



## POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE

POLICY BRIEF 5

MARCH 2008

### WHICH MRSA IS IT?

Case 1: A high school football player goes to the doctor with what looks like a persistent spider bite on his leg. Case 2: An ICU patient on a ventilator suddenly slides into a coma with severe pneumonia. The diagnosis in both cases: MRSA (methicillin-resistant *Staphylococcus aureus*). While the bacteria causing both infections are called by the same name, are they really the same thing? Are the bacteria genetically identical or are they different?

At one level, MRSA cases have been differentiated based on where the patient acquired the bacteria. If they were acquired in a hospital or a long-term care facility, such as a nursing home—our ICU patient, for instance—the infection is deemed to be healthcare associated (HA-MRSA). If they were picked up “in the community”—in the locker room, in the case of our football player—the infection is community associated (CA-MRSA). For practical purposes, infections are classified based upon a patient’s recent medical history. If the patient was in a high-risk healthcare site not long before diagnosis (or has been admitted in a facility for over 72 hours before the infection appears), the bacteria will be categorized HA-MRSA; if not, the assumption is CA-MRSA. These classifications are useful, but it isn’t always clear precisely where the offending bacteria were acquired (see Box 1).

A fundamental question still remains, however: are these types of bacteria genetically identical? The short answer is no. This isn’t surprising when one considers that at any given time, one-third to one-half of the population is “colonized” with staph (*S. aureus*, living in the nasal passages or other warm, dark areas, but not causing illness), and hundreds of millions of doses of penicillin and related antibiotics have been used both inside and outside the hospital since the 1950s.

This widespread and extended use of antibiotics exerts “drug pressure”—the force that causes natural selection to favor antibiotic-resistant bacteria. As a

result, hundreds of different drug-resistant strains exist in different settings, and the most robust have spread widely, both in healthcare settings and in the community. Because all the common forms are resistant to the penicillin family of antibiotics (the most commonly used antibiotics since their advent), they’re all lumped together as MRSA.

### The Appearance and Spread of CA-MRSA

Hospitals have fought MRSA infections since the late 1960s, but only within the past 15 years have severe MRSA cases become prominent in the community, affecting healthy, young people with no recent link to the healthcare system. CA-MRSA are not simply HA-MRSA strains that escaped the hospital and began spreading in the community, however. DNA analysis of CA-MRSA strains reveals that most are more closely related to MSSA (methicillin-susceptible *S. aureus*) than they are to common HA-MRSA strains.

Today’s predominant CA-MRSA might actually be an evolved version of a penicillin-resistant staph clone that spread through both hospitals and communities in the 1950s.<sup>1</sup> In the 1960s, the bacteria appeared to be wiped out when newer antibiotics (still in the penicillin family) were introduced. However, genetic similarities between this bacteria and CA-MRSA strains common today suggest that perhaps this old nemesis acquired the genes for resistance to newer antibiotics (including methicillin) and in its “improved” form is spreading in communities again.

An outbreak of CA-MRSA infections was noted in the early 1980s among injection drug users in Detroit.<sup>3</sup> More outbreaks were recognized in the 1990s in specific population groups, including prison inmates, military recruits, Native Americans, children in daycare centers, and student athletes. CA-MRSA—like other staph bacteria—mainly caused superficial skin infections that manifested as boils or pimples and

### Box 1: The Difficulty of Distinguishing CA-MRSA and HA-MRSA

Identifying MRSA as community- or healthcare-associated may seem simpler than it is.

Consider this: a patient exposed to MRSA can carry the bacteria for days, years, or a lifetime without becoming infected and showing any symptoms. A patient first showing signs of infection at home may have actually become colonized with MRSA during an earlier hospital stay. Likewise, a patient with an infection first diagnosed in the hospital may have brought the bacteria from the community with him or her and become self-infected with CA-MRSA.

Definitions based on when an infection appears are likely to *overestimate* the actual burden of CA-MRSA by including patients colonized earlier in a hospital or other healthcare facility. Definitions based on exposure to healthcare risk factors may *underestimate* the actual number of CA-MRSA cases.

In an effort to add clarity to this issue, researchers at the Centers for Disease Control and Prevention (CDC) developed a nomenclature with three categories of MRSA:<sup>2</sup>

- *Community-associated*: patients with no known healthcare risk factors
- *Healthcare-associated, community-onset*: patients with one or more of these risk factors:
  1. presence of invasive device (e.g., a catheter or implant)
  2. history of MRSA infection or colonization
  3. history of surgery, hospitalization, dialysis, or long-term care facility in the past year
- *Healthcare-associated, hospital-onset*: patients with MRSA infection occurring in a normally sterile site (mainly blood) more than 48 hours after hospital admission

The three categories distinguish both the place of infection onset (hospital or community) and where the bacteria were likely transmitted (healthcare facility or community). Even these more specific definitions will not always accurately classify a patient, but they are an improvement. As CA-MRSA becomes increasingly common, more and more patients are likely to be misclassified as having HA-MRSA when, in fact, they entered the hospital colonized.

cleared up without treatment. The infections were recognized as MRSA only when they developed into more serious skin infections that did require treatment, such as cellulitis, and penicillin-type antibiotics failed. Early on, most CA-MRSA infections responded to other antibiotics and serious disease was rare, though not unknown. In 1999, however, four children died of severe MRSA infections, presumed to be community-acquired.<sup>4</sup> While antibiotic resistance and increased virulence develop separately, when these traits coincide—as is now happening more frequently with CA-MRSA—the situation can be dire for the patient.

That scenario may account, at least in part, for the increase in hospitalized patients with MRSA. The number of all hospitalized MRSA cases nearly doubled between 1999 and 2005, but the number with serious skin and soft-tissue infections—most of them assumed to be CA-MRSA—nearly tripled over that time (see [Counting MRSA Cases](#)).<sup>6</sup>

### The Genetic Basis of Antibiotic Resistance in CA-MRSA and HA-MRSA

Chromosome segments (“gene cassettes”) responsible for antibiotic resistance in CA- and HA-MRSA strains contain somewhat different information that causes the strains to be resistant to different antibiotics. HA-MRSA is more likely to be multi-drug resistant, while until recently, most CA-MRSA strains have been resistant only to the penicillin family of antibiotics. The CA-MRSA version of the cassette is smaller than the one in HA-MRSA, which may explain CA-MRSA’s faster growth rate.<sup>5</sup> The smaller size of the CA-MRSA cassette might also make it more easily transferred from one bacterium to another, helping CA-MRSA to spread quickly (see Box 2). A better understanding of the mechanics of CA-MRSA is needed to fully understand these differences and their implications for CA-MRSA treatment and prevention.

The major CA-MRSA strains today belong to a group of related strains named “USA300,” discovered in 2000. USA300 infections fit the typical profile for CA-MRSA: mainly skin and soft tissue infections, usually treatable with non-penicillin type antibiotics, and affecting patients with no record of hospitalization or healthcare procedures. As is typical for CA-MRSA, USA300 owes its antibiotic resistance to a small gene cassette. The USA100 strains, predominant in

hospitals in the United States, have a much larger gene cassette and are resistant to many more antibiotics. Because they typically spread in hospitals, USA100 infections are more likely to be invasive. They also may have more serious consequences, as patients who get them tend to be elderly and have other serious health conditions.

### CA-MRSA and Hospitals

HA-MRSA strains have never been identified as a major cause of staph infections in the community, but USA300 CA-MRSA now seem to be a source of hospital infections. USA300 caused one-third of bloodstream infections at a public hospital in Atlanta,

## Box 2: How Antibiotic Resistance is Acquired by Bacteria

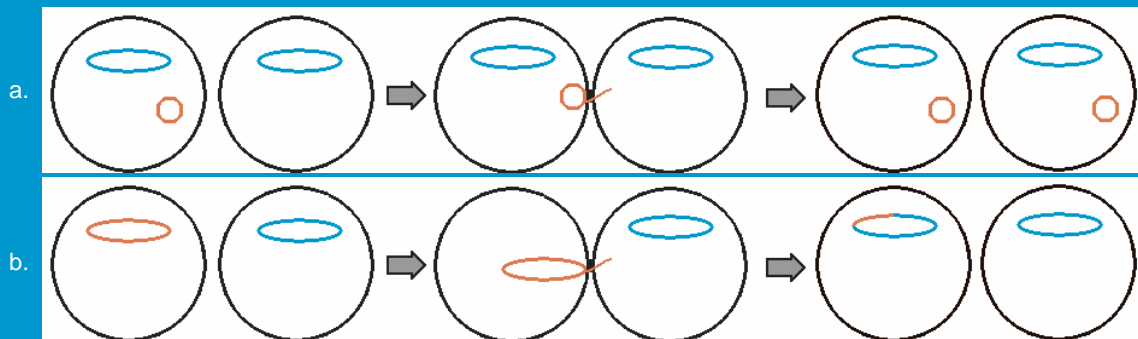
In most organisms, genetic information is transferred from parent to offspring in “vertical genetic transfer.” This is true of organisms that reproduce sexually (in which case genes from both parents contribute to the offspring’s genetic makeup) and those that reproduce asexually (in which case the single parent’s genetic material is passed on). Changes do occur through random mutation, with natural selection deciding whether the mutation stays or goes, but this is a very slow process.

Bacteria, however, can quickly spread new genes throughout a population by transferring genetic material directly from one bacterium to another in “horizontal genetic transfer.” In some cases, even bacteria of very different species can do this. Horizontal genetic transfers can happen in three ways:

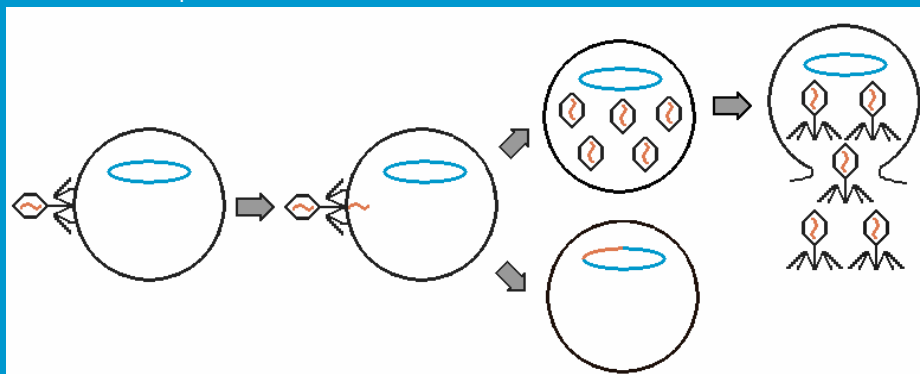
1. **transformation:** taking up free DNA in the environment (typically released by dead bacteria)



2. **conjugation:** receiving genetic information, as either a plasmid (a) or gene cassette (b), through direct contact with another bacterium



3. **transduction:** receiving genetic information carried from another cell by a bacterial “phage”—a virus that infects bacteria. The phage’s genetic information either causes the bacterium to make copies of the phage until rupturing or the information becomes incorporated into the bacterium’s chromosomal DNA.



GA during part of 2004, with most of those infections transmitted within the hospital setting.<sup>7</sup> At the University of California Medical Center at Davis, again, one-third of the infections acquired in the hospital were caused by USA300 strains.<sup>8</sup> Although some patients might have been colonized with CA-MRSA and carried it into the hospital before showing signs of infection, it seems likely that USA300 is now spreading directly in hospitals. The USA300 isolates collected at this hospital were also more resistant to non-penicillin antibiotics than most USA300 isolates, suggesting they might have acquired additional resistance genes from USA100 strains already resident in the hospital—further blurring the distinction between HA-MRSA and CA-MRSA. In a third study in Chicago’s Stroger Hospital, hospital-onset bloodstream infections caused by typical CA-MRSA genotypes (mostly USA300) grew from 24 to 49 percent of the total from 2000 to 2006.<sup>9</sup>

Further evidence that USA300 strains are now spreading in hospitals comes from the Centers for Disease Control and Prevention (CDC). In a sample of hospitals from around the country, USA300 caused 16 percent of HA-MRSA in 2005.<sup>2</sup>

### Responding to CA-MRSA

CA-MRSA, which has been spreading throughout communities in the United States, is now also spreading in hospitals, where the burden of HA-MRSA is already substantial. This means that it is even more important for hospitals to adopt infection control measures appropriate to local conditions.<sup>10</sup> Although only a small proportion of the population is colonized by CA-MRSA, the chances of a person entering a hospital with it are increasing.

Currently, there are no official guidelines for MRSA control in the community. General hygiene precautions, such as bleach cleanings, handwashing, and warning people not to share personal items may help to combat local outbreaks, but their degree of effectiveness is unknown. Understanding whether CA-MRSA is spread primarily through the environment (for example, on surfaces touched by many people) or via skin-to-skin contact would help improve current local practices and could also lead to national guidelines that can help prevent new MRSA outbreaks.

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