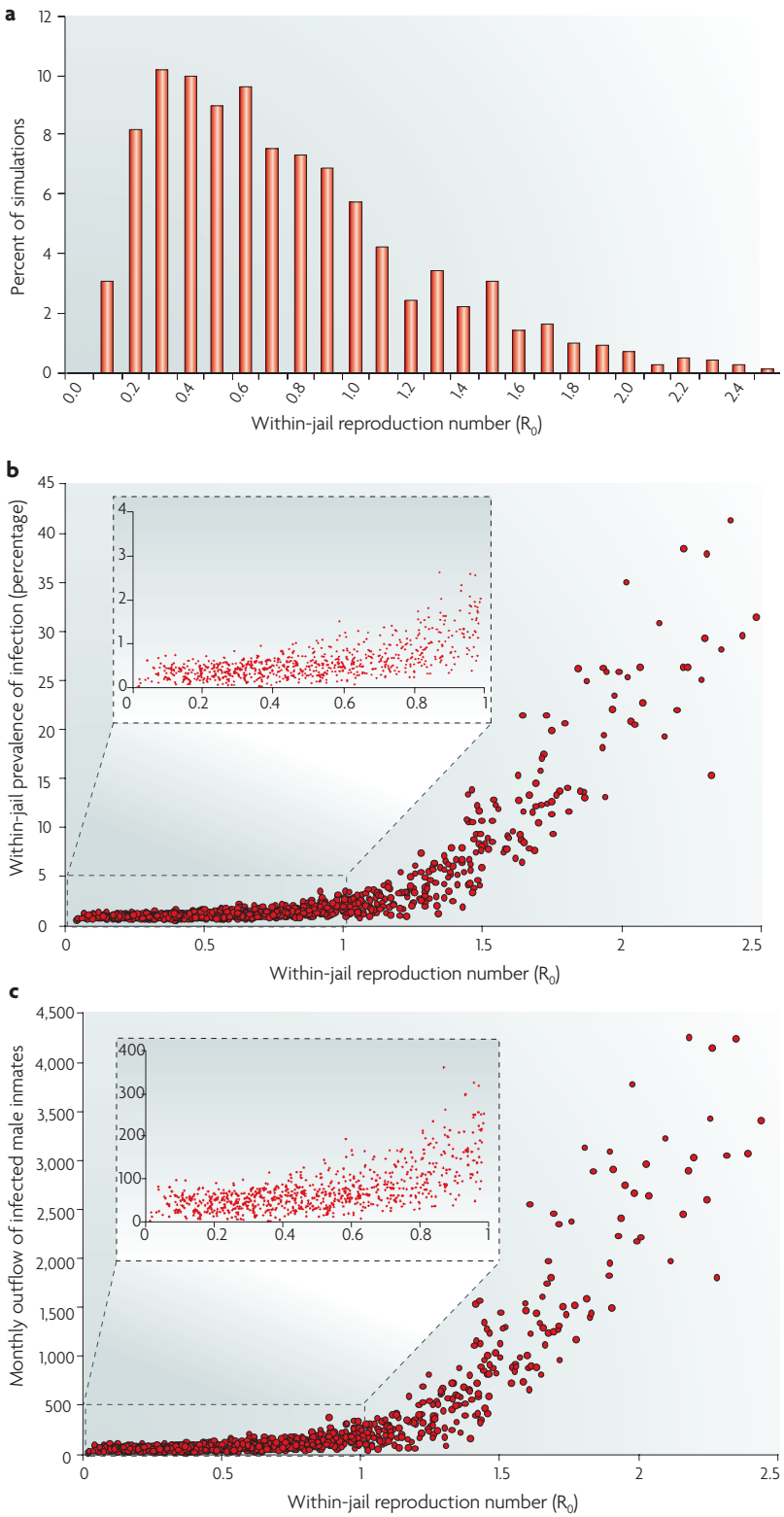

Figure 5 | **R_0 analysis. a** | Frequency distribution of the basic reproduction number (R_0) for male inmates in the Los Angeles County Jail; this distribution was determined by a multivariate uncertainty analysis[44] of the R_0 formula (see equation 4, BOX 1) and by using the parameter values shown in TABLE 1. **b** | The within-jail infection prevalence for male inmates as a function of R_0 (from multivariate uncertainty analysis results using the stochastic version of the deterministic model). **c** | The monthly outflow of infected male inmates as a function of R_0 (from multivariate uncertainty analysis results using the stochastic version of the deterministic model).

these values are found to be substantially larger than the actual incarceration times — the critical incarceration time was calculated to be 83 days for male inmates and 60 days for female inmates (FIG. 6a). The conclusion from this analysis is that if inmates had been incarcerated for longer than these critical incarceration times then the value of R_0 for the outbreak would have been greater than 1, and the within-jail prevalence of infection (FIG. 5b), incidence of infection (FIG. 6b) and incidence of colonization (FIG. 6b) would have risen to catastrophic levels. Under these catastrophic conditions, the prevalence of infection within the jail would have increased to approximately 40% (FIG. 5b), and several thousand colonized and infected inmates would have been released into the community each month (FIG. 5c). In conclusion, these stochastic simulations show that the LACJ outbreak was large but not catastrophic, and would have been substantially worse if inmates had been incarcerated for more than 2–2.5 months.

Designing interventions for controlling outbreaks

It is straightforward to use transmission models to design effective interventions for controlling outbreaks and epidemics if there is no immigration of infected individuals. The necessary level of the interventions can be determined by identifying which parameter values need to be adjusted so that R_0 is less than 1 (REF. 1). For example, if the contact rate had been high (and R_0 had been greater than 1) then quarantine measures could have been enforced to decrease the contact rate to a level at which the value of R_0 became less than 1. The situation is more complex when infected individuals can immigrate into the population. Under these conditions the outbreak can be maintained because: R_0 is greater than 1 and therefore transmission within the population is high enough to maintain the outbreak without any immigration of infected individuals; R_0 is less than, but close to, 1 and therefore transmission is high, but a small inflow of infectious individuals is necessary to maintain the outbreak; or R_0 is substantially less than 1 and therefore transmission is low and a large inflow of infectious individuals is necessary to maintain the outbreak.

If transmission within the population is sufficient to maintain the outbreak without any immigration of infected individuals, then the interventions for controlling the outbreak should concentrate on decreasing transmission within the population (that is, the jail or hospital) to try to decrease R_0 from greater than 1 to less than 1. For example, one could treat the active cases to cure infections and treat the asymptomatic cases to ensure that decolonization decreases transmission; the degree to which this reduces transmission would depend on the percentage of cases that receive treatment. If R_0 is less than, but close to, 1 and therefore transmission is high, but a small inflow of infectious cases is necessary to maintain the outbreak, the control interventions should focus on decreasing transmission within the population. However, they should also focus on decreasing or preventing the inflow of infectious individuals, for example, by screening individuals that enter the population and

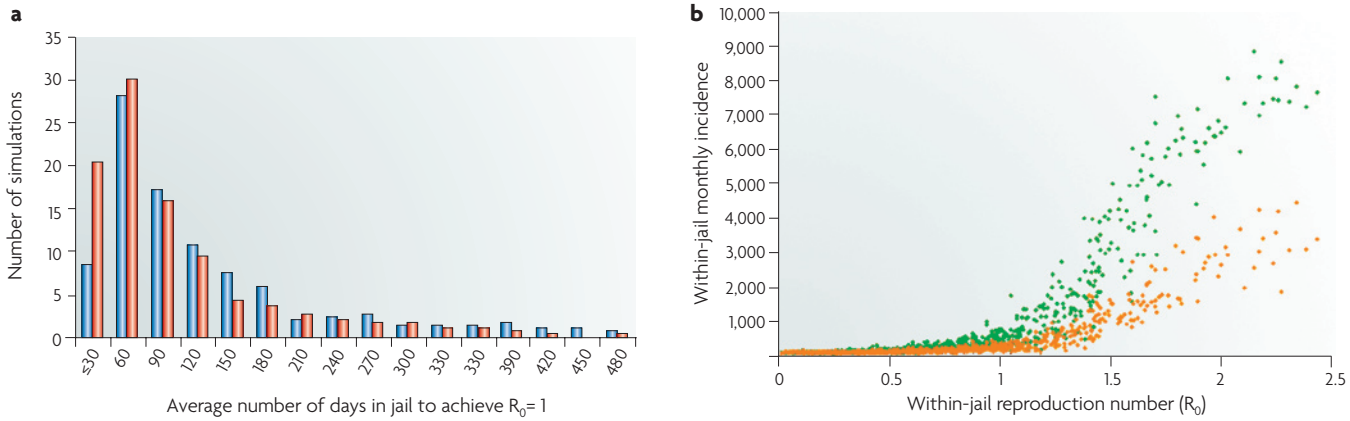

Figure 6 | **Results from the deterministic and stochastic versions of the within-jail transmission model.** **a** | Frequency distribution of the critical values for the average incarceration times that ensure that the basic reproduction number (R_0) equals 1; critical values were calculated for male inmates (blue bars) and female inmates (red bars) using the R_0 formula (see equation 4, BOX 1) and the parameter values shown in TABLE 1. **b** | Shows the within-jail incidence of colonization (green data points) and infection (orange data points) for male inmates as a function of R_0 (from multivariate uncertainty analysis results using the stochastic version of the deterministic model).

treating or isolating colonized and infected individuals. If R_0 is substantially less than 1 and therefore transmission is low and a large inflow of infectious individuals is necessary to maintain the outbreak, the control interventions should concentrate mainly on trying to decrease and prevent the inflow of infectious cases.

As R_0 was found to be substantially less then 1 in the LACJ, and therefore a large inflow of infectious individuals from the community sustained the CA-MRSA outbreak, the most effective control intervention at the beginning of the outbreak (in 2002) would have been to decrease or prevent the inflow of infectious individuals from the community. At this stage, the outbreak could have been controlled if a large-scale highly effective screening programme of entering inmates had been developed to identify both colonized and infected individuals who could then have been treated and/or quickly isolated. However, as the LACJ books hundreds of new inmates each day (TABLE 1), this intervention strategy would not have been feasible for economic and logistical reasons.

Since the autumn of 2002, several interventions (including treatment, hygiene control and intensified surveillance) have been implemented within the jail to try to control the outbreak. The spread of MRSA is hard to control in a correctional facility because of the crowded living conditions, suboptimal hygiene and the constant high turnover of inmates. Furthermore, inmates' poor mental health, lack of education and other behavioural problems limit the necessary observance of infection-control and hygiene practices[41]. Therefore, not surprisingly, the LACJ outbreak is continuing and might be contributing to the continuing rise of CA-MRSA in Los Angeles County. Even if it becomes possible to control the outbreak by decreasing within-jail transmission, it will be essential to stop the continual re-introduction of the pathogen. To indicate what interventions would have been effective in controlling the LACJ outbreak once it had been established it would be necessary to add additional complexities into the simple transmission model, such as the treatment of active cases, screening programmes, hygiene control and quarantine. Once these interventions are included in the model a sensitivity analysis could be performed to identify which of these interventions would have been most effective in the past, and would be most effective currently, to reduce within-jail transmission.

Conclusions

Our simple model is only applicable to the first 9 months of the LACJ outbreak, but it could now be expanded to include greater complexity and used to analyse the later stages of the outbreak. The effects of treatment, intensified surveillance, heterogeneity in incarceration time, recidivism and the time variation (possibly including seasonality) in the number of colonized and infected inmates that are admitted, as well as the role of environmental contamination, could be included. Although the LACJ has a high recidivism rate, we did not include recidivism in the model as we were only modelling the first nine months of the outbreak and recidivism, over this time period, is assumed to be low. Excluding recidivism from long-term studies would probably lead to an under-estimation of the magnitude of within-jail transmission, because inmates who are re-admitted to the jail with an active CA-MRSA infection that was acquired during an earlier incarceration would be counted as cases of CA-MRSA acquired in the community, rather than as cases of CA-MRSA acquired at the LACJ.

We have explained how to construct a simple transmission model, and how to use the model as a tool to understand the dynamics of an outbreak of an emerging pathogen by illustrating that simple transmission models can provide significant non-intuitive insights into the dynamics of infectious diseases. Using the example of an ongoing CA-MRSA outbreak in a correctional

Simulation
An analysis of a model that is carried out with a computer. The model is programmed using a computer language and then run using specific parameter values. Each run of the model is called a simulation, or a scenario.

facility, we have reconstructed the outbreak dynamics, quantified the severity of the outbreak, identified the conditions (that is, the length of incarceration time) that would have caused a catastrophic outbreak and estimated the potential magnitude of a catastrophic outbreak. These analyses have revealed that the LACJ outbreak, although large, is not catastrophic, but would have become catastrophic if inmates had been incarcerated for more than 2–2.5 months. The modelling also revealed that the outbreak was only sustained because of the continuous inflow of colonized and infected individuals from the community, and not by within-jail transmission. Therefore, the model has enabled us to identify where to focus an effective intervention strategy for controlling the outbreak. More complex models can now be developed, using the simple transmission model as a platform, so that additional quantitative insight can be gained into outbreak dynamics.

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Acknowledgements

The authors acknowledge J. Boscardin, R. Breban, N. Freimer, V. Supervie, R. Vardavas, D. Wilson and all the staff at the Los Angeles County Jail and the Los Angeles County Department of Public Health. T. Pylko is also acknowledged for helpful clinical discussions during the course of this research. Financial support was received from the National Institute of Allergy and Infectious Diseases in the National Institutes of Health (R01 AI04 935).

Competing interests statement

The authors declare no competing financial interests.

DATABASES

Entrez Genome Project: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj
Staphylococcus aureus

FURTHER INFORMATION

Sally Blower's homepage:
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