Transmission Dynamics of Epidemic Methicillin-Resistant Staphylococcus aureus and Vancomycin-Resistant Enterococci in England and Wales

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A simple epidemiological framework for the analysis of the transmission dynamics of hospital outbreaks of epidemic methicillin-resistant Staphylococcus aureus (EMRSA) and vancomycin-resistant enterococci (VRE) in hospitals in England and Wales is presented. Epidemic strains EMRSA-15 and EMRSA-16 are becoming endemic in hospitals in the United Kingdom, and theory predicts that EMRSA-15 and EMRSA-16 will reach respective endemic levels of 158 (95% confidence interval [CI], 143–173) and 116 (95% CI, 109–123) affected hospitals with stochastic fluctuations of up to 30 hospitals in each case. An epidemic of VRE is still at an early stage, and the incidence of hospitals newly affected by VRE is growing exponentially at a rate \( r = 0.51 \text{/year} \) (95% CI, 0.48–0.54). The likely impact of introducing surveillance policies if action is taken sufficiently early is estimated. Finally, the role of heterogeneity in hospital size is considered: “Super-spreader hospitals” may increase transmission by 40%–132% above the expected mean.

The rapid increase in the frequency with which multiply resistant organisms are recovered from patients in clinical environments presents new challenges to infection control [1–3]. The number of hospitals in England and Wales affected with epidemic strains of methicillin-resistant Staphylococcus aureus (EMRSA) has continued to rise from 40/month in 1993 to >100/month in 1997 [4]. In the United States, the pattern of emergence has been similar: the case resistance frequency increased from 2% in 1975 to 35% in 1996 [5]. Vancomycin-resistant enterococci (VRE) have recently emerged as nosocomial pathogens, which, in the absence of available therapies, also pose a serious threat to the welfare of patients in hospitals and long-term care facilities in the United Kingdom and other countries [6, 7]. Reports of the extensive spread of vancomycin-resistant (heteroresistant) MRSA strains in Japanese hospitals [8, 9], after 30 years of vancomycin use as the drug of choice for the treatment of MRSA, are of particular concern in light of observations that the high-level VanA vancomycin resistance genes can be transferred from enterococci to staphylococci in vitro [10].

Although colonization and infections remain primarily restricted to hospitals, the presence of both MRSA and VRE in communities has been demonstrated [11–13]. The transfer of patients between hospitals and back into the community may therefore provide a mechanism for the transmission of multiply resistant organisms (or genetic information) and propagation of an epidemic [14, 15]. However the extent to which long-term care facilities and the community at large form reservoirs for further transmission remains largely unknown [13, 16]. Transmission of MRSA in and among hospital settings has been well documented [14, 17, 18]. Since enterococci form a natural part of the human enteric flora, most infection had, however, been attributed to endogenous sources. Recent studies have shown that patient-to-patient direct transmission and indirect transmission via contact with the hands of health care workers are important transmission routes [7, 19–22]. Direct and indirect transmission routes become even more important when patients and staff are moved between institutions [14, 23], and it is here that surveillance opportunities to control the spread of outbreaks arise [5, 7, 18, 24, 25].

In many instances, hospital outbreaks have proved difficult to eradicate, requiring careful surveillance and effective infection control measures [20, 26, 27]. The longer an outbreak persists, the greater the likelihood that it may spread to other hospitals or into the community and the greater the economic cost [28]. Reductions in the duration of outbreaks and the transfer of colonized or infected patients are therefore of the utmost importance during the early stages of an epidemic, when greatest impact can be achieved. Here we describe a theoretical framework to study the introduction and spread of multiply resistant bacteria between hospitals. Using the model, we analyze available data for the spread of EMRSA and VRE in England and Wales and in New York City and predict the likely effects of surveillance policies on reducing the magnitude of the current EMRSA epidemic.

Methods

Hospitals are classified as either unaffected (outbreak-free and hence susceptible) or having a confirmed outbreak (infectious).
Outbreaks may arise as a result of de novo introduction (from sources such as nursing homes) or selection of resistant organisms (at a per-hospital rate $\sigma$) or by the transfer of colonized patients and staff between hospitals. Once an outbreak is confirmed, it is assumed to persist for an average duration $D$ time units (where $\gamma = 1/D$ is the eradication rate, which may depend on hospital size, surveillance procedures, and other factors). Hospitals are assumed to return to an outbreak-free state and are no more or less likely to suffer further outbreaks. This is a reasonable first approximation, although it does not take into account implementation changes in infection control after an outbreak has been contained. Since $D$ measures the average outbreak duration, some hospitals may have outbreaks lasting much longer than $D$ and can therefore be classified as endemic. If the total number of hospitals is $N$ and remains fixed for the duration of the epidemic, and $y(t)$ is the number of hospitals affected by outbreaks at time $t$, then $y(t)$ is determined by the differential equation

$$dy(t)/dt = a(N - y) + \beta y(N - y) - \gamma y$$ \hspace{1cm} (1)$$

The transmission parameter $\beta$ is equal to the prevalence of colonization in the affected (source) hospital multiplied by the patient transfer rate between hospitals and the probability that a colonized admission will induce an outbreak in the unaffected hospital. Estimation of the transmission parameter $\beta$ requires careful analysis of patient records, transfer details, and microbiologic techniques. This form of transmission is known as “mass-action” and assumes that every hospital interacts with every other. In reality, hospitals will have contacts with only a number of other hospitals depending on size, location, and patient mobility constraints. The true transmission parameter should therefore be a function of the number of hospitals, $\beta(N)$, although for analytical simplicity, correction terms will not be considered.

The rate of new introductions or selection of new symptomatic infections that trigger an outbreak ($aN$) compared with the transmission rate between hospitals ($\beta N$) gives qualitative differences in the shape of the epidemic. At one extreme, when there is no transmission at all and no affected hospitals at time $t_0$, then

$$y(t) = K[1 - \exp\{-(\sigma + \gamma)(t - t_0)\}]$$ \hspace{1cm} (2)$$

with carrying capacity $K = aN(\sigma + \gamma)$. During the early stages, the number of affected hospitals will grow linearly at a rate $aN$ with time, until the rate of new outbreaks is balanced by the eradication rate. Where the number of affected hospitals is growing faster than linearly (e.g., figure 1A), transmission between hospitals can be implicated. At the other extreme, where there are no de novo introductions ($aN = 0$), $r = \beta N - \gamma$ and $K = r/\beta$, the number of affected hospitals takes the form

$$y(t) = (K\theta\exp[\theta(t - t_0)])/(\theta\exp[\theta(t - t_0)] + K - y_0).$$ \hspace{1cm} (3)$$

For the pure transmission process, it is customary to define a reproductive number $R_0$, equal to the number of secondary hospitals affected by outbreaks from a single hospital when all others are susceptible. For the logistic model, $R_0 = \beta ND$, and hence the growth rate $r$ and carrying capacity $K$ are

$$r = (R_0 - 1)/D,$$

$$K = N(1 - 1/R_0).$$ \hspace{1cm} (4)$$

Estimation of $r$ and $K$ can therefore yield valuable information on duration of outbreak ($D$) and the magnitude of transmission ($R_0$). During the early stages of an epidemic, equation (3) has an exponentially increasing form in which the growth rate is determined by the outbreak duration, $D$, and the number of secondary hospital outbreaks, $R_0$. As the epidemic progresses, more and more hospitals become affected and it becomes harder to find unaffected hospitals susceptible to transmission (i.e., a form of density-dependence). Eventually an endemic equilibrium is reached (i.e., the carrying capacity, $K$), determined solely by the reproductive number, $R_0$.

The true solution is likely to lie between these two extremes. During the very early emergence phase, selection of resistant organisms at individual hospitals will maintain resistance at very low levels (with typically $\sigma ND$ hospitals affected). Without transmission, these sporadic outbreaks may persist for long periods with relatively few affected hospitals. Once transmission becomes important, the epidemic will take off exponentially, and by the time concern is raised at the growing numbers of outbreaks, equation (3) will provide an accurate description of the underlying dynamics. Therefore, one of the key predictions of the theory is a long period of relatively few affected hospital outbreaks maintained by selection, followed by a rapidly increasing transmission phase and a slow approach to equilibrium.

If the dynamics of the epidemic are sufficiently rapid, during the exponentially increasing phase, stochastic fluctuations about the exact solution are not significant (although changes in the time taken to reach this phase may be). When the number of affected hospitals nears the endemic carrying capacity, $K$, stochastic fluctuations become important. A stochastic version of the model shows that the probability of $i$ hospitals being affected, $\pi_i$, is approximately normally distributed with mean $<(K) = K - 1/(R_0 - 1)$ and variance $\sigma^2 = (K)/rD$ [29].

The introduction of active surveillance policies can be very effective in limiting both the number and the severity of outbreaks. Screening new patients, coupled with vigorous infection control practices, can reduce both the transmission parameter $\beta$ and outbreak duration $D$. If a proportion $p$ of hospitals implement surveillance, giving reductions of $\beta^p$, then $\beta(p) = \beta(1 - pq)$ and $D(p) = D(1 - pq)$. Reductions in either $\beta$ or $D$ will be equally effective in reducing the long-term carrying capacity. However, reductions in $\beta$ produce greater short-term reductions in growth rate and lower incidences of new outbreaks.

**Results**

*Epidemic MRSA in England and Wales.* EMRSA are colonizing hospital patients throughout England and Wales [30]. The number of hospitals reporting the 2 most common strains,
Figure 1.  A. Hospitals affected each month by EMRSA-3, EMRSA-15, or EMRSA-16 [4]. Curves show model predictions for parameters shown in table 1. For EMRSA-3, mean and 95% confidence interval calculated from data are shown. B. Equilibrium probability of i hospitals being affected, \( p_i^* \), gives indication of likely fluctuations once EMRSA becomes endemic. Exact results are in excellent agreement with normal approximation (see [29] for further details).
EMRSA-15 and EMRSA-16, have risen from little over 10 each per month at the beginning of 1993 to >100 per month in 1997 [4] (figure 1A). By contrast, outbreaks of strain EMRSA-3 remain at relatively low equilibrium levels, suggesting that \( \sigma ND \approx 14.4 \) hospitals (95% confidence interval [CI], 4.3–24.5) with only limited transmission. Recent outbreaks of EMRSA-15 have been widely spread, whereas EMRSA-16 is more concentrated in the South East and Thames regions. For EMRSA-15 and EMRSA-16, de novo introductions are assumed to be low (\( \sigma N = 0 \)), and the model has three unknown parameters: \( r, K \) and \( y_0 = \chi(1993) \). With use of maximum likelihood techniques (see [31]), parameter estimation gives broadly similar

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>EMRSA-15</th>
<th>EMRSA-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hospitals</td>
<td>( N )</td>
<td>400</td>
<td>400*</td>
</tr>
<tr>
<td>Carrying capacity</td>
<td>( K ) (hospitals)</td>
<td>158 (143–173)</td>
<td>116 (109–123)</td>
</tr>
<tr>
<td>Growth rate</td>
<td>( r ) (year)</td>
<td>1.08 (0.94–1.20)</td>
<td>1.40 (1.21–1.59)</td>
</tr>
<tr>
<td>Initial outbreaks</td>
<td>( y_0 = \chi(1993) )</td>
<td>13.2 (10.8–15.6)</td>
<td>12.7 (10.7–14.7)</td>
</tr>
<tr>
<td>Reproductive number</td>
<td>( R_0 )</td>
<td>1.66</td>
<td>1.41*</td>
</tr>
<tr>
<td>Outbreak duration</td>
<td>( D ) (days)</td>
<td>219</td>
<td>106*</td>
</tr>
<tr>
<td>Transmission parameter</td>
<td>( \beta ) (hospitals/year)</td>
<td>0.0068</td>
<td>0.0120</td>
</tr>
<tr>
<td>Fluctuations</td>
<td>( \theta ) / ( K )</td>
<td>1.54</td>
<td>2.50</td>
</tr>
<tr>
<td>Maximum likelihood ( \chi^2 )</td>
<td>( \chi^2 )</td>
<td>42.34</td>
<td>24.03</td>
</tr>
<tr>
<td>Goodness of fit</td>
<td>( P )</td>
<td>0.703</td>
<td>0.998</td>
</tr>
</tbody>
</table>

- * If \( D_o = 219 \) days, \( N = 253 \) and \( R_0 = 1.84 \).

subset of 21 of the early samples indicated two distinct resistance patterns (\( VanA \) and \( VanB \)) and revealed evidence of in vivo transfer of resistance characteristic of a highly mobile genetic element. The rapid transfer of resistance between different strains of enterococci may imply that the transmission dynamics for the various resistance patterns can be combined, implying that the transmission parameter, \( \beta \), for VRE transfer between hospitals may include both genetic transfer (within-host) and clonal transmission (between-hosts) components. Once introduced into a hospital, VRE has proved very difficult to eradicate [6, 7, 22, 26]. If the outbreak duration is longer than the length of the original study, \( \chi(t) \) is approximately the cumulative number of hospitals with VRE. Maximum likelihood methods give predicted growth rate \( r = 2.3 \) year \( (95\% \ CI, 2.1–2.5) \) with a carrying capacity \( K = 59 \) hospitals \( (95\% \ CI, 39–79) \).

**Emergence of VRE in England and Wales.** The emergence of VRE in hospitals in the United Kingdom is of particular concern, since vancomycin use tends to be restricted to the treatment of MRSA and other multiply resistant infections. VRE was first detected in the United Kingdom in 1987 and had been found in a total of 71 hospitals by the end of 1995. During 1995, VRE was detected in 47 hospitals in the United Kingdom, including 27 where it had not been found previously [4]. The number of hospitals reporting VRE for the first time has been growing exponentially (figure 3B), suggesting transmission, although no single epidemic strain has been identified. This may be a result of the highly mobile resistance element being transmitted between hosts (and subsequently to other hospitals) or the fact that transfer of epidemic strains between hospitals is still very localized. Maximum likelihood estimates give a growth rate \( r = 0.51 \) year \( (95\% \ CI, 0.48–0.54) \); however, the carrying capacity, \( K \), remains bounded only from below \( (95\% \ CI, 147–400) \) because the epidemic is at a very early stage. VRE is increasing with a growth rate 50% of that of EMRSA, suggesting that intervention policies can be equally effective.

**Heterogeneity in hospital size.** Having identified transmission as an important factor in the spread of epidemic strains of MRSA and VRE, it is essential to try to characterize the extent to which heterogeneity influences the levels of transmission and hence the scale of the epidemic. National Health Ser-
Figure 2.  

A. Effect of reductions of 10%, 20%, and 30% in transmission parameter $\beta$, and outbreak duration $D$, on incidence $\frac{dy}{dt}$ of EMRSA-15 during epidemic.  

B. Predicted number of EMRSA-15 outbreaks, $n(t) = \int_{t_{\text{in}}}^{t_{\text{end}}} \frac{dy}{dt} dt / D$, during period 1993–1998 as function of percentage of hospitals implementing surveillance, $p$. Surveillance begins in 1993 and is assumed to affect reductions of 10%, 20%, and 30% in transmission parameter, $\beta$, and duration of outbreak, $D$, in those hospitals with surveillance.
vice (NHS) trusts in England and Wales are classified according to mean number of beds available during a financial year and by regional organization (figure 4A). The regional distributions of NHS trusts by size are broadly similar, although there are notable exceptions in the North West and West Midlands. When regions are grouped together, maximum likelihood techniques show that the probability distribution \( p(x) \) for NHS trusts in England and Wales according to number of available beds \( x \) is accurately described by a truncated normal distribution with mean \( \mu = 432.5 \) (95% CI, 378.7–486.3) and variance \( \sigma^2 = 410.7 \) (95% CI, 373.5–446.6). The corresponding mean number of available beds per trust is \( \langle x \rangle = 542.7 \) with variance \( \sigma_x^2 = \langle x^2 \rangle - \langle x \rangle^2 = 108,862 \) (figure 4B).

Adapting the simple transmission framework of equation (1) to mirror heterogeneity in hospital size leads to derivations for the hospital reproductive ratio, \( R_0 \), as a function of hospital size \( x \) of the form \( R_0(x) = R_0(1 + \sigma^2/\langle \sigma \rangle^2) \). The reproductive number can therefore be significantly larger than the simple mean behavior if the standard deviation \( \sigma \) is greater than the mean \( \langle x \rangle \), as it is for the NHS trusts in England and Wales. If both transmission and outbreak duration scale with hospital size, \( R_0(x) = R_0 \langle x \rangle / \langle x \rangle^3 \). This is one way of saying that so-called super-spreaders (large hospitals) can play a disproportionate role in the maintenance of transmission; their importance scales as \( x^2 \) or \( x^3 \), not simply \( x \). The distribution of NHS trusts by number of available beds gives \( R_0(x) = 1.39R_0 \) when outbreak duration remains constant or \( R_0(x) = 2.32R_0 \) when outbreak duration increases with hospital size. In other words, heterogeneity in hospital size, with large hospitals, acts to increase the net effective transmission potential of the drug-resistant infections.

**Discussion**

The continued spread of multiply resistant organisms throughout our hospitals poses a serious threat to patient welfare. Moreover, the associated costs of controlling outbreaks of infection present a considerable burden on health care resources. Understanding the transmission dynamics of the spread of such organisms is a challenge that promises to yield
Figure 4.  
A. Distribution of National Health Service (NHS) trusts in England and Wales by mean number of available beds in financial year to 1997 and organizational region.  
B. Combined distribution and fitted values using truncated normal distribution, $\chi^2 = 20.0$ ($P = .13$).
great benefits for both planning and implementation of surveillance and control measures. The spread of epidemic strains of MRSA throughout hospitals in the United Kingdom is reaching endemic levels, with outbreaks of strains EMRSA-15 and EMRSA-16 now being reported in >100 hospitals each per month. Furthermore, the incidence of new hospitals reporting VRE outbreaks is growing exponentially in a characteristic epidemic manner. The introduction of careful surveillance and eradication policies has been shown to be effective in reducing both the duration and severity of outbreaks of MRSA and VRE, and it is during the rapid exponential phase of an epidemic that intervention policies can have greatest effect.

A simple epidemiologic framework is used to study the spread of MRSA and VRE. We assume that the spread is a result of either de novo outbreaks (which may be due to selection or contact with an environmental source such as nursing homes) or transmission from other affected hospitals. When the total number of hospitals remains constant, the model reduces to a logistic equation with immigration. Theory predicts that de novo introductions can maintain outbreaks of MRSA and VRE at relatively low levels for long periods. After transmission begins (as a result of staff and patient transfer between hospitals), the number of affected hospitals will grow exponentially with a growth rate $r$. Eventually, the number of susceptible hospitals falls and the number of outbreaks tends monotonically to an endemic carrying capacity $K$. Transmission can be characterized by the reproductive number $R_0$, which defines the number of secondary outbreaks induced by a single affected hospital outbreak when all other hospitals are unaffected.

Two strains of MRSA are approaching endemic equilibrium, while transmission of a third (EMRSA-3) has yet to become significant. This observation suggests that the relative contributions of de novo outbreaks is much smaller than that of transmission in the overall spread of MRSA. EMRSA-15 and EMRSA-16 have broadly similar reproductive numbers, although the spread of EMRSA-16 has remained relatively localized in the South East. This localization has given rise to a higher growth rate and greater transmission. The number of hospitals affected by strains EMRSA-15 and EMRSA-16 are now close to their respective carrying capacities $K_{15} = 158$ and $K_{16} = 116$. Once the endemic state is reached, stochastic fluctuations become important, particularly where intervention policies are concerned. Theory predicts that the number of hospitals affected by outbreaks can fluctuate from the carrying capacity by up to 30 hospitals for either strain. When surveillance measures are introduced, stochastic fluctuations may lead to decreases in the number of outbreaks, which, if $<30$, need not be associated with success. Conversely, increases in the number of outbreaks need not be associated with failure.

The associated costs of managing hospital outbreaks are considerable, with increases in morbidity, mortality, and patient stay. One study showed that the control of a single MRSA outbreak produced savings of £630,000 [32]. In another study, each patient affected by MRSA was found to incur additional costs of £2500 [28]. Intervention policies can reduce transmission and outbreak duration. Reductions in transmission will have greatest short-term effect, producing longer epidemics with lower incidence. Although surveillance measures may be costly, the cost savings in prevented outbreaks may be considerable, depending on implementation levels and efficacy. For example, if 25% of hospitals had implemented infection control programs resulting in reductions of 30% in transmission, >100 EMRSA-15 outbreaks might have been prevented in the period 1993-1998.

In New York City, the rapid dissemination of VRE among the 81 hospitals provides some indication of possible transmission routes [33]. Unlike epidemic MRSA, no single strain was responsible for the outbreak, and more important, in vivo transfer of a highly mobile transposable element was implicated. In the United Kingdom, 5 epidemic strains of Enterococcus faecium have been identified [6]. The most common strain, EVREM3, has been primarily restricted to the London region and had been detected in 15 hospitals by the end of 1995 [6]. The number of affected hospitals is growing exponentially, with a growth rate $r = 0.51$/year, which is comparable with that of EMRSA, although estimation of the eventual carrying capacity is not yet possible. Some outbreaks have proved hard to eradicate, and since $R_0 = 1 + rD$, should outbreaks last ~1 year, then $R_0 = 1.5$, and about one-third of hospitals will be endemic affected by VRE outbreaks. Furthermore, since $rD$ is a measure of the expected fluctuations, the predicted variance will be about double this number.

Heterogeneities in the location and size of hospitals may have considerable influence on the transmission of multiply resistant organisms between hospitals. The spread of VRE appears to be influenced by spatial factors, particularly during this early phase. For VRE, the transmission model is perhaps currently more applicable on regional scales, where the total number of hospitals $N$ may be ~200. Once strains become more widely disseminated, as in the case of EMRSA, spatial considerations become less important. Hospitals in England and Wales show considerable variations in size. Precise classification is difficult, because bed availability is collated by NHS trust rather than at a hospital level. When size heterogeneities are included, theory demonstrates how the reproductive number becomes a function of both the mean number of beds, $\langle x \rangle$, and variance, $\sigma^2$. When the standard deviation is much larger than the mean, so-called super-spreaders play a disproportionate role. In England and Wales, super-spreaders may increase $R_0$ by between 39% and 132% over and above that expected without heterogeneity.

The simple model presented provides an accurate description of the underlying transmission dynamics of EMRSA in the United Kingdom. For the case of VRE, for which the epidemic is only beginning to unfold, predictions are much more difficult.
The impacts of surveillance and infection control programs are, however, likely to be similar in both instances. Data are currently given on a hospital basis rather than a case-by-case approach. This clearly shows a gap in our knowledge of the true epidemiology of VRE. A better modeling framework must incorporate patient-patient contact rather than the hospital-patient-hospital contacts we have assumed here. The extent to which the community provides a reservoir for de novo outbreaks remains unknown. Studies have indicated both high prevalences of MRSA in nursing homes [13] and community carriage of VRE [11]. Theory makes specific predictions about the shape of an epidemic and shows that during the exponential phase transmission between hospitals is the principal component. The number of institutions might, however, need to be extended beyond hospitals to include other long-term care facilities.

Recent concerns over the appearance of heteroresistant strains of vancomycin-resistant *S. aureus*, coupled with the demonstration of in vitro transfer of VanA resistance genes from enterococci to *S. aureus*, appear to suggest that the appearance of VanA or VanB phenotype vancomycin-resistant *S. aureus* is inevitable. Given that VRE outbreaks may soon be occurring in hospitals already experiencing EMRSA, this hazard appears real, although the risk is not yet quantifiable.

Acknowledgments

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References