

# Can antibiotic-resistant nosocomial infections be controlled?

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Three decades ago infection-control programmes were created to control antibiotic-resistant nosocomial infections, but numbers of these infections have continued to increase, leading many to question whether control is feasible. Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci were major problems during the 1990s. Many hospitals have tried antibiotic control but with limited efficacy against these pathogens. Studies of antibiotic restriction, substitution, and cycling have been promising, but more definitive data are needed. Increased compliance with hand hygiene would help but is unlikely to control this problem alone as a result of frequent contamination of other surfaces even when hands are cleansed and high transmission rates when hand hygiene is neglected. For 17 years, the Centers for Disease Control and Prevention have recommended contact precautions for preventing nosocomial spread of important antibiotic-resistant pathogens. Many studies confirm that this approach works when sufficient active-surveillance cultures are undertaken to detect the reservoir for spread. However, most health-care facilities have not yet tried this approach.

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Antibiotic-resistant nosocomial infections have been linked to prolonged suffering, significantly higher mortality,<sup>1,2</sup> and significantly greater hospital costs than infections caused by antimicrobial-susceptible strains of the same species.<sup>1,3</sup> Many guidelines have been published urging control of such infections.<sup>4,5</sup> The important issue remains whether antibiotic-resistant nosocomial infections can be controlled by means of such guidelines or in any other way.

The common wisdom is that antibiotic resistance is a natural consequence of antibiotic use and, as such, really cannot be controlled to any meaningful degree. The inexorable increase in resistance to methicillin in *Staphylococcus aureus* (MRSA) causing nosocomial infections (figure 1),<sup>6</sup> closely resembles the earlier evolution of resistance to penicillin in this organism (figure 2).<sup>7</sup> The increasing rates of resistance to vancomycin among enterococci (VRE) causing nosocomial infections (figure 3)<sup>6</sup> could be cited as additional evidence that current control measures certainly do not work and raise questions as to the availability and practicability of any other control measures.

Effective control measures require clear understanding of the cause. The clearest elucidation of why antibiotic resistance increases so much in hospitals was, ironically, offered by someone who never heard of antibiotics; Charles Darwin

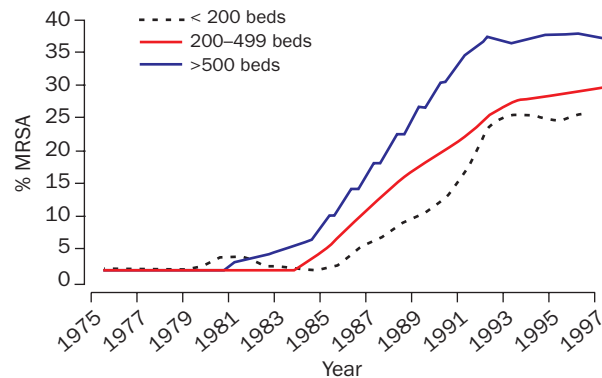


Figure 1. Proportion of *S aureus* resistant to methicillin among nosocomial infections by hospital bed size from 1975 to 1997. Adapted from National Nosocomial Infection Surveillance (NNIS) System.<sup>6</sup>

observed that competition occurs in every environment and that nature selects the strain or species most suited to survive within a particular environment.<sup>8</sup> Almost half of hospital patients and almost all intensive-care patients receive antibiotics. That microbes are transmitted from patient to patient in hospitals has been known for 150 years. Transmission of an antibiotic-susceptible microbe is unlikely to be noticed in this setting, and the microorganism is less likely to survive in antibiotic recipients. By contrast, transmission of an antibiotic-resistant microbe to patients on antibiotic therapy results in an increased likelihood that that microbe will survive and proliferate. This process results in continual amplification of the reservoir of antibiotic-resistant pathogens in the health-care setting.

Mechanisms of antimicrobial resistance vary widely with different combinations of microbe and drug. For some combinations, presence of the drug induces resistance to that drug and/or to others among microbes with a gene encoding such inducible resistance. For this pattern of resistance, avoidance of use of the inducing agent is obviously important. For other microbe–drug combinations, resistance is deemed “constitutive” and persists whether the drug is present or not. This pattern poses greater challenges to control.

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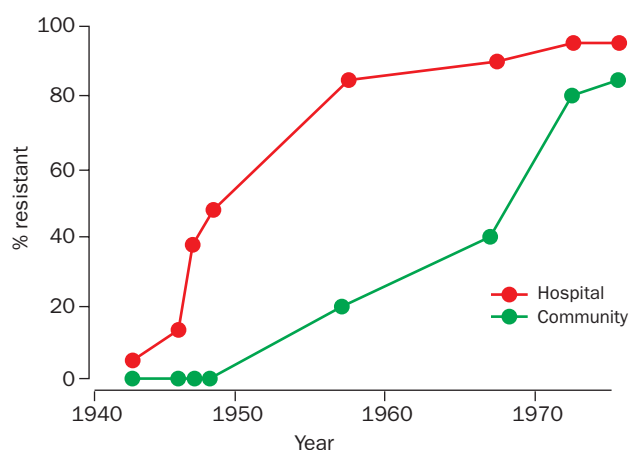


Figure 2. Secular trends of approximate prevalence rates for penicillinase-producing, methicillin-susceptible strains of *S aureus* in hospitals and the community.<sup>7</sup>

Because MRSA and VRE have been among the most problematic antibiotic-resistant pathogens in hospitals recently, this review focuses on whether they can be controlled. Epidemiological studies have shown that the two most important risk factors for patients' acquiring such pathogens have been the volume of antibiotic usage and patient-to-patient spread.<sup>9-12</sup>

### Control of antibiotic use

Because the prevalence of antimicrobial therapy is a risk factor for colonisation and infection by antibiotic-resistant microbes, many investigators have chosen to focus on modifying this factor alone to control the problem. The cessation of all antibiotic use was reported to have effectively halted an outbreak of antibiotic-resistant klebsiella infections in an intensive-care unit in 1970,<sup>13</sup> but this approach has not been considered practical in most settings since that time.

Switching from use of a single drug, to which one or more pathogens show advancing resistance, to use of another drug with activity against the pathogen has in many situations resulted in a lower prevalence of resistance to the former but a higher prevalence of resistance to the latter.<sup>14</sup> Other data, however, suggest that antibiotic control does not always lower the prevalence of resistance. For example, the greatly decreased use of penicillin over the past few decades has not resulted in a lower frequency of penicillin-resistant *S aureus*. Likewise, decreased use of penicillinase-resistant penicillins such as nafcillin has not lowered the prevalence of MRSA.<sup>15</sup> Although most hospitals have implemented the recommendation of the US Centers for Disease Control and Prevention (CDC) to restrict use of vancomycin, this restriction has had little or no effect on the prevalence of VRE colonisation or infection.<sup>16,17</sup> One reason for this lack of effect may be that other antimicrobials also serve as risk factors for colonisation and infection by antibiotic-resistant pathogens such as MRSA and VRE. For example, in some studies third-generation cephalosporins and metronidazole were more important risk factors for colonisation or infection with VRE than was vancomycin itself.<sup>10,18</sup> A derivation of the approach of substituting one antimicrobial for another has involved

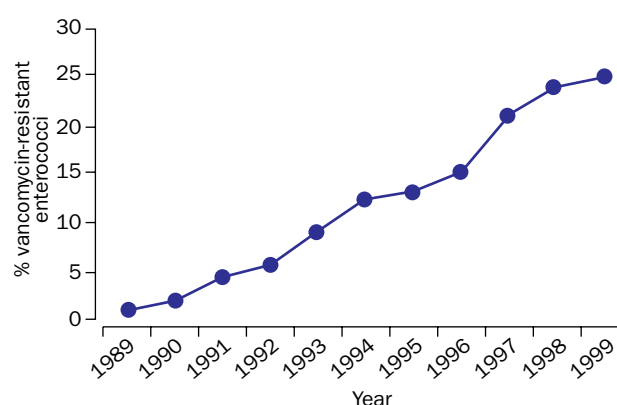


Figure 3. Proportion of enterococci resistant to vancomycin among nosocomial infections from 1989 to 1999. Adapted from NNIS System.<sup>6</sup>

regular rotation of antibiotics that are used for particular applications in intensive-care units. This practice was reported to be beneficial in two recent studies.<sup>19,20</sup> Confirmation by other investigators in different populations is still needed before the approach can be recommended for routine use, however.<sup>21</sup> Another derivation involves the substitution of particular drugs for others because the latter appear to be more highly associated with development of resistance to yet another class of agents (eg, substitution of piperacillin-tazobactam for third-generation cephalosporins because of different degrees of association with epidemic VRE).<sup>22</sup> This approach also needs confirmation before it can be recommended, especially since the study implemented new measures to prevent spread as well as antibiotic controls,<sup>22</sup> and since another study found that piperacillin-tazobactam greatly potentiated the proliferation of VRE.<sup>23</sup>

Reduction of total antibiotic use by eliminating excessive and inappropriate use has long been advocated.<sup>24</sup> Cost savings and possible improvements in antibiotic resistance have been reported with this method.<sup>25-27</sup> One study suggested a beneficial impact on the incidence of some antibiotic-resistant pathogens including MRSA nosocomial infection or colonisation.<sup>28</sup> Follow-up 5 years later at the same hospital, however, suggested that the prevalence of MRSA had probably increased and that of VRE had definitely increased substantially despite continuation of the antibiotic-control programme, although support for prevention of spread and measurement of incident cases had been reduced (B E Batteiger, Indiana University, Indianapolis University, USA, personal communication). One recent study suggested that switching from use of third-generation cephalosporins to first-generation cephalosporins for surgical prophylaxis in association with some new infection-control measures was associated with a decline in the incidence of MRSA infections.<sup>29</sup> The frequency of MRSA infections at most hospitals that used first-generation cephalosporins for surgical prophylaxis during the past decade has continued to rise, however, suggesting that this approach is not a complete answer to the problem.<sup>15</sup>

In some settings, agricultural use of antibiotics, which greatly exceeds the volume of use for human beings, has clearly potentiated the development of resistance and resulted in spread of resistant pathogens such as VRE to people

through the food chain.<sup>30</sup> Better societal controls over this source of resistant pathogens are needed in many countries.

Control of clinical antibiotic use has seemed attractive because of the idea that the cost of controlling antibiotic resistance could be minimised by getting physicians to choose the most appropriate antibiotics, but the increase in pathogens like VRE and MRSA in the USA during the past decade despite almost ubiquitous antibiotic-control efforts suggests that further research is needed to identify better methods of antibiotic control.<sup>31</sup> The other avenue for control of antibiotic resistance may involve control of the other main risk factor—patient-to-patient transmission.

### Control of patient-to-patient spread

#### **Proportion of MRSA and VRE infections attributable to spread**

Nosocomial spread of pathogens has long been recognised, and a similar pattern in antibiotic-resistant pathogens is therefore not surprising. Nevertheless, some researchers have suggested that MRSA and VRE usually do not spread in the healthcare environment even when infection-control measures are lacking.<sup>16,32,33</sup> Instead, they suggest that these microbes are arising through de-novo mutation to resistance in individual patients. Other data suggest that most patients with nosocomial MRSA and VRE have these infections because of spread from patient to patient.<sup>10–12,15,34–37</sup> For example, in one outbreak of MRSA in a neonatal intensive-care unit, all 20 isolates were of the outbreak strain.<sup>12</sup> During the 9 years (and 90 000 patient-days) after control of the outbreak, no neonate had a culture positive for MRSA in that unit, which suggests a very low frequency of de-novo mutation even in a population with long hospital stays and frequent exposure to antibiotics.<sup>38</sup> In another MRSA outbreak in a neonatal intensive-care unit, clonal spread for over 4 years was reported.<sup>36</sup> After control of a hospital outbreak of VRE in which 100% of patients in one intensive-care unit had the same strain of VRE, that unit was then kept free of VRE for more than a year as documented by weekly cultures of all patients in the unit.<sup>38</sup> This absence of infections occurred despite a very high prevalence of antibiotic exposure in the unit and the lack of an antibiotic-control programme in the hospital at the time. It is difficult to understand how these data could be compatible with the hypothesis that most patients with MRSA and/or VRE infections acquire the organisms with resistance through de-novo mutation. In other settings where the problem has been out of control for years and little effort has been expended to control it, some researchers have maintained that a polyclonal pattern with many different strains of VRE means that nosocomial spread is not occurring and that the problem therefore cannot be controlled by prevention of spread.<sup>16,22,39</sup> In one hospital in which a polyclonal pattern and high prevalence were noted years after the onset of a VRE epidemic, elaborate epidemiological studies found that spread had been the cause of most new cases.<sup>40</sup> A high previous frequency of colonisation was the most important predictor of generating new cases in a multivariate analysis.

Numbers of community-acquired MRSA infections have increased during the past decade. Some data suggest that such strains with co-resistance to two or fewer other classes of

antibiotics may be arising de novo, but other studies have found that such strains account for a quarter of their health-care-associated isolates<sup>41</sup> and that patients found to have “community-acquired” MRSA were likely to have chronic illnesses and require frequent contact with the health system in outpatient visits.<sup>11,15,34,35</sup> Disinfection of equipment between patients is less frequent and hand hygiene may be less well observed in the outpatient setting. These features are germane to the subject of this review because compliance with measures to prevent nosocomial spread will probably decrease further if clinicians begin to feel that MRSA is widespread in the community.

For decades random samples of people in the community have shown that about a third carry *S aureus*, about half of these chronically and the other half transiently. If a large proportion of these colonising *S aureus* isolates are now methicillin resistant, there would be evidence of a wide spread throughout the community and less enthusiasm for preventing spread in healthcare settings. A recent culture survey of 500 children and their carers in New York City, where nosocomial MRSA infections have been rampant, found only one MRSA colonisation (0.2%) in a child who had recently had hospital care.<sup>42</sup> The strain was one of the clones recognised to cause nosocomial infection frequently in New York. The same prevalence (0.2%) was found in a larger population survey (n=3266) including airforce recruits, high-school students, and children in day-care centres in Portugal, where MRSA accounts for 47% of nosocomial *S aureus* isolates. Three of seven MRSA isolates were recognised to be strains that commonly caused nosocomial infections.<sup>43</sup> Two other US studies in which culture samples were taken from patients on hospital admission from home found that 2.6%<sup>11</sup> and 2.9%<sup>35</sup> were colonised with MRSA; all of those affected had had frequent contact with the healthcare system and had recognised risk factors for MRSA carriage. These studies do not support the idea that MRSA has become widespread in the general community. In certain segments of the community, however, where local conditions may favour spread, MRSA has been more common, such as among aboriginal people in Canada. Although a variety of strains have been noted among aboriginal Canadians, MRSA has mostly been clonal within reservations, suggesting that a rare mutation associated with unusual socioeconomic or medical conditions favouring spread (eg, diabetes mellitus, impetigo, frequent antibiotic therapy) could result in an increased community prevalence of MRSA without the need for many de-novo mutations.<sup>44</sup> This would be a preferable explanation according to Occam's razor (ie, that a simple answer is more probable than a convoluted one). Pockets of community spread have been found recently in a day-care centre, among wrestlers and football players, among injection-drug users, and in one prison in the USA.

Domestic transmission of *S aureus* has been recognised for decades, and a recent study found that patients acquiring MRSA in hospital transmitted the same strain to 15% of their household contacts after hospital discharge, suggesting that the large number of colonised patients being discharged may thus be contributing to the larger numbers being noted in the community.<sup>41</sup> The relative risk of MRSA colonisation in these households was 15.6–75.6 times higher than in other US community surveys described above.<sup>11,35,41,42</sup> Although survival

and proliferation of such strains are amplified when they spread to patients on antibiotic therapy, such therapy is not essential for transmission. For example, over 90% of children become at least transiently colonised with *S aureus* during infancy, and most of the colonising strains have been penicillin resistant in recent years, even among children who have never received any antibiotic. Taken together, these data suggest that such spread is increasing the prevalence of traditionally nosocomial pathogens in some communities.

#### **Contamination of clinicians' hands, clothing, and equipment**

Spread of MRSA and VRE between patients is facilitated because hands, equipment, and clothing are infrequently disinfected between contacts with patients. A recent study documented contamination of clinicians' gloves, gowns, and/or stethoscopes after two-thirds of examinations of patients with VRE, whether clinically infected or asymptotically colonised.<sup>45</sup> The investigators concluded that spread will occur via contaminated hands, clothing, and equipment unless colonised patients are identified and placed in contact isolation. Another study found that the concentration of VRE in colonic faecal contents did not differ between patients with clinical infection and those with symptomatic-free colonisation, suggesting a similar potential for contagion from the two groups.<sup>46</sup> This similarity may explain why the rate of contamination of the clinicians' clothing was similar from colonised and infected patients.<sup>45</sup> Another study showed that gowns were frequently contaminated after care of patients with MRSA or VRE infections, and that gowns reliably prevented contamination of clothing beneath the gown;<sup>47</sup> when a white coat was worn instead of a gown, it became contaminated in two-thirds of cases, and clean hands could become contaminated by touching the coat.<sup>47</sup> A fourth study found 65% of nurses' gowns or uniforms were contaminated after they had carried out morning care activities for patients with MRSA in urine or a wound.<sup>48</sup>

#### **Environmental contamination with MRSA and VRE**

Environmental contamination of hospital rooms was found to occur for 73% of MRSA-infected patients and 69% of colonised patients.<sup>48</sup> The same study documented contamination of nurses' gloves with MRSA on 42% of occasions when they had touched surfaces in the room without touching the patient. There have been many reports of surface and equipment contamination in hospital rooms of patients with VRE colonisation or infection.<sup>40,48-51</sup> One recent study found that enterococci and staphylococci can survive for weeks to months on fabric or plastic surfaces such as are commonly found in the hospital environment.<sup>52</sup> In another study conventional disinfection of surfaces in hospital rooms of patients with VRE was inadequate on 16% of occasions, but these surfaces were uniformly free of VRE after more intensive disinfection.<sup>49</sup> One study reported control of an outbreak after an increase in the intensity of environmental disinfection, which was associated with a decrease in the proportion of environmental cultures being found positive from 29% to 1%.<sup>51</sup> Environmental VRE contamination was detected in 29% of clinic examination

rooms after examination of persistently colonised outpatients, and increased disinfection was required for reliable clearing of environmental surfaces.<sup>53</sup>

#### **Role of active surveillance cultures and isolation**

Many studies during the past two decades have shown that identification and isolation of patients colonised with MRSA<sup>12,15,36,37,54-56</sup> or VRE<sup>10,50,57-59</sup> can prevent nosocomial infections in the absence of an antibiotic-control effort (other than vancomycin restriction, which was used in several VRE containment efforts but has not been shown to be an independent predictor of control of VRE outbreaks). During one such study of a 3-year hospital-wide outbreak of MRSA, the outbreak strain came to account for 40% of all nosocomial *S aureus* bloodstream infections and 49% of surgical-site infections (table); the outbreak was then completely controlled (eradicating the MRSA strain from the hospital) by an approach of active surveillance cultures to identify colonised patients and placing them in contact isolation with no antibiotic-control measures (figure 4).<sup>36</sup> We emphasise that continued spread and rising rates of infection had occurred throughout the preceding 3 years when only the subset of colonised patients with clinically obvious infection were being put into such isolation. During that time most colonised and contagious patients were not recognised (figure 5).<sup>37</sup> Another study found that MRSA spread to other patients was 15.6 times lower when colonised patients were recognised by active surveillance cultures and placed in contact isolation (which at the time involved use of gown, gloves, and mask)<sup>12</sup> than with standard precautions, which rely on use of gloves for touching secretions, excretions, or drainage and handwashing between all patient contacts to prevent spread. These findings accorded with the results of a mathematical model, which found that handwashing alone at a much higher rate than is usually achievable in clinical settings (ie, after 80% of patient contacts) would have only a modest effect on spread of VRE because of the high rate of transmission that was associated with failure to wash after the remaining 20% of contacts.<sup>60</sup> During another study, active surveillance cultures and contact isolation for colonised patients promptly contained a VRE outbreak on eight wards.<sup>10</sup> That study again documented that a large majority of the colonised patients would not have been detected by testing of routine clinical specimens, leaving them unrecognised and unisolated. Because spread between facilities plays such an important part in the epidemiology of these infections, the recent success of a public-health initiative involving all acute and long-term health-care facilities throughout an entire health district provides a role model for other large health systems that share patients and pathogens.<sup>61</sup>

**Increasing prevalence of MRSA despite isolation of patients known to have MRSA from routine clinical cultures<sup>37</sup>**

	Prevalence of MRSA (%)		
	1977	1979	1980
Pneumonia	0	19	24
Bloodstream infection	0	13	40
Surgical-site infection	0	27	49

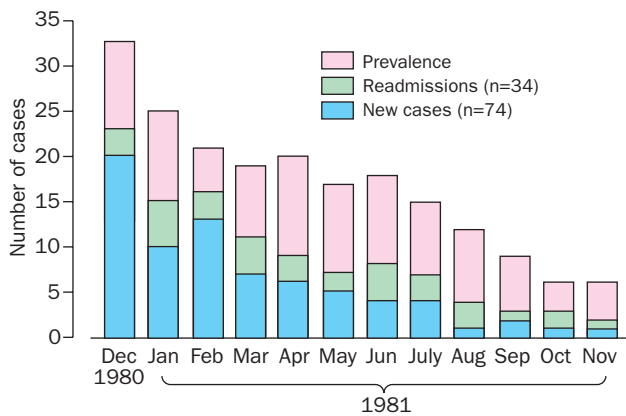


Figure 4. Effect of control measures. After more than 2 years of increasing rates of MRSA nosocomial infections, the prevalence was progressively reduced hospital-wide following implementation of a programme of active surveillance cultures and contact isolation of all colonised patients ( $p < 0.001$ ).<sup>37</sup>

### Claims that VRE and MRSA infections cannot be controlled

The results of several studies have been used to suggest that the CDC Guideline for Control of VRE do not work because some parts of the guideline have been used without apparent benefit.<sup>16,17,22,39,62</sup> Three hospitals reported that they restricted use of vancomycin with no apparent effect on VRE prevalence. However, a meta-analysis found that vancomycin is not a particularly strong risk factor for VRE infection.<sup>18</sup>

Several hospitals have reported that active surveillance cultures had no effect on VRE infection rates, but cultures were done only on patients in a tiny minority of the hospital beds. For example, in two of these hospitals the patients tested were in 1.8% and 4.6% of beds, respectively—only a small fraction of the total reservoir for VRE spread.<sup>16,17</sup> These two studies suggest that restriction of such control efforts to intensive-care units will have little effect on hospital-wide rates of antibiotic-resistant infections, even if some control is documented in the intensive-care unit.<sup>54</sup> Control of the eight-ward VRE outbreak described above would have been unlikely had surveillance cultures been limited to one or two of the eight wards.<sup>10</sup>

Morris and colleagues<sup>16</sup> maintained that control of VRE was not possible because many different strains were observed by DNA fingerprinting, which implied that spread was not occurring even though there was documented violation of isolation precautions in 44% of clinician visits to isolation rooms and lack of identification and isolation of most of the reservoir for spread throughout the hospital. Although 45 unique patterns on pulsed-field gel electrophoresis were observed among 85 isolates, there are epidemiological problems with this interpretation. First, with the assumptions of random spread of all 45 observed strains and that each patient could have only one strain, a sample size of 85 is inadequate to show all patterns of spread (because it is fewer than two per strain). A sample size ten to 20 times larger would have been more appropriate for showing the amounts of spread by all strains. Second, since each patient can have several strains of VRE,<sup>40,63</sup> the study design may have prevented detection of spread because the report did not record whether investigators looked for

multiple strains per patient. Finally, and perhaps most importantly, the investigators did not report looking for transposons, mobile genetic elements that can move from strain to strain bearing a gene for vancomycin resistance. In 1992 CDC investigators noted the polyclonality of VRE in hospitals in New York City and reported that this feature probably meant that one or more transposons were spreading from enterococcus to enterococcus.<sup>64</sup> Patient-to-patient faecal-oral spread of VRE as shown in many studies<sup>10,50,57–59</sup> can obviously still occur with VRE bearing such a transposon, but this can result in a polyclonal pattern on pulsed-field gel electrophoresis due to transposon spread to virtually all VSE strains in all patients' colons. Transposon 5482 was found to be the basis for virtually all the polyclonality in a VRE outbreak in a cancer hospital in New York City.<sup>65</sup> These epidemiological shortcomings make it impossible to conclude from the data presented that VRE was not spreading in the hospital as suggested.

One of the major arguments of those suggesting that spread of VRE or MRSA cannot be prevented is that it keeps happening and therefore isolation precautions must not work.<sup>66</sup> The major problem with this argument is that a large majority of health-care facilities (for both acute and long-term care) have never identified the reservoir for spread by use of active surveillance cultures. Recent studies have suggested that 95% of the VRE reservoir<sup>67</sup> and at least 66% of the MRSA reservoir<sup>15</sup> go undetected in the absence of active surveillance cultures. Two large surveys found that a minority of hospitals had used active surveillance cultures to identify patients colonised with MRSA, VRE, or both,<sup>31,66</sup> and one showed that the few hospitals using this method used too few cultures to detect the reservoir for spread reliably.<sup>31</sup>

Some have suggested that prevention of nosocomial MRSA transmission is impossible because MRSA does not spread.<sup>32</sup> Others have suggested that most MRSA in hospitals is community acquired and that spread is only rarely found, so there can be little justification for active identification of colonised patients to prevent spread.<sup>33</sup> If these claims are true, implementation of active surveillance cultures and contact isolation for colonised patients would not have been associated with a significant reduction in the frequency of MRSA infection as documented in many studies.<sup>12,15,36,37,54–56</sup> The probability that any one of these reductions occurred by chance alone is small. The joint

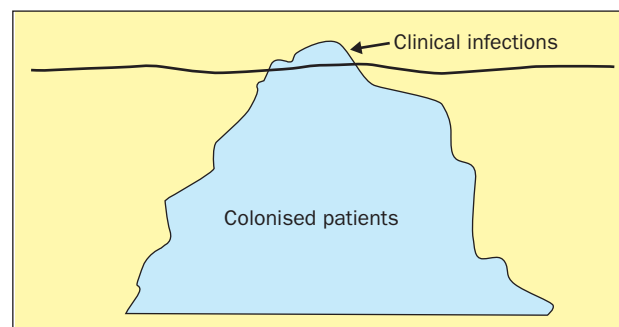


Figure 5. Reservoir for spread. The reservoir for spread of antibiotic-resistant nosocomial pathogens consists of a relatively small number of patients with clinically obvious infection (the tip of the iceberg) and a much larger subset of colonised patients who remain unrecognised and unisolated in the absence of active surveillance cultures.

probability of all of them having independently happened by chance alone would be much smaller still. Consistency of evidence across many studies by different investigators supports the notion that the association was causal,<sup>21</sup> but we should point out that not all studies of this approach have reported success. Reboli and colleagues reported initial success in controlling an MRSA outbreak in a neonatal intensive-care unit, but then relapse of the outbreak before they added weekly umbilical surveillance cultures to the others being done and introduced hexachlorophene handwashing between patient contacts.<sup>68</sup> Failure to detect colonised patients or to comply correctly with contact precautions could result in hand contamination and continuing transmission that might have been halted by these additional measures.

#### Are gowns necessary for preventing spread?

For patients found to have MRSA or VRE infections, full contact isolation with gowns has been used because of the findings of frequent contamination of clinicians' clothing when gowns were not worn and the many examples of documented success in control by this approach.<sup>10,12,15,36,37,50,54-59</sup> One study reported control of two VRE outbreaks with use of gloves and gowns but the first outbreak had not been controlled when gloves alone were used for barrier precautions.<sup>50</sup> Another study on the importance of gowns found that use of gloves alone was as effective as use of gowns and gloves for preventing spread of VRE in an intensive-care unit,<sup>17</sup> but isolation precautions were frequently violated in both groups and a majority of the patients who acquired VRE did so within a week of transfer to the intensive-care unit from other wards throughout the hospital. That study may therefore have been confounded by exposures occurring before transfer elsewhere in the hospital where colonised patients were not being detected or isolated or after transfer when precautions were violated.

#### Could better compliance with hand hygiene control MRSA and VRE?

Hand hygiene is often referred to as the single most important measure for preventing spread of nosocomial infections.<sup>4</sup> For pathogens like MRSA and VRE, however, it is not clear that hand hygiene is the most important method for preventing spread. In one study surveillance cultures and contact precautions reduced spread 5.6-fold compared with standard precautions, which rely in most cases on hand hygiene.<sup>12</sup> In another study, a mathematical model predicted that the prevalence of VRE would be only modestly decreased if an 80% rate of compliance with hand hygiene was achieved owing to the high rate of spread after the 20% of cases in which hand hygiene was neglected.<sup>60</sup>

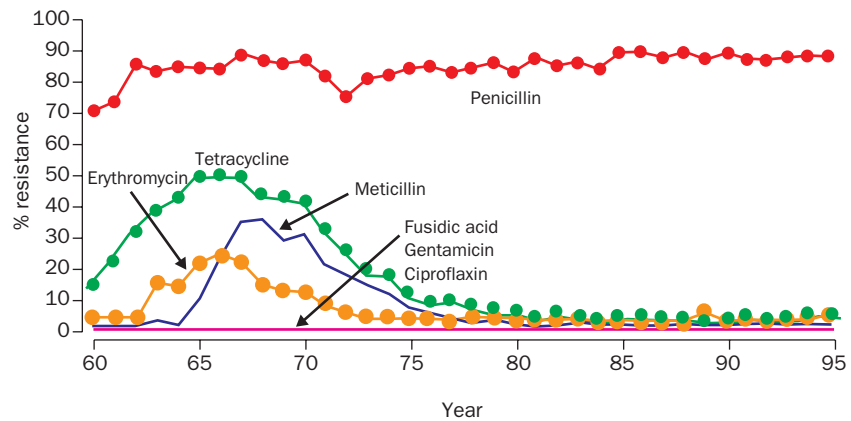


Figure 6. Proportion of *S aureus* blood isolates resistant to antimicrobials in Denmark 1960 to 1995. Source: DANMAP Report, 1997.<sup>75</sup>

Several other studies have published data bearing on this question. The first reported a 37.5% increase in compliance with hand hygiene from 1994 to 1997 and a 67.5% reduction in the incidence of nosocomial MRSA bacteraemia between 1994 and 1998.<sup>69</sup> A programme of active surveillance cultures to detect patients colonised with MRSA and isolate them was implemented in the same hospital in 1993, when 1863 cultures were done.<sup>56</sup> The number of cultures done annually then progressively increased by 467% over the next 4 years to 10 566 in 1997. Because both interventions proceeded simultaneously and because the increase in detection and isolation was much greater than that in compliance with hand hygiene, the contribution of improved hand hygiene to the improvement in the MRSA rate is difficult to judge.

Another report claimed a massive decrease in numbers of VRE infections as a result of an increase in hand hygiene alone.<sup>70</sup> That study implemented a programme to increase compliance with hand hygiene in one of two similarly sized hospitals, the exact methods of which were not described. Compliance with hand hygiene was monitored by counters in soap dispensers in two units in each of the hospitals. No evidence that counts in the two units were representative of hand hygiene throughout the facility was provided. Despite no observed change in counts during the intervention period, the researchers reported that hospital-wide VRE infections declined by 44% in the intervention hospital. From baseline to follow-up, the VRE infection rate declined by 85% in the intervention hospital and 44% in the control hospital. This is the only such study concluding that hand hygiene alone can have such a massive effect on VRE (while having an insignificant effect on MRSA), and since the exact methods of the intervention were not stated, interpretation is difficult. A further complication is that there was no attempt to measure the proportion of hand hygiene opportunities that resulted in hand hygiene. In some hospitals this compliance rate has ranged from 20–40%. If the intervention hospital had started off with a compliance rate of 20% and increased by a relative 171% to a compliance rate of 54%, such dramatic control of VRE would be difficult to believe.

**Search strategy**

Medline searches of publications in English from 1966 to 2000 on the major topic headings "drug resistance", "microbial", "beta-lactam resistance", "met(h)icillin resistance", "vancomycin resistance", "infection control", and "control", as well as personal Reference Manager files were used as the database for this review. References were selected because of results bearing on the question whether antibiotic resistance could be controlled. The review focused on the two most frequently studied pathogens, MRSA and VRE.

**Can hospitals afford to prevent spread?**

Although there is a cost for prevention of spread, there is also a cost for ignoring spread. Several studies have suggested that the costs of MRSA and VRE infections exceed those of prevention.<sup>54,71-73</sup> These findings suggest that controlling this problem should pay important dividends over the long term. Such control has been convincingly demonstrated in Denmark, where the rate of nosocomial MRSA infections decreased from 34% to less than 1% and has remained at that proportion for the past two decades (figure 6).<sup>74</sup> The societal cost of maintaining such a low rate of MRSA infection in Denmark is likely to be much lower per head than the cost of allowing a high rate of MRSA infection to grow still higher in countries like the USA and the UK. Belgium is now reportedly following the Danish example.<sup>55</sup>

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