

Colonization, Fomites, and Virulence: Rethinking the Pathogenesis of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infection

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Community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) infection is increasingly common worldwide and causes considerable morbidity and mortality. Of concern, community-associated MRSA infections are often recurrent and are highly transmissible to close contacts. The traditional tenet of pathogenesis is that MRSA colonization precedes infection. This has prompted persons involved in efforts to prevent community-associated MRSA infection to incorporate the use of intranasal topical antibiotics for nasal decolonization. However, data from outbreaks of community-associated MRSA infection suggest that skin-skin and skin-fomite contact represent important and common alternative routes of acquisition of the infecting strain. Furthermore, strain characteristics of the most successful community-associated MRSA strain, USA300, may contribute to a distinct pathogenesis. As we develop strategies to prevent community-associated MRSA infection, we must reconsider the pathogenesis of *S. aureus*. Reliance on models of health care-associated MRSA transmission for prevention of community-associated MRSA infection may result in the development of flawed strategies that attenuate our ability to prevent this serious and potentially deadly infection.

Staphylococcus aureus is a ubiquitous pathogen and a common cause of invasive and life-threatening infections. Until the current decade, methicillin-resistant *S. aureus* (MRSA) infections occurred almost exclusively in hospitalized persons or persons with extensive contact with the medical system [1]. The prevalence of MRSA disease has increased dramatically during this decade as a result of the emergence of community-associated MRSA (CA-MRSA). CA-MRSA has caused outbreaks of disease among children [2–4], prisoners [5], participants on sport teams [6, 7], military personnel [8], and men who have sex with men (MSM) [9, 10]. CA-MRSA infection is now endemic in many locales and is no longer confined to populations with unique exposures or risk factors.

Most (80%–90%) CA-MRSA infections manifest as skin or skin structure infections [11–16], although more-serious and

lethal manifestations, such as necrotizing pneumonia, necrotizing fasciitis, and sepsis, have been caused by CA-MRSA [17–19]. CA-MRSA infection is notable for its ability to recur in patients and to spread within households [20, 21]. Patients with CA-MRSA infection commonly experience repeated infection, typically involving the skin [20–22]. Reports of MRSA transmission among household members are common [6, 7, 21, 23]. Therefore, there is considerable interest in the prevention of CA-MRSA infection among persons with recurrent infection and among close contacts of infected persons.

At present, data are lacking on the efficacy of interventions to prevent CA-MRSA infection in persons who experience repeated infections or among close contacts of infected persons. Some researchers have used nasal decolonization and decolonization of other body sites as a means to prevent CA-MRSA infection [21, 23–25]. Decolonization strategies are based on robust literature involving this strategy to prevent health care-associated MRSA (HA-MRSA) infection, a context in which the model of pathogenesis is based on the tenet that infection is preceded by colonization [26]. Decolonization as a means to prevent CA-MRSA infection implies that the reservoir of MRSA resides in endogenous sources. However, there are data

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to suggest that stepwise progression of colonization to infection may not commonly occur in community settings.

The purpose of this article is to address the pathogenesis of CA-MRSA infection. Recent data have suggested that nasal colonization may play a less important role in the pathogenesis of CA-MRSA infection and that, instead, skin-skin and skin-fomite contact could represent important transmission routes. Furthermore, there may be unique molecular characteristics of CA-MRSA strains that render the pathogenesis of CA-MRSA infection to be distinct from that of HA-MRSA infection. If the pathogenesis of CA-MRSA is different from that of HA-MRSA and of community-associated methicillin-susceptible *S. aureus* (MSSA), then strategies to prevent CA-MRSA infections need to address the distinct pathogenesis characteristics of CA-MRSA.

CA-MRSA INFECTION: A LESSER ROLE FOR ANTECEDENT COLONIZATION?

The ecologic niche for *S. aureus* in humans is in the anterior nares, where *S. aureus* can be identified most consistently in humans [27]. One-quarter to one-third of healthy persons harbor *S. aureus* in the nose at any time [27]. Although *S. aureus* can also be found on the skin or in the rectum or vagina, the nose appears to be the primary reservoir for replication and spread to other bodily sites. This idea is supported by studies that have revealed that, if *S. aureus* nasal carriage is temporarily eliminated by use of an intranasal topical antibiotic (e.g., mupirocin), colonization often simultaneously disappears from other colonized body sites [28]. Nasal *S. aureus* isolates are often identical to strains that later cause clinical infection, as assessed by PFGE [29, 30].

The proof of principle demonstrating the importance of nasal colonization's role in the pathogenesis of *S. aureus* infection is that, when colonization is eradicated, the risk of clinical infection is lowered [27]. This observation has spurred attempts to eradicate *S. aureus* from the nose to prevent infection among high-risk groups. Unfortunately, nasal decolonization strategies have limitations. Short-term eradication is generally successful, but patients are often later recolonized with the same strain [26, 28, 31]. This suggests that recolonization from sources exogenous to the nose can occur. Another limitation is that recolonizing strains are sometimes resistant to the previously used intranasal topical antibiotic [32].

The relationship between colonization and infection has been a fundamental tenet in the pathogenesis of *S. aureus*. However, there are very few data on the association between CA-MRSA infection and nasal MRSA colonization, and there are even fewer data from prospective studies. Indeed, a common feature of outbreak and nonoutbreak (i.e., endemic) CA-MRSA infections is the lack of identifiable endogenous sources of MRSA (i.e., asymptomatic carriage in the anterior nares).

To illustrate, 2 outbreak investigations of CA-MRSA infections in football teams revealed that the responsible CA-MRSA clone was not found in the nares of infected players, uninfected teammates/staff, or the environment [7, 33]. This suggests that the strain was acquired from a nonnasal endogenous source or an environmental source. An investigation of community-dwelling rural Alaskans with CA-MRSA infection found that the majority of cases of *S. aureus* disease (>85%) were caused by MRSA, but most nasal colonizations (67%) in infected persons, household members, and uninfected control subjects involved MSSA [34]. Taken together, these studies suggest that CA-MRSA infection was not “the tip of the iceberg” that represented a clinical progression of massive background colonization. Instead, the findings suggested that CA-MRSA nasal colonization, while uncommon, could be associated with an uncommonly high risk of CA-MRSA infection. Alternatively, CA-MRSA could be acquired from nonnasal body sites or contaminated environments.

Data on CA-MRSA infection among MSM—especially HIV-infected MSM—have provided additional insight into the role of colonization in CA-MRSA infection. CA-MRSA infection among MSM has been associated with high-risk behaviors, including use of methamphetamines and other illicit drugs, high-risk sexual behavior, use of the Internet to find sexual contacts, occurrence of skin-abrading sex, and history of sexually transmitted infections [10, 35–37]. CA-MRSA infection often occurs at sites in which skin-skin contact occurs during sexual activities. In one investigation, 32 (27%) of 118 MSM in San Francisco, California, and 47 (39%) of 121 MSM from Boston, Massachusetts, had CA-MRSA infection involving the buttocks and/or genitoperineal sites [38]. Others have reported the occurrence of CA-MRSA infection in the buttocks and genitoperineal sites associated with heterosexual sexual activity [39]. The high disease burden involving buttocks and/or genitoperineal sites caused by CA-MRSA suggests that CA-MRSA strains may be transmitted during sexual contact as a result of direct skin-skin contact and may even be considered to be an agent of sexually transmitted infection.

Another investigation has shed light on the pathogenesis of CA-MRSA in MSM. In a point prevalence study of MRSA colonization among community-dwelling HIV-infected MSM (among whom CA-MRSA infections occurred frequently), nasal MRSA colonization was uncommon (7 [4%] of 158 MSM); it was relatively uncommon when compared with MSSA colonization (36 [23%] of 158 MSM) [40]. Among the 6 patients with recent, prior MRSA infection, only 1 was colonized with MRSA, suggesting that nasal colonization may have only a modest role in infection pathogenesis and that the CA-MRSA infection was acquired via other routes.

Other data support the role of nonnasal colonization in the pathogenesis of CA-MRSA. One investigation of 65 patients

with acute CA-MRSA infection found that 40% were colonized with MRSA and that the prevalences of MRSA colonization in the nares, axilla, inguinal area, and rectum were 26%, 8%, 20%, and 15%, respectively [41]. In contrast, in 35 subjects with acute CA-MSSA, HA-MRSA, or HA-MSSA infection, nonnasal *S. aureus* colonization was rare (3% of subjects). This suggests that colonization patterns in CA-MRSA infection may be distinct from the patterns of traditional *S. aureus* infection and thus play a role in, for example, the sexual transmission of CA-MRSA.

THE ROLE OF FOMITES IN OUTBREAKS OF CA-MRSA INFECTION

Outbreaks of CA-MRSA infection have repeatedly occurred among athletes. In these outbreaks, players are believed to spread the infection through repeated skin-skin contact, especially contact between broken skin, which occurs in games and practices [33]. In these outbreaks, CA-MRSA infection was associated with exposures to various contaminated fomites, including whirlpools, shared razors, and shared towels [7, 33]. Other fomites implicated in outbreaks of sports team-associated CA-MRSA infection include benches, body suits worn by fencers, and even a bar of soap [6, 33, 42]. In non-sports team outbreaks, sauna benches have been implicated [34]. In non-outbreak settings, close contact with a person who has a skin infection was also associated with CA-MRSA infection [43]. Because *S. aureus* can colonize commonly touched household objects, such as toilet handles, doorknobs, and kitchen sinks [44], it is feasible that households can serve as reservoirs for CA-MRSA strains and may play an important role in recurrent infections that can plague households [20, 21, 23].

Environmental sources of *S. aureus* as a cause for infection are not new or unique to CA-MRSA infection. In hospitals, *S. aureus* and MRSA have been isolated from stethoscopes, pagers, bed spaces, workstations, and other places [45–47]. Aggressive control of MRSA strains in the environment has contributed to effective strategies to prevent MRSA infection. For example, in The Netherlands, the so-called “search-and-destroy” policy has minimized HA-MRSA infections to such a degree that they have become uncommon, and the rate of HA-MRSA in The Netherlands is far below the rates in neighboring countries [48]. One key component of the search-and-destroy method is aggressive environmental (hospital ward) cleaning, in which wards where MRSA has been isolated are closed and extensively cleaned [49]. Although the reason behind the success of the search-and-destroy method is almost certainly multifactorial (e.g., it also involves aggressive screening and decolonization of patients and health care workers, among other measures) [49], its heavy emphasis on environmental decontamination may be a key component. Its success compared with other MRSA control measures lends credence to the notion that en-

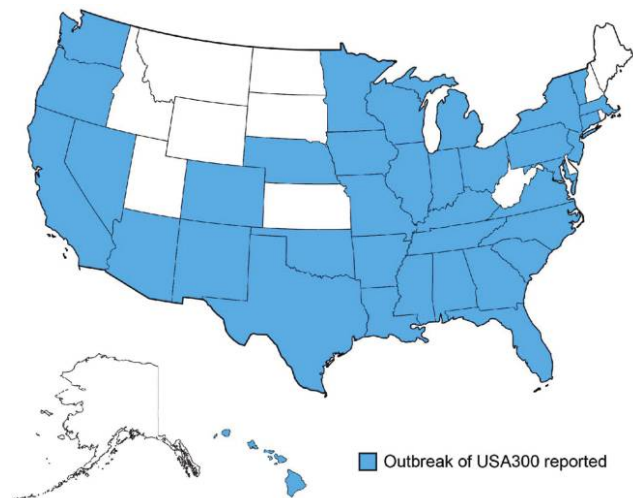


Figure 1. Outbreaks of community-associated methicillin-resistant *Staphylococcus aureus* infection due to USA300 in the United States, as documented to date.

vironmental sources are an important component of MRSA pathogenesis.

Clearly, the dynamics of community living differ markedly from the dynamics of health care settings. On the basis of CA-MRSA outbreak data, it is possible that infection pathogenesis relies much more on acquisition from environmental sources and less on antecedent nasal colonization. In fact, a conceptual model of CA-MRSA transmission highlights noncolonization routes of CA-MRSA acquisition. This model, the “Five Cs of CA-MRSA Transmission” [50, 51], was developed by the Centers for Disease Control and Prevention and suggests that MRSA infection results from the following constellation of risks: (1) contact (direct skin-skin contact); (2) cleanliness; (3) compromised skin integrity; (4) contaminated objects, surfaces, and items; and (5) crowded living conditions. Some have added a 6th “C”: exposure to antibiotic capsules (and tablets, liquids, etc.) on the basis of data that prior antibiotic use is a risk for CA-MRSA acquisition [33, 34, 52]. The 5 Cs model is important in that it helps explain CA-MRSA infections found in outbreak situations. This model’s role outside of outbreaks may not be as clear, because crowding living situations may not play a major role (e.g., New York City, to date, has experienced a relatively low rate of CA-MRSA infection) [53]. Taken in sum, data from outbreaks of CA-MRSA infection and from endemic infections suggest that antecedent nasal colonization may play a much less prominent role in the pathogenesis of CA-MRSA than was previously believed.

USA300: THE PROTOTYPICAL CA-MRSA STRAIN

The prevalence of MRSA disease in the United States has increased dramatically as a result of the emergence of the CA-

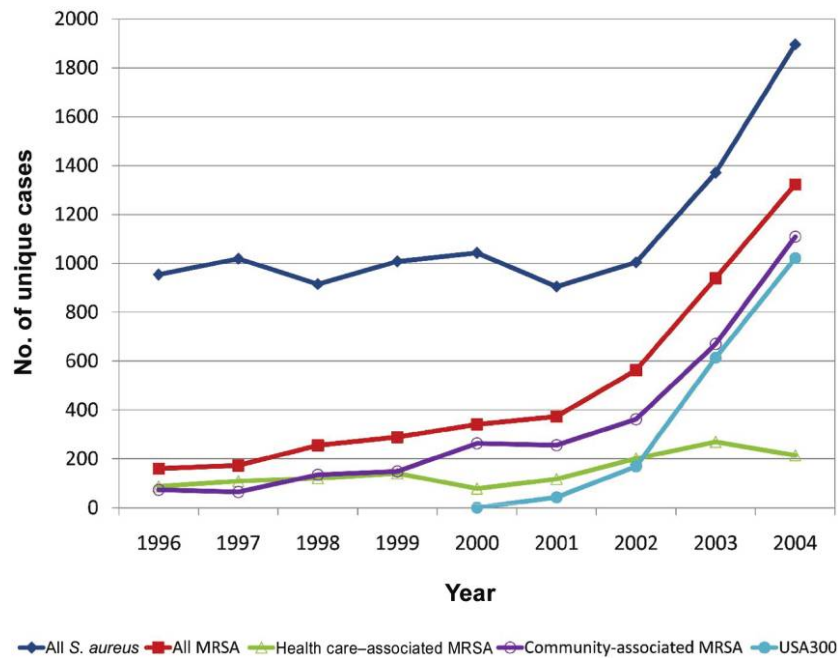


Figure 2. Community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) clinical isolates identified through laboratory-based surveillance at the San Francisco Community Health Network (San Francisco, CA) from 1 January 1996 through 31 December 2004. Community-associated MRSA isolates were obtained from a clinical specimen from an outpatient or within the first 72 h after hospital admission. Health care-associated MRSA isolates were obtained after 72 h of hospital admission or from patients residing in long-term care facilities. USA300 was defined by PFGE with *Sma*I.

MRSA clone USA300. First isolated in 2000 [54], USA300 has been implicated in epidemiologically unassociated outbreaks in at least 38 US states (figure 1) [5–7, 10, 20, 33, 39, 42, 52, 54–68]. Although many USA300 infections occur in the context of outbreaks, many are sporadic and do not involve any well-defined populations [69, 70]. USA300 is now also epidemic in many communities across the United States and accounts for >50% of all *S. aureus* infections [53, 71, 72]. Longitudinal analysis of *S. aureus* disease at an urban medical center in the United States illustrates the epidemic character of this clone (figure 2) [73, 74]. The frequency of CA-MRSA disease increased >15-fold between 1996 and 2004, resulting in a concomitant doubling of overall *S. aureus* disease. This epidemic could be attributed entirely to the rapid dissemination of a single clone of this species: from 1 case involving USA300 in 2000 to 1021 cases involving USA300 in 2004 (figure 2).

The international spread of USA300 has been recently reported, with outbreaks of infection in Canada and many European countries [75–81]. Exportation of USA300 may be facilitated by a history of recent travel to the United States [75–77]. It is of interest that USA300 first gained a foothold in Canada among persons with a history of incarceration, illicit drug use, and homelessness [82]; the same risk factors were noted among the early patients infected with the USA300 strain described in the United States [5, 54, 55, 73], suggesting that USA300 may emerge in the more marginalized populations

with increased frequency of person-person contact. However, this strain has clearly also established itself in nonmarginalized populations, such as healthy children [72]. The long history of effective MRSA control and prevention in some countries, such as The Netherlands, could be unraveled by community dissemination of USA300.

USA300 has become such a globally successful CA-MRSA clone in terms of causing human disease that it is reasonable to think of it as the prototypical CA-MRSA strain. Thus, understanding the pathogenesis of USA300 infection may be critical to understanding the pathogenesis of CA-MRSA infection. Its unique molecular characteristics may also be key components of the pathogenesis of CA-MRSA.

DISTINCT MOLECULAR MAKEUP OF USA300 CA-MRSA STRAINS

Presence of Pantone-Valentine leukocidin (PVL) is epidemiologically strongly associated with USA300 and other CA-MRSA strains. The vast majority PVL-positive *S. aureus* isolates found worldwide are clustered in just 4 CA-MRSA lineages: ST1/MW2, the US Midwest clone; ST8/USA300, the epidemic-prone American clone; ST30/USA1100, the Southwest Pacific Oceania clone; and ST80, the European clone. The linkage of PVL to the 4 CA-MRSA genetic backgrounds may explain some of the unique epidemiological properties associated with CA-MRSA

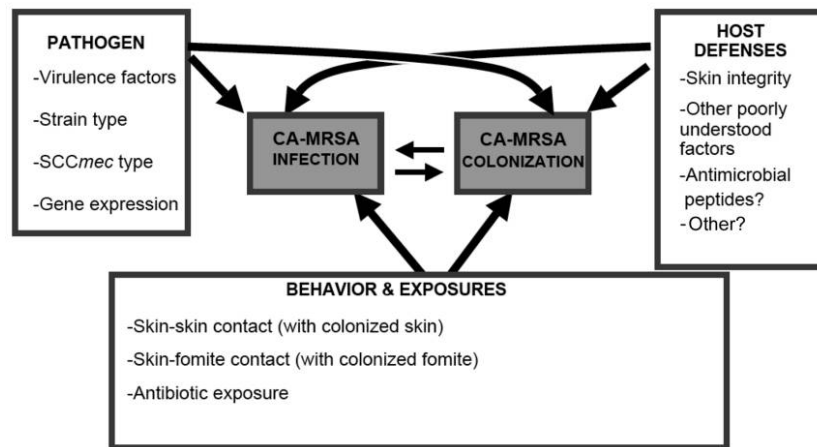


Figure 3. Conceptual model of the pathogenesis of community-associated (CA-) methicillin-resistant *Staphylococcus aureus* (MRSA). Rather than a stepwise progression of exposure to MRSA, followed by colonization, followed by infection, CA-MRSA acquisition may arise from a variety of forces that may result in either colonization or infection (without preceding colonization). In turn, colonization may lead to infection or infection to colonization.

strains, although PVL's role in the spread of CA-MRSA is not clear [83]. The role of PVL in disease pathogenesis is also controversial. Some animal studies have failed to find PVL as a major virulence factor [84], although others have found that it has a role in the pathogenesis of the pulmonary infection [85].

USA300 and other CA-MRSA strains also contain a different staphylococcal chromosomal cassette *mec* (*SCCmec*), conferring resistance to the entire class of β -lactam antibiotics. In the absence of antibiotic treatment, *SCCmec* is thought to reduce the biological fitness of MRSA [86–88]. CA-MRSA, however, carries an allotype of *SCCmec* that is smaller in size than those typically found in nosocomial strains; this may impose only a slight cost to fitness, because it does not contain resistance genes other than *mecA*, which encodes an altered target penicillin-binding protein 2a. CA-MRSA may also contain other genomic adaptations that allow it to overcome the presumed fitness cost of *SCCmec*. Integrated next to the type IV *SCCmec* element is a putative pathogenicity island called type I arginine catabolic mobile element (ACME) [89]. Type I ACME is uniquely found in USA300 and not in other *S. aureus* strains. The physical linkage between ACME and type IV *SCCmec* suggests that selection for enhanced fitness could coselect for increasing frequencies of not only β -lactam resistance but also other multidrug resistant determinants, including multidrug resistance conjugative plasmids, which are carried by a subset of USA300 strains [89].

The ACME-*SCCmec* linkage is of great interest, because it was first discovered in the USA300 genome [89]. Horizontal acquisition of ACME from the ubiquitous skin commensal *Staphylococcus epidermidis* may enhance the growth and survival of USA300 in the host—particularly on the human skin [89]. Deletion of ACME resulted in attenuated virulence of a

clinical USA300 in a rabbit infection model [90]. Because the type I ACME found in USA300 has not been found in other CA-MRSA lineages, ACME could contribute to the epidemic character unique to this clone. Indeed, only USA300 exhibits enhanced capacity to cause widespread epidemic disease and to displace other ACME-negative CA-MRSA clones, including ST1/MW2, ST30/USA1100, and ST80 [57, 73, 76, 91]. Moreover, recent comprehensive proteomic analysis revealed that USA300 produced many virulence determinants in greater abundance than did ST1/MW2, including α -hemolysin, enterotoxins Q and K, staphylokinase, and proteases [92]. In summary, there are likely pathogen-level factors in CA-MRSA strains that enhance its pathogenicity. Compared with other CA-MRSA strains, USA300 strains may have features that are particularly well suited to cause disease, although these features are, at this time, poorly understood.

HOST DEFENSES AGAINST *S. AUREUS*

The role of human host defenses against *S. aureus* is a final key factor in the pathogenesis of CA-MRSA and *S. aureus* infections. Clearly, qualitative deficiencies in neutrophil function are associated with *S. aureus* infection [93]. Other host factors associated with infection risk include antimicrobial peptides [94], although our current understanding of host response to *S. aureus* is very limited.

Skin integrity is also key to prevention of *S. aureus* infection [33]. A distinct feature of CA-MRSA disease is the high disease burden among healthy community-dwelling individuals. Many patients with CA-MRSA infection, however, have reported a breach in skin integrity that served as the portal of infection. For example, skin infections often resulted from activities that resulted in skin trauma, such as those resulting from physical

contact sports [7, 33, 42], injection drug use [95], and shaving of the genital area before sexual activity [39, 96]. Many children do not have recognized breeches in skin integrity before infection. Whether this means there was none or that these breeches were not recognized or recalled is not clear. The role of other host defenses in the pathogenesis of CA-MRSA, however, remains poorly understood.

SUMMARY

Data from outbreaks of infection and from endemic infections suggest that CA-MRSA behaves in a manner that is pathogenically distinct from HA-MRSA. Although longitudinal natural history studies have not been performed, epidemiologic and basic studies suggest that nasal colonization plays a less prominent role in the transmission and pathogenesis. These studies also suggest that CA-MRSA colonization may not commonly precede infection. Direct person-person and fomite-person transmission appear to be important routes of CA-MRSA infection. It is possible that the genetically distinct CA-MRSA strains have important nonnasal niches (e.g., inguinal regions) that act as reservoirs for transmission (e.g., via sexual behavior) or perhaps even reinfection. Unique molecular characteristics of CA-MRSA strains—especially the USA300 strain—may facilitate their pathogenicity and spread. Host factors play an important but poorly understood role in CA-MRSA pathogenesis.

There are now compelling data suggesting that the pathogenesis of CA-MRSA is unique and distinct from that of HA-MRSA. Rather than using the model of HA-MRSA that asserts that there is a stepwise progression from MRSA colonization to MRSA infection [26], we think that a model for CA-MRSA pathogenesis should consider the distinct epidemiological phenomena of CA-MRSA (figure 3). Reliance on models of HA-MRSA transmission for prevention of CA-MRSA infection may result in the development of suboptimal prevention strategies. For example, decolonization strategies that rely only on nasal decolonization may not be successful, because they do not address nonnasal colonization or decolonization of the patient's environs. Prevention efforts may require total body decolonization, decolonization of close or household contacts, and/or decolonization of the patient's household or workplace. Successful efforts to prevent CA-MRSA reinfection or transmission will need to be based on a firm understanding of the unique CA-MRSA pathogenesis. Longitudinal investigations will be key in helping us further understand CA-MRSA pathogenesis.

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