Methicillin-resistant *Staphylococcus aureus*

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Abstract | Since the 1960s, methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged, disseminated globally and become a leading cause of bacterial infections in both health-care and community settings. However, there is marked geographical variation in MRSA burden owing to several factors, including differences in local infection control practices and pathogen-specific characteristics of the circulating clones. Different MRSA clones have resulted from the independent acquisition of staphylococcal cassette chromosome *mec* (SCC*mec*), which contains genes encoding proteins that render the bacterium resistant to most β-lactam antibiotics (such as methicillin), by several *S. aureus* clones. The success of MRSA is a consequence of the extensive arsenal of virulence factors produced by *S. aureus* combined with β-lactam resistance and, for most clones, resistance to other antibiotic classes. Clinical manifestations of MRSA range from asymptomatic colonization of the nasal mucosa to mild skin and soft tissue infections to fulminant invasive disease with high mortality. Although treatment options for MRSA are limited, several new antimicrobials are under development. An understanding of colonization dynamics, routes of transmission, risk factors for progression to infection and conditions that promote the emergence of resistance will enable optimization of strategies to effectively control MRSA. Vaccine candidates are also under development and could become an effective prevention measure.

Staphylococcus aureus is a Gram-positive, nonmotile, coagulase-positive coccoid bacterium of the Firmicutes phylum. Although the *Staphylococcus* genus includes 52 species and 28 subspecies (List of Prokaryotic names with Standing in Nomenclature), *S. aureus* is by far the most clinically relevant. *S. aureus* is found in the human commensal microbiota of the nasal mucosa in 20–40% of the general population[1,2]. The reported prevalence varies owing to differences in the size and demographics of the study populations, quality of sampling and culture techniques utilized[3]. When the cutaneous and mucosal barriers are disrupted, for example, owing to chronic skin conditions, wounds or surgical intervention, *S. aureus* can gain access to the underlying tissues or the bloodstream and cause infection. Persons with invasive medical devices (such as peripheral and central venous catheters) or compromised immune systems are particularly vulnerable to *S. aureus* infection[4].

Methicillin-resistant *S. aureus* (MRSA) was first described in England in 1961 (REF.[5]), soon after methicillin was introduced into clinical practice. Methicillin was initially widely used; however, because of its toxicity, it is now no longer marketed for human use and has largely been replaced by similar, more-stable penicillins such as oxacillin, flucloxacillin and dicloxacillin[6]. Nevertheless, the term methicillin-resistant *S. aureus* continues to be used. In the decade following its initial description, MRSA was responsible for hospital outbreaks (health-care-associated MRSA (HA-MRSA)) in many parts of the world[7]. A substantial change in MRSA epidemiology was observed when it was detected in individuals without previous health-care contact (referred to as community-associated MRSA (CA-MRSA)), notably among indigenous populations in Australia in the 1980s[8] and otherwise healthy persons, including children, in the United States in the 1990s[9]. Since the mid-2000s, it has also been associated with livestock exposure (livestock-associated MRSA (LA-MRSA))[10].

Several *S. aureus* clones (that is, bacteria that are indistinguishable from each other by a variety of genetic tests (for example, pulsed-field gel electrophoresis, multilocus enzyme electrophoresis or ribotyping) or that are so similar that they are presumed to be derived from a common parent[11]) have developed into MRSA by uptake via horizontal gene transfer of staphylococcal cassette chromosome *mec* (SCC*mec*)[12], a mobile genetic element that encodes the genes *mecA* or *mecC*, which confer resistance to methicillin and, therefore, to most

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β-lactam antibiotics. MRSA is often also resistant to multiple other antibiotic classes. Indeed, *S. aureus* has the remarkable ability to acquire resistance to any antibiotic[7], which has major implications for current as well as future treatment options for this pathogen.

Individuals with MRSA colonization or carriage (that is, the presence of bacteria that do not cause a detectable host immune response, cellular damage or clinical signs and symptoms of infection) have an increased risk of subsequent infection and are an important source of person-to-person transmission. Health-care facilities host persons who are predisposed to infection (for example, owing to invasive procedures and/or immune compromise) and are environments with high antibiotic selection pressure (which can contribute to the selection of antimicrobial resistance in bacteria) and frequent contact between individuals. These conditions have facilitated the epidemic spread of MRSA in hospitals; MRSA is now endemic in many health-care facilities throughout the world and, as a consequence, it has become a major focus for infection control efforts globally.

This Primer reviews the epidemiology, pathophysiology, diagnosis, prevention, management and clinical effect of MRSA, focusing on HA-MRSA, and discusses future research priorities. In some aspects of the epidemiology and pathophysiology, where methicillin resistance does not substantially affect the behaviour of the species, data regarding *S. aureus* in general have also been included.

Epidemiology

The emergence and worldwide spread of MRSA represent some of the most important events in the epidemiology of infectious diseases. Although MRSA was first reported in the early 1960s[5], whole-genome sequencing (WGS) of 209 early MRSA isolates suggests that MRSA emerged in the mid-1940s — that is, much earlier than the introduction of methicillin[13]. In fact, it has been hypothesized that it was the extensive use of penicillin rather than the introduction of methicillin that drove the emergence of MRSA[13].

Many countries have experienced an increasing burden of MRSA since the 1960s. The burden of MRSA has notable geographical variation, ranging from low prevalence in Scandinavia to the highest prevalence in parts of America and Asia[14] (FIG. 1). The spread of MRSA seems to occur by at least two mechanisms: spread of existing resistant clones and acquisition of SCC*mec* by a methicillin-sensitive *S. aureus* (MSSA) strain (a strain is a descriptive subdivision of a species based on phenotypic and/or genotypic characteristics[11]). Details of the mechanism of horizontal transfer of SCC*mec* are not well understood, but epidemiological evidence shows that this resistance mechanism has spread to most clones of *S. aureus*, in both human and animal pathogenic strains[15,16]. The following sections discuss the epidemiology of MRSA in different regions; in general, less comprehensive data are available from low-income and middle-income countries.

MRSA in Europe

Surveillance data from European countries show a general trend towards increasing MRSA prevalence from the north to the south of the continent, with <5% of *S. aureus* isolated from invasive infections being methicillin-resistant in northern Europe (for example, the Netherlands, Norway, Sweden and Denmark) compared with 25–50% in southern Europe (for example, Portugal, Spain, Italy and Greece)[17] (FIG. 2). Varying infection control practices and antimicrobial usage are thought to contribute to the observed differences[18].

After years of increasing MRSA prevalence, since the early 2000s, steady or decreasing prevalence has been observed in a number of countries[17] (FIG. 2). This decline has been associated with the implementation of improved national control interventions. However, some experts argue that widespread declines in previously hyperendemic MRSA clones are attributable to changes in the organism itself, with loss in survival fitness resulting in shifts in circulating clones[19,20].

With the declines largely occurring in HA-MRSA, there has been increasing recognition of animal reservoirs for human MRSA in Europe, particularly from food-producing animals such as pigs, cattle and poultry[21]. This LA-MRSA, predominantly belonging to clonal complex 398 (CC398), has primarily caused infections in those who work with livestock (particularly in the Netherlands, northwestern Germany[22] and Spain[23]), but LA-MRSA infections have also been observed among the general population[24,25]. However, at present, sustained person-to-person transmission of LA-MRSA seems to be uncommon[25,26].

MRSA in America

In the United States, ~53% of *S. aureus* clinical isolates were methicillin-resistant in 2005 (REF.[27]). MRSA has also been identified as the most common cause of skin and soft tissue infections (SSTIs) presenting to US hospital emergency departments, which is largely attributed to the emergence of CA-MRSA (particularly the USA300 clone in the early 2000s)[28,29] (FIG. 3). The changes in epidemiology since the emergence of CA-MRSA in the

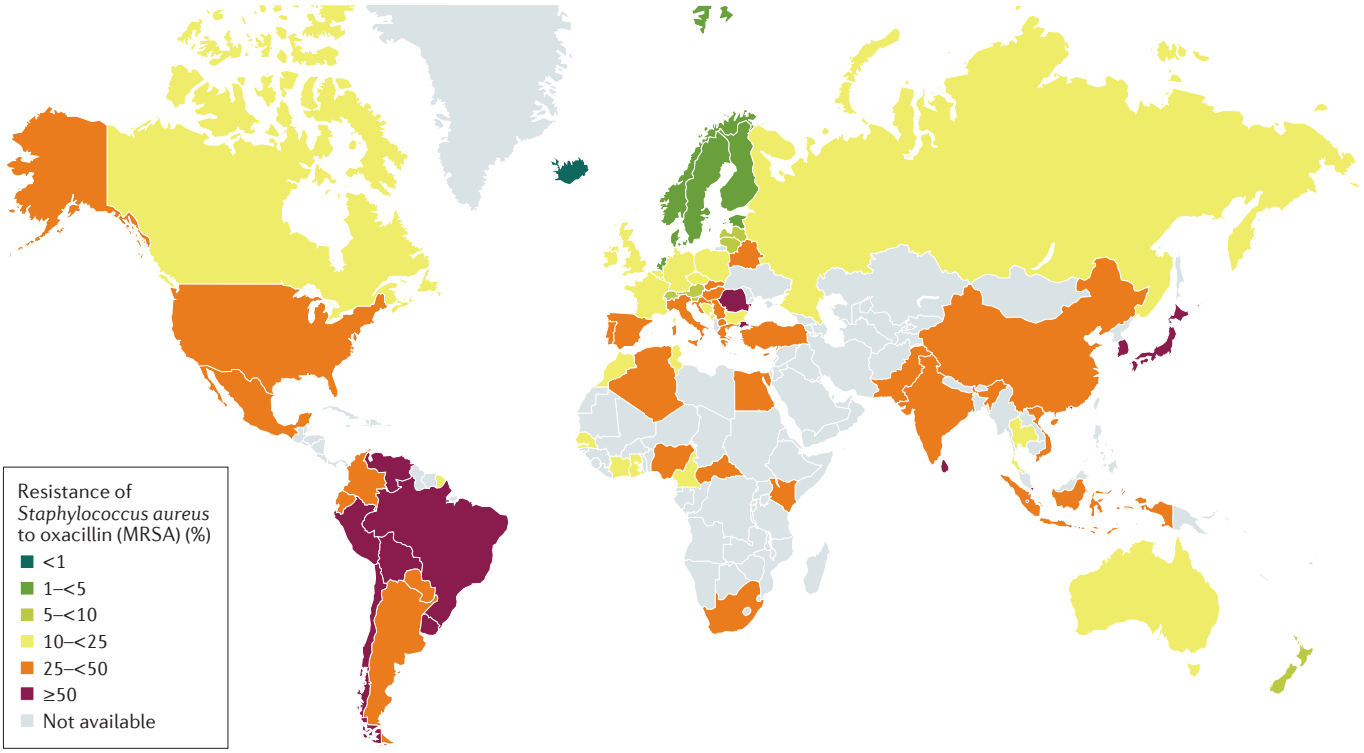

Figure 1 | **Worldwide prevalence of MRSA.** The percentage of *Staphylococcus aureus* isolates that are resistant to oxacillin (that is, methicillin-resistant *S. aureus* (MRSA) isolates) is shown. Data include aggregated resistance rates. Owing to differences in the scope of collections and testing methods, caution should be exercised in comparing data across countries. Data represented are adapted from the Center for Disease Dynamics, Economics & Policy Resistance Map; data for the following countries are adapted from REF.[223], Elsevier: Algeria, Bolivia, Brazil, Cameroon, Central African Republic, Chile, Colombia, Egypt, Hong Kong, Indonesia, Ivory Coast, Japan, Kenya, Malta, Morocco, Nigeria, Paraguay, Peru, Senegal, Singapore, South Korea, Sri Lanka, Tunisia and Uruguay.

country have made the distinction between CA-MRSA and HA-MRSA less clear[30,31]. A parallel epidemic of CA-MRSA closely related to USA300, the USA300 Latin-American variant (USA300-LV), was first identified in Colombia in 2005 and has emerged as the most prevalent CA-MRSA clone in northern South America[32]. The geographical spread of USA300 clones from South America to Europe has also been documented by genomic analysis of MRSA isolates in Switzerland[33].

Similar to experiences in Europe, the incidence of HA-MRSA in the United States has shown decreasing trends since 2005, with hospital-onset HA-MRSA infections decreasing by 54%[34]. In 2007, Veterans Affairs Hospitals throughout the United States introduced a multifaceted prevention strategy including universal MRSA screening, contact precautions, hand hygiene promotion and institutional culture change[35]. This programme was associated with a significant reduction in MRSA infections by 62% in intensive care units (ICUs) and 45% in other hospital wards. In addition, many US states mandated specific MRSA control measures, and in 2008, the Centers for Medicare and Medicaid Services introduced financial penalties to hospitals for preventable health-care-acquired infections, although a large evaluation of this intervention showed no evidence that it was associated with a reduction in health-care-associated infections[36].

MRSA in the Asia–Pacific region

MRSA is endemic in most hospitals in Asia, and some Asian countries have among the highest MRSA prevalence in the world[37]. However, most available data are from high-income countries (for example, Japan, South Korea and Singapore), with limited information from other nations. Although there is country-to-country variability, MRSA accounts for up to 50% of *S. aureus* bloodstream infections in parts of Asia[37]. Japan and South Korea have particularly high MRSA prevalence — with >70% of clinical isolates in South Korea being MRSA on the basis of regional surveillance data from 2011 (REFS[37,38]). High methicillin resistance rates are thought to be related to widespread inappropriate antimicrobial use (for example, self-medication and over-the-counter use) as well as high population density facilitating rapid transmission of multidrug-resistant organisms[37]. Nevertheless, some countries in Asia (for example, Taiwan[39]) that experienced a peak in HA-MRSA prevalence in the late 1990s have shown declining prevalence since the early 2000s[38].

In Australia, among health-care-associated *S. aureus*, MRSA has accounted for 20–33% of isolates since 2001 (REF.[40]). Like Europe and the United States, Australia has implemented a range of local and national interventions that have been associated with a reduction in HA-MRSA bloodstream infections since 2002 (REF.[41]). Since the

earliest reports of CA-MRSA in remote indigenous populations in Western Australia in the late 1980s[8], several distinct CA-MRSA clones circulating in the region have been identified, including virulent clones such as sequence type 93 (ST93; Queensland clone) and ST30 (Southwest Pacific clone)[42].

MRSA in Africa

MRSA prevalence data from Africa are variable in coverage and quality. Published data are available for South Africa, Nigeria and countries from the Mediterranean basin, but there is a paucity of data from other nations[43]. Most data are also from single-centre studies, and information from broader surveillance systems is lacking. In addition, most studies have relied on phenotypic methods to identify MRSA, and these tests might be less reliable than genotypic methods depending on the choice of antibiotic used to detect MRSA[43].

MRSA prevalence is estimated at <50% in most countries, with several countries reporting prevalence of <25%[43]. However, MRSA prevalence has been increasing since the early 2000s in reports from most countries, although it has started to decrease in South Africa (from 36% in 2006 (REF.[44]) to 24% during 2007–2011 (REF.[45]))[43]. Differences in the availability and use of antimicrobials, incidence of HIV infection (a risk factor for MRSA colonization[46]) and infection control practices could potentially account for some of the variation between countries.

Mechanisms/pathophysiology

Staphylococcus aureus colonization

S. aureus colonization precedes the development of infection in most cases[47]. Less commonly, infection can occur in the absence of known *S. aureus* colonization, for example, as a result of contamination of catheters or wounds owing to suboptimal infection control practices by health-care workers. The principal site of *S. aureus* colonization is the nose, although colonization at other sites occurs, notably in the throat and perineum[48]. Longitudinal studies have identified three temporal patterns of *S. aureus* (including both MSSA and MRSA) colonization[49]. Continuous *S. aureus* colonization was found in ~15% of individuals (known as persistent carriers), intermittent colonization was present in 70% of individuals (which means that the majority of individuals can repeatedly acquire *S. aureus* and spontaneously clear it), and *S. aureus* was never detected in 15% of

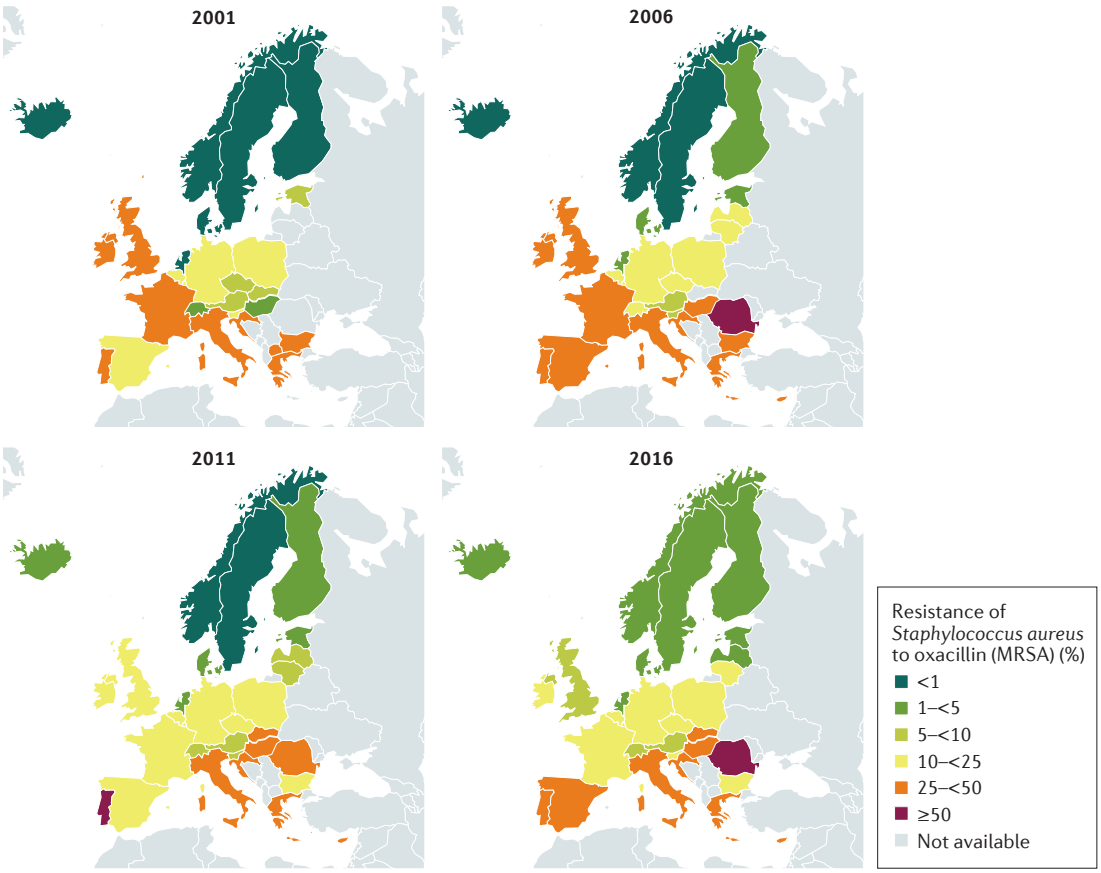

Figure 2 | **Prevalence of MRSA in Europe.** Surveillance data show that methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence generally increases from the north to the south of Europe. Between 2001 and 2016, several European countries reported a decreasing trend in the prevalence of MRSA. For example, France and the United Kingdom have experienced declining MRSA rates since the early 2000s, which are largely attributed to improved multifaceted national infection control programmes[224,225]. Figure adapted with permission from Surveillance Atlas of Infectious Diseases, European Centre for Disease Prevention and Control.

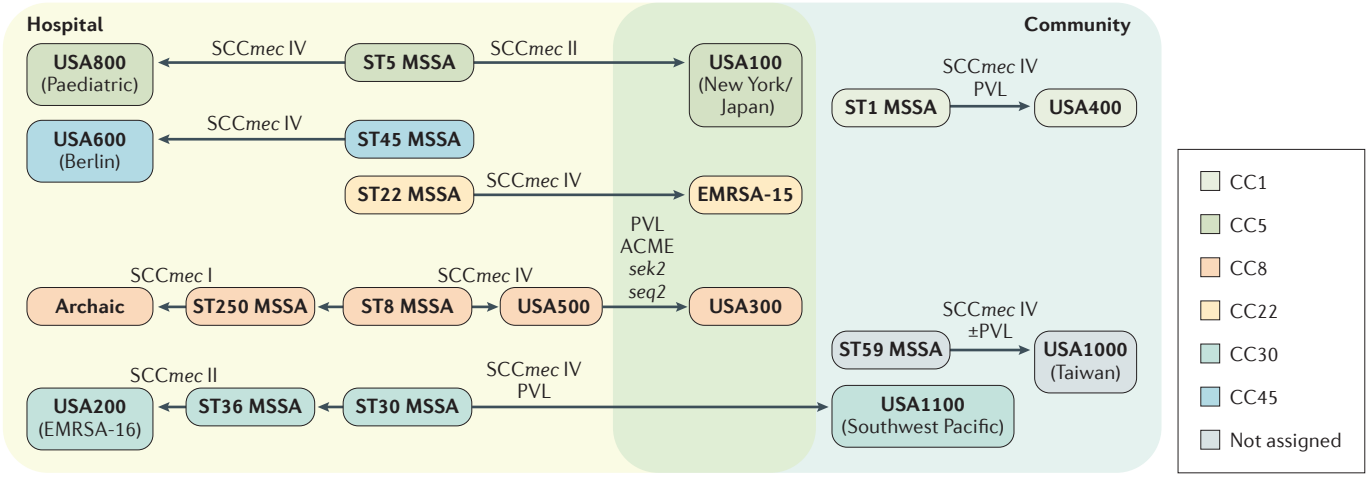

Figure 3 | **Most frequent MRSA clones.** Sequence types (STs) of methicillin-sensitive *Staphylococcus aureus* (MSSA) are grouped into clonal complexes (CCs) by their similarity to a founder allelic profile (genotype)[226]. STs have different molecular properties that enable monitoring of the geographical spread of different clones. STs of MSSA can evolve into MRSA by acquiring staphylococcal cassette chromosome *mec* (SCC*mec*), of which there are different types (represented by roman numerals). Commonly used clone names are within parentheses. Numbers in the names of MRSA USA clones are based on pulsed-field gel electrophoresis analysis. ACME, arginine catabolic mobile element; EMRSA, epidemic MRSA; PVL, Panton–Valentine leukocidin; *sek2* and *seq2* are staphylococcal genes encoding enterotoxins. Figure adapted with permission from REF.[227], Oxford University Press.

individuals (referred to as non-carriers)[49]. Similar results were found by other studies[50]. Studies exploring specific host polymorphisms in genes involved in the inflammatory response[51] indicate that there are underlying host factors that determine the carriage status. However, the precise nature of these underlying factors is not completely understood. For MRSA in particular, the duration of colonization is variable, and reported estimates could be biased by antibiotic treatment, which can shorten the duration of colonization. In one study in patients with MRSA colonization at the time of hospital discharge[52], the median duration of colonization was 282 days; in this population, 81% of individuals had chronic skin lesions, a known risk factor for MRSA colonization, which may have contributed to prolonged carriage. Besides host factors, factors associated with the pathogen itself as well as the nasal microbiota can influence host carrier status.

Dynamics of colonization. During *S. aureus* colonization, initial bacterial adherence to the host's epithelial cells is mediated by teichoic acid on the cell wall, whereas microbial surface components recognizing adhesive matrix molecules play a part at a later stage of nasal colonization[53,54]. Of these components, *S. aureus* clumping factor B (ClfB), has been studied in vitro and in human volunteers[55]. A wild-type strain and its single locus *clfB* knockout variant were inoculated into the nose; the knockout variant was cleared significantly more rapidly than the wild-type strain. However, ClfB-deficient strains can still interact with nasal cells, indicating that there are several independent microbial surface components that play a part in colonization[56]. It must also be noted that only one strain was used in this study.

Besides host and pathogen factors, the interaction of *S. aureus* with other nasal-colonizing species (for example, *Corynebacterium* spp., *Propionibacterium acnes*, *Staphylococcus lugdunensis* and *Staphylococcus epidermidis*) has a role in *S. aureus* colonization. Studies of the nasal microbiota have shown that the presence of some species correlates with the presence or absence of *S. aureus* (for example, *S. epidermidis* has been positively correlated with the presence of *S. aureus*)[57,58]. The organisms of the nasal microbiota are in competition with each other in several ways. For example, they compete for adhesion sites and nutrients: there are low amounts of nutrients in the human nose. *S. aureus* can survive in environments with lower levels of nutrients than coagulase-negative staphylococci can[59], possibly owing to differences in metabolism, and hence is better adapted to the human nose. However, no difference in nutrient levels has been observed between carriers and non-carriers[59]. Microbiota species also compete by antibiosis, that is, certain strains can produce antimicrobial molecules that inhibit their microbial competitors. *S. lugdunensis*, for example, produces an antimicrobial compound called lugdunin that inhibits and destroys *S. aureus* (including MRSA) in vitro and in a mouse model, possibly by leading to rapid breakdown of bacterial energy resources[60]. In humans, nasal colonization with *S. lugdunensis* has been associated with a sixfold lower risk of colonization with *S. aureus*. These findings are certainly interesting but explain only a minority of carriage patterns, as *S. lugdunensis* colonization has been reported in only 9 – 26% of the general population[60,61]. Finally, *S. aureus* also competes by induction of host defences, that is, it induces the production of host antimicrobial proteins that are less harmful to *S. aureus* than to other commensal bacteria[62]. Many studies support the role of these mechanisms in the interactions between *S. aureus* and the commensal microbiota, but a single mechanism is insufficient to explain all observed carriage patterns.

Table 1 | **Major *Staphylococcus aureus* virulence factors and corresponding host ligands**[a]

Type of virulence factors	Virulence factors	Corresponding host ligands
MAMPs		
Chemotactic MAMPs	• Formylated peptides • Phenol-soluble modulins (PSMs)	• *N*-Formyl-peptide receptor (FPR) 1 and FPR2
Non-chemotactic MAMPs	• Lipoproteins[b] • DNA • Peptidoglycan	• Toll-like receptor (TLR) 2 and TLR9 • Nucleotide-binding oligomerization domain-containing protein 2 (NOD2)
Adhesins		
Surface proteins	• Fibronectin-binding protein A (FnBPA) and FnBPB • Collagen adhesin (Cna)[b] • Iron-regulated surface determinant protein A (IsdA)	• Fibronectin • Collagen • Cytokeratin 10 (also known as KRT10) • Loricrin
Glycopolymers	• Wall teichoic acid (WTA)	• Scavenger receptors
Evasins		
MAMP receptor inhibitors	• Chemotaxis inhibitory protein of *S. aureus* (CHIPS)[b] • FPR-like 1 (FPRL1) inhibitory protein (FLIPr)[b] • FLIPr-like[b] • Staphylococcal superantigen-like protein 3 (SSL3)[b] • SSL5[b]	• FPR1 • C5a anaphylatoxin chemotactic receptor (C5aR1) • FPR2 • TLR2
Chemokine receptor inhibitors	• SSL5[b] • SSL10[b]	• Several chemokine receptors
PMN extravasation inhibitors	• SSL5[b] • Extracellular adherence protein (Eap)[b]	• P-Selectin glycoprotein ligand 1 (PSGL1) • Intercellular adhesion molecule 1 (ICAM1)
Coagulation factors	• Coagulase (Coa) • Secreted von Willebrand factor binding protein (vWbp) • Clumping factor A (ClfA) • ClfB	• Prothrombin • Fibrinogen
Anticoagulants	• Staphylokinase[b]	• Plasmin
Complement inhibitors	• Zinc metalloproteinase aureolysin • Staphylococcal complement inhibitor (SCIN)[b] • Fibrinogen-binding protein (Efb)[b] • Extracellular complement-binding protein (Ecb, also known as extracellular fibrinogen-binding protein)[b] • SSL7[b] • Immunoglobulin-binding protein Sbi[b]	• Complement proteins C3, C3b, C3bBb and C5a • Complement factor H
Opsonophagocytosis inhibitors	• *Staphylococcus* protein A (SpA) • Immunoglobulin-binding protein Sbi[b] • Microcapsule[b] • FLIPr[b]	• Immunoglobulin G (IgG) • Immunoglobulin-γ receptor (FcγR)
Synthases of anti-phagocytic mediators	• Adenosine synthase (AdsA)	• Adenosine monophosphate
Inhibitors of PMN killing	• Catalase • Superoxide dismutase [Mn] 1 (SodA) • Staphyloxanthin • Eap[b] • Staphylococcal peroxidase inhibitor (SPIN) • O-Acetyltransferase A (OatA) • Multiple peptide resistance factor (MprF) • D-alanine transfer protein A (DltA), DltB, DltC and DltD • Thermonuclease (Nuc)	• Reactive oxygen species • Elastase • Lysozyme • Defensins • Neutrophil extracellular traps (NETs)
Toxins		
Pore-forming protein toxins	• α-Toxin • Bi-component γ-Haemolysin (Hlg) AB • Bi-component HlgCB • Leukocidin (Luc) ED[b] • LucAB • Panton–Valentine leukocidin (PVL)[b]	• Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) • Several chemokine receptors • Duffy antigen/chemokine receptor (DARC, also known as atypical chemokine receptor 1) • C5aR1
Pore-forming peptide toxins	• PSMα1–PSMα4 • PSMβ1 and PSMβ2 • SCC*mec*-encoded PSM (PSM*mec*)[b] • δ-Toxin (also known as δ-haemolysin, Hld)	• Host cell membranes

Table 1 (cont.) | **Major *Staphylococcus aureus* virulence factors and corresponding host ligands**[a]

Type of virulence factors	Virulence factors	Corresponding host ligands
Toxins (cont.)		
Superantigen toxins	• Toxic shock syndrome toxin 1 (TSST1)[b] • Enterotoxins types (SE) A-Q[b] • Staphylococcal enterotoxin-like X (SEIX)[b]	• Major histocompatibility complex (MHC) class II • T cell receptor
Sphingomyelinase	• β-Haemolysin (Hlb)[b]	• Sphingomyelin
Proteolytic toxins	• Exfoliative toxins (Etx)[b]	• Desmoglein 1

This list is not exhaustive of all the virulence factors and host ligands reported. KRT10, keratin, type I cytoskeletal 10; MAMP, microorganism-associated molecular pattern; PMN, polymorphonuclear leukocyte; SCC*mec*, staphylococcal cassette chromosome *mec*. [a]With crucial roles in the infection of wounds, abscess formation and subsequent dissemination to the bloodstream. [b]Presence, integrity or allelic identity varies substantially between clones[63,64,230].

Virulence

S. aureus has an extensive arsenal of virulence factors (including adhesive, host-cell damaging and immunomodulatory molecules) that vary in their presence or specificity between clones[63,64], a variability that is reflected by the high diversity of infections that *S. aureus* can cause[65,66] (TABLE 1). Many virulence genes are found on mobile genetic elements; thus, their combination differs substantially between clones and even between closely related strains. The potential association of specific virulence factors with certain types or aggressiveness of *S. aureus* infections remains elusive, probably because many of these factors have redundant, partially overlapping functions. Furthermore, many virulence factors cannot be investigated in animal models because they are human-specific[67]. This section focuses on the most prominent virulence mechanisms and typical routes of invasion.

Initiation of infection. *S. aureus* SSTIs are usually initiated by bacterial transfer (probably via hand contact) from the major reservoir in the nose to open microlesions and wounds on the skin[68,69] (FIG. 4a). *S. aureus* surface proteins (for example, fibronectin-binding protein A (FnBPA), FnBPB, clumping factor A (ClfA), ClfB and collagen adhesin (Cna)) bind to extracellular matrix proteins and enable the bacteria to attach to and multiply on wounded tissues[70]. The capacity of *S. aureus* to adhere to and form biofilms (that is, sticky agglomerations of microorganisms embedded in an extracellular matrix; biofilms facilitate resistance to mechanical interference, host defences and antibiotic treatment) on artificial plastic or metal surfaces renders *S. aureus* a frequent cause of catheter-associated or joint-replacement-associated infections or of ventilator-associated pneumonia[71]. The subsequent influx of polymorphonuclear leukocytes (PMNs) is manipulated by *S. aureus*[72], which shapes local inflammation[73].

Abscess formation. The *S. aureus* coagulase proteins cause the formation of a fibrin pseudo-capsule surrounding bacteria and infiltrated PMNs, thereby preventing further leukocyte influx[74] (FIG. 4b). *S. aureus* can impede opsonization, for instance, by production of a polysaccharide microcapsule[66] and inhibition of the complement cascade[75]. However, the microcapsule is absent from important MRSA clones such as USA300 (REF.[63]). Bacteria that are phagocytosed by PMNs can survive not only by counteracting PMN killing mechanisms[72,76,77] but also by gradually destroying them with the help of cytolytic toxins. For example, many CA-MRSA clones produce pore-forming peptide (phenol soluble modulins (PSMs)) and protein toxins (α-toxin (also known as α-haemolysin) and several bi-component leukocidins such as the Panton–Valentine leukocidin (PVL)), which are host species-specific and bind to host leukocyte membranes, leading to the formation of pores and causing lytic cell death[7,78], thereby increasing bacterial virulence. The massive inflammation elicited by activated or necrotic PMNs is further increased by *S. aureus* superantigen toxins, which bind to the major histocompatibility complex (MHC) class II of antigen-presenting cells and activate a large percentage of T cells nonspecifically, causing systemic hyper-inflammation referred to as 'cytokine storms'[79].

Systemic infection. Abscesses might be disrupted at later stages, releasing pus and live bacteria either towards the skin surface to promote pathogen transmission or towards the bloodstream to cause bacteraemia (FIG. 4c). Endovascular *S. aureus* can adhere to endothelial surfaces and platelets[80,81], and this adhesion can initiate endocarditis, promote the formation of metastatic abscesses or induce bacterial uptake into endothelial cells, where the bacteria are difficult to reach by antibiotics and host defence molecules[82]. The agglutinating activity of coagulases is thought to contribute to systemic blood coagulation, and massive release of microorganism-associated molecular pattern molecules along with superantigen toxin-induced cytokine storms leads to fulminant systemic inflammation, sepsis and multi-organ failure if the endovascular spread of the bacteria cannot be contained[83].

Regulation and adaptation. Most of the *S. aureus* virulence factors are differentially regulated by the accessory gene regulator (Agr) quorum-sensing system and other regulatory networks[84]. Many CA-MRSA clones such as USA300 have very active Agr systems, which leads to abundant expression of toxins and corresponds to a high capacity to cause SSTIs and invasive infections even in healthy individuals[85]. By contrast, many HA-MRSA clones contain an additional SCC*mec*-encoded phenol-soluble modulin (PSM; PSM*mec*),

whose mRNA dampens Agr expression[86]. Accordingly, Agr is not very active in many HA-MRSA clones, which produce lower amounts of toxins but higher levels of adhesins and often cause bacteraemia via infected catheters or implanted medical devices. High virulence seems to even be detrimental for *S. aureus* in bacteraemia, with many isolates from bloodstream infections found to bear Agr-inactivating point mutations[87]. Elucidating virulence mechanisms whose inhibition would render *S. aureus* most vulnerable will be crucial for the development of new preventive and therapeutic strategies against MRSA.

Mechanisms of methicillin resistance

A crucial event in the evolution of *S. aureus* was the independent acquisition of the SCC*mec* complex in the early 1960s by several multidrug-resistant strains (resistant to penicillin, streptomycin, tetracycline and erythromycin[88]), rendering *S. aureus* resistant to most members of the β-lactam family of antibiotics[5] (FIG. 3). Twelve known SCC*mec* types (I–XII) have been identified and are classified according to the type of cassette chromosome recombinase (*ccr*) complex and the class of the *mec* complex (TABLE 2). Types I, II and III are large SCC*mec* elements harbouring genes that confer resistance to

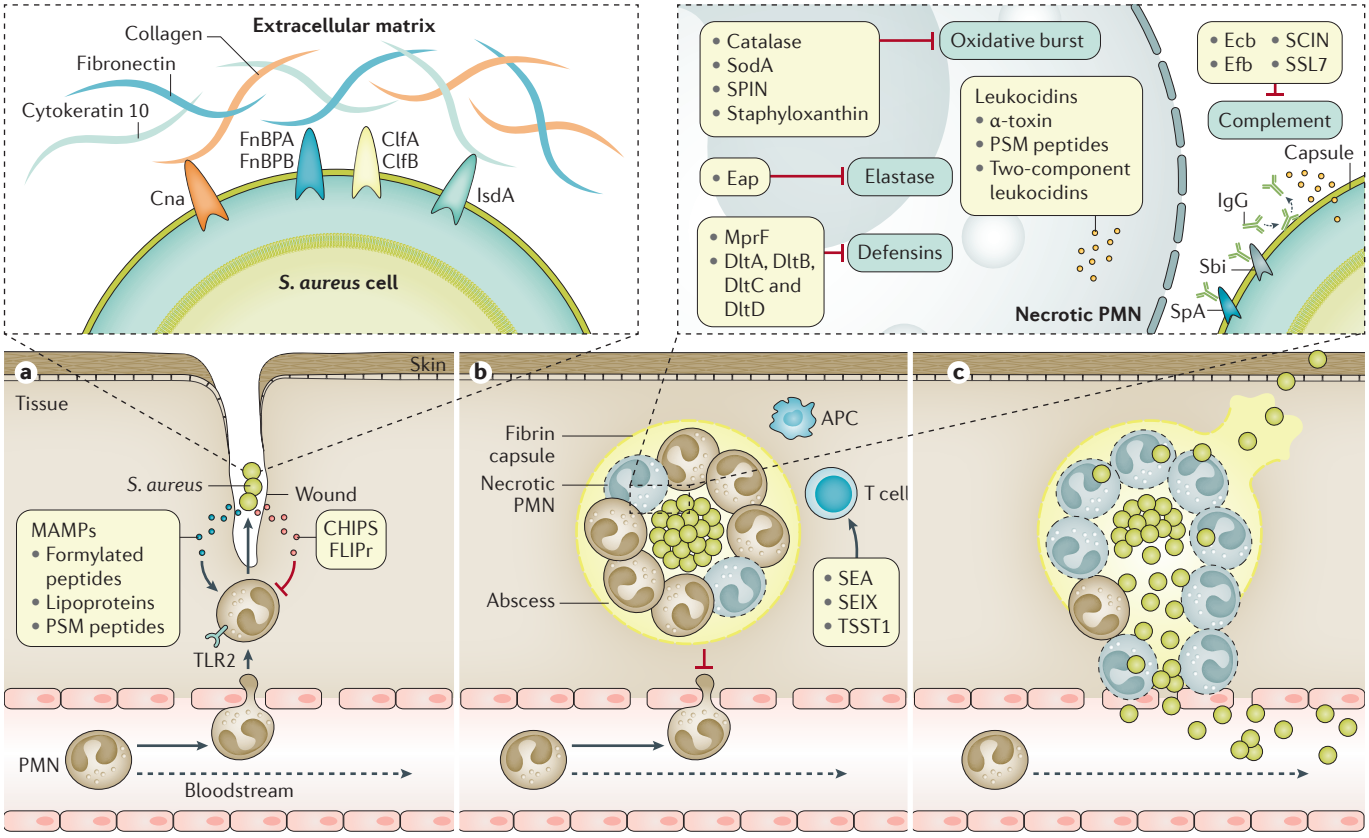

Figure 4 | **Stages of *Staphylococcus aureus* infection. a** | Bacteria obtain access to sterile tissues via open wounds and use adhesin proteins, such as fibronectin-binding protein A (FnBPA), FnBPB, iron-regulated surface determinant protein A (IsdA), clumping factor A (ClfA), ClfB and collagen adhesin (Cna), for specific attachment to extracellular matrix proteins, such as fibronectin, cytokeratin 10 and collagen, among others. *Staphylococcus aureus* can also in part regulate polymorphonuclear leukocyte (PMN) influx in subtle ways involving activators (formylated peptides and phenol-soluble modulin (PSM) peptides) and inhibitors (for example, chemotaxis inhibitory protein of *S. aureus* (CHIPS) and FPRL1 inhibitory protein (FLIPr)) of PMN chemotaxis[72]. PSM peptides also promote the release of pro-inflammatory lipoproteins, the major *S. aureus* microorganism-associated molecular pattern (MAMP) molecules, which activate Toll-like receptor 2 (TLR2) and contribute to local inflammation[73]. **b** | *S. aureus* produces coagulases to polymerize fibrin and form an encapsulated abscess around the infection site. The capacity of PMNs, which are found in high numbers in an abscess, to eliminate *S. aureus* is limited by leukocidins and by virulence factors interfering with opsonophagocytosis and PMN killing. *S. aureus* can compromise effective opsonization by antibodies using a polysaccharide microcapsule and surface proteins (*Staphylococcus* protein A (SpA) and immunoglobulin-binding protein Sbi) binding immunoglobulin G (IgG) via the crystallizable fragment (Fc) domain in a futile way[66]. The bacteria can also inhibit the complement signalling pathway by small secreted inhibitors such as staphylococcal complement inhibitor (SCIN), fibrinogen-binding protein (Efb), extracellular complement-binding protein (Ecb) or staphylococcal superantigen-like protein 7 (SSL7), among others. Phagocytosed bacteria can survive within the PMNs by producing catalase, superoxide dismutase [Mn] 1 (SodA), staphylococcal peroxidase inhibitor (SPIN), staphyloxanthin (against the bactericidal oxidative burst generated by the PMNs)[72] and extracellular adherence protein (Eap) (against elastase)[76], and the cell envelope modifications mediated by multiple peptide resistance factor (MprF) and the D-alanine transfer proteins DltA, DltB, DltC and DltD protect against defensins. *S. aureus* also secretes cytolytic toxins that can kill PMNs; *S. aureus* leukocidins include large pore-forming proteins (α-toxin and several two-component leukocidins, such as Panton–Valentine leukocidin (PVL))[64] and small peptide (PSM peptides)[228] toxins. Superantigen toxins (toxic shock syndrome toxin 1 (TSST1), enterotoxin type A (SEA), staphylococcal enterotoxin-like X (SEIX) and several others) contribute to exuberant inflammation by nonspecific T cell activation. **c** | Abscesses can release live bacteria to the surface of the skin and/or the bloodstream at later stages; the plasminogen-activating protein staphylokinase might contribute to bacterial dissemination. APC, antigen-presenting cell.

Table 2 | **Currently identified SCC*mec* types in *Staphylococcus aureus* strains**

SCC*mec* types	*mec* determinant	*ccr* gene complexes[a]	*mec* gene complexes	High-prevalence setting
I	*mecA*	1 (A1B1)	B	HA-MRSA
II	*mecA*	2 (A2B2)	A	HA-MRSA
III	*mecA*	3 (A3B3)	A	HA-MRSA
IV	*mecA*	2 (A2B2)	B	CA-MRSA and HA-MRSA
V	*mecA*	5 (C1)	C2	CA-MRSA and HA-MRSA
VI	*mecA*	4 (A4B4)	B	HA-MRSA
VII	*mecA*	5 (C1)	C1	NA[b]
VIII	*mecA*	4 (A4B4)	A	NA[b]
IX	*mecA*	1 (A1B1)	C2	NA[b]
X	*mecA*	7 (A1B6)	C1	NA[b]
XI	*mecC*	8 (A1B3)	E	LA-MRSA
XII	*mecA*	9 (C2)	C2	NA[b]

[a]Parentheses indicate the *ccr* gene(s) in the *ccr* gene complex. [b]Not possible to assign this SCC*mec* type because there is insufficient information concerning its occurrence. CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; HA-MRSA, health-care-associated methicillin-resistant *Staphylococcus aureus*; LA-MRSA, livestock-associated methicillin-resistant *Staphylococcus aureus*; NA, not applicable. Adapted with permission from International Working Group on the Staphylococcal Cassette Chromosome elements.

several antibiotic classes and are primarily found in HA-MRSA[89]. Smaller elements, such as types IV and V SCC*mec*, are found in CA-MRSA, such as USA300 and USA400, but also in some widespread HA-MRSA clones, such as ST22-MRSA-IV, ST45-MRSA-IV and ST5-MRSA-VI (FIG. 3; TABLE 2). However, over the years, the distinction between the two epidemiological groups (HA-MRSA and CA-MRSA) has become blurred[90].

All SCC*mec* types contain *mecA* (with the exception of type XI, which contains the homologue *mecC*), which encodes penicillin-binding protein 2a (PBP2a)[91], a peptidoglycan transpeptidase. PBP2a has extremely low affinity for most β-lactam antibiotics; in the presence of β-lactam antibiotics that inhibit the function of the four native *S. aureus* penicillin-binding proteins (PBP1, PBP2, PPB3 and PBP4), PBP2a can take over the transpeptidase function of peptidoglycan biosynthesis (FIG. 5). A variant of *mecA*, named *mecC*, was identified in several *S. aureus* clones from animal and human isolates[92]; *mecC* encodes $PBP2a_{LGA}$, named after the MRSA strain LGA251 from which it was first isolated. The mechanism of the control of β-lactam resistance in strain LGA251 was compared with the resistance mechanism in MRSA strains that carry *mecA*[93,94]; in the LGA251 strain, the level of methicillin resistance depends on *mecC* and on genes in the genetic background of the strain. In 2018, plasmid-borne methicillin resistance based on *mecB* has been identified in *S. aureus*[95], but the mechanism of resistance encoded by *mecB* is yet to be clarified.

The primary control of the expression of *mecA* depends on the regulators encoded by *mecI*, *mecR1* and *mecR2* (REFS[96,97]) and on the regulators of the expression of the genes *blaZ*, *blaI* and *blaRI* (REF.[98]). In addition, a surprisingly large number of genes — auxiliary or *fem* genes — has a profound influence on the resistant phenotype[99]. Three lines of evidence show that the level of *mecA* transcription is not predictive of the degree of methicillin resistance. First, the stringent stress response (that is, the bacterial reaction to different stress conditions, such as amino acid, fatty acid and iron limitation and heat shock) induced by the antibiotic mupirocin triggers an increase in PBP2a activity without affecting *mecA* transcription[100]. Second, inactivation of *vraS* (a member of the two-component regulatory system involving sensor protein VraS and response regulator protein VraR (VraS–VraR) involved in the control of the cell wall peptidoglycan biosynthesis) induced *mecA* transcription but did not increase the level of PBP2a activity[101]. Third, the chaperone foldase protein PrsA alters the levels of properly folded PBP2a in the membrane and, therefore, methicillin resistance without affecting *mecA* transcription[102]. The crucial role of the stringent stress response in *mecA* expression has been demonstrated using different experimental approaches[99,103]. A new line of investigation is focusing on the discovery of inhibitors of the stringent stress response that act in combination with β-lactam antibiotics[103].

Of note, over the years, some MRSA clones have also acquired resistance to vancomycin[104], the first-line treatment of invasive MRSA infections in hospitalized patients since the 1960s (BOX 1).

Diagnosis, screening and prevention

MRSA can cause a wide range of infections, such as SSTIs, pneumonia, osteoarticular infections, toxic shock syndrome (a rare, potentially life-threatening complication of infection with certain types of bacteria, including *S. aureus*, caused by the release of bacterial toxins and presenting with clinical features that can include fever, rash and hypotension) and bacteraemia, which may be complicated by endocarditis or severe sepsis[4]. The clinical presentations and risk factors for infection vary between HA-MRSA, CA-MRSA and LA-MRSA strains.

HA-MRSA

HA-MRSA is a cause of bacteraemia, pneumonia and, less commonly, SSTIs (particularly related to invasive procedures, for example, at surgical wounds or vascular access sites) in hospitalized patients[105]. The organism is often associated with invasive devices, such as intravascular catheters, endotracheal tubes and urinary catheters, probably owing to its capacity to form and survive in biofilms[71].

Individuals who have had lengthy hospitalization, ICU admission, residency in a nursing home, antibiotic exposure (particularly to cephalosporins and fluoroquinolones, leading to antibiotic selection pressure), surgery, haemodialysis, chronic wounds or indwelling invasive devices have an increased risk of infection with HA-MRSA[106]. In addition, asymptomatic colonization with MRSA is a risk factor for subsequent infection, as individuals with MRSA colonization on admission had a relative risk of infection of 13 (95% CI 2.7–64.0) compared with those with MSSA colonization or 9.5 (95% CI 3.6–25.0) compared with those without *S. aureus* colonization[107].

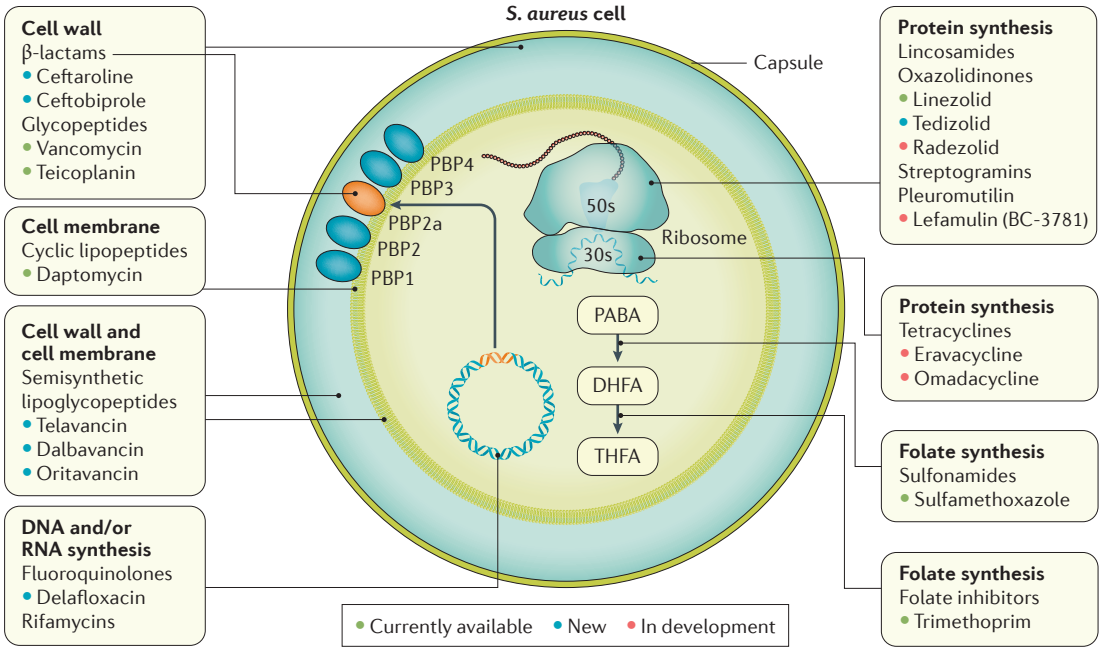

Figure 5 | **Bacterial targets of antibiotics active against MRSA.** Antibiotics have diverse mechanisms of action and target different bacterial structures or metabolic pathways. Existing antibiotic options are in green, new antibiotics approved and on the market are in blue and antibiotics in the pipeline are in orange. DHFA, dihydrofolic acid; PABA, para-aminobenzoic acid; PBP, penicillin-binding protein; *S. aureus*, *Staphylococcus aureus*; THFA, tetrahydrofolic acid. Figure adapted from REF.[229], Macmillan Publishers Limited.

CA-MRSA

The most common clinical presentation for CA-MRSA is SSTI, which is often associated with abscesses or pus formation and accounts for ~90% of cases[29]. CA-MRSA can cause particularly virulent infections. Fulminant infections with CA-MRSA strains have been reported, such as necrotizing pneumonia and necrotizing fasciitis (a rapidly progressive infection of the fascia with secondary necrosis of the subcutaneous tissues)[108,109]. Possible explanations for the increased virulence observed with CA-MRSA strains are very active Agr systems and the production of PVL. However, the presence of PVL varies from strain to strain, suggesting that other virulence factors contribute[7].

Individuals with CA-MRSA infection usually lack the traditional risk factors associated with HA-MRSA strains. Populations or settings in which outbreaks of CA-MRSA infection have been reported include sports teams, military personnel and prisons[110,111]. On the basis of these observations, close contact with MRSA carriers (as occurs in households or other communal living environments), shared equipment or personal items and skin trauma (including trauma caused by injecting drug use or body shaving) might be associated with an increased risk of CA-MRSA infection. However, the distinction between CA-MRSA and HA-MRSA is becoming increasingly blurred, with transmission of CA-MRSA strains now being observed in health-care settings in some countries with high CA-MRSA burden, such as Greece[112].

LA-MRSA

LA-MRSA has been associated with localized infections, such as SSTIs (including abscesses and wound infections) and otitis, as well as severe and invasive infections, such as bacteraemia, pneumonia, osteoarticular infections and endocarditis[22]. LA-MRSA predominantly colonizes and infects individuals who have direct contact with livestock (including cattle, horses, chickens and turkeys but particularly pigs) and their household members through transmission within the household[25]. However, there are reports of LA-MRSA in individuals with no connection to livestock, and in these cases, spread via environmental contamination or, less commonly, food-borne transmission has been postulated[25].

Microbiological diagnosis

Microbiological specimens from which MRSA can be isolated can be broadly classified into clinical and screening samples. Clinical samples (for example, specimens of purulent discharge, deep tissues, sputum and blood) are collected from individuals with symptoms or signs to investigate for active infection, whereas screening samples (for example, nasal, perineal and throat swabs) are obtained to detect asymptomatic colonization. An array of phenotypic and non-phenotypic methods can be used to detect MRSA directly from clinical or screening samples or to identify MRSA from presumptive staphylococcal colonies isolated from clinical samples. Phenotypic methods are usually preferred for clinical diagnostics.

Phenotypic methods. Pure *S. aureus* cultures, obtained by plating clinical samples on relevant culture media, can be screened for methicillin resistance by the disk-diffusion method. This method involves applying a cefoxitin disk on Mueller-Hinton agar or supplementing Mueller-Hinton agar with 6 micrograms per millilitre

oxacillin and 4% NaCl (Clinical and Laboratory Standards Institute (CLSI) recommendations)[113].

Initially, oxacillin was utilized as the marker antibiotic to detect MRSA; however, CLSI now recommends cefoxitin, as it is a better inducer of *mecA* and *mecC* than oxacillin and results in a clear recognizable phenotype[113]. The disk-diffusion method requires strict adherence to temperature (35 °C) and time (reading after 24 hours) to prevent false negative results. This is because the *mecA* encoded PBP2a is less efficient at crosslinking the pentapeptide chains of the cell wall peptidoglycan during cell wall synthesis, resulting in slower growth of the resistant isolates. This phenomenon leads to a heteroresistant population, wherein cells exhibit different levels of resistance and some are phenotypically susceptible[114]. The above-mentioned susceptibility testing guidelines enable the slower growing MRSA subpopulation to reach detectable levels in a heteroresistant population. Rarely, MRSA may present with phenotypic sensitivity to cefoxitin (and oxacillin) and require an overnight exposure to low concentrations of cefoxitin to exhibit resistance[115]. In this case, the presence of inducible *mecA* should be considered. Methicillin resistance in *S. aureus* colonies and cultures can also be detected by means of an antigen–antibody-based latex agglutination test that detects PBP2a by using an anti-PBP2a antibody. Moreover, several automated instruments performing identification and antimicrobial susceptibility testing of staphylococci have shown high sensitivities and specificities for the MRSA strains tested (reviewed in REF.[116]).

Box 1 | **Vancomycin resistance**

Vancomycin has been the drug of choice for treating invasive methicillin-resistant *Staphylococcus aureus* (MRSA) infections in hospitalized patients since the early 1960s. However, over the years, MRSA has acquired resistance to vancomycin[104]. Vancomycin intermediate-resistant *S. aureus* (VISA) appeared in Japan in 1997 (REF.[215]), and since then, it has been identified worldwide. The VISA phenotype results from mutations acquired during antibiotic therapy[216]. Despite its low vancomycin minimum inhibitory concentration (MIC; the lowest concentration of an antibiotic that prevents bacterial growth) of 3–8 micrograms per millilitre, VISA has been associated with treatment failures[215]. When cultured, heterogeneous VISA (hVISA) strains are phenotypically susceptible to vancomycin but contain subpopulations of VISA colonies at frequencies of 10^{-6} to 10^{-5} of the cells in the whole population. hVISA seems to be the stage that precedes the development of VISA[217]. The clinical relevance of hVISA has been extensively debated.

Vancomycin failure has been reported for some hVISA or VISA infections; nevertheless, several studies have failed to detect an association between infection with hVISA and poor outcomes with therapy with vancomycin[218,219]. For specific cases of hVISA and/or VISA infection, viable alternatives to vancomycin include a combination of high-dose daptomycin with another antibiotic such as gentamicin, rifampin, linezolid, trimethoprim–sulfamethoxazole or a β-lactam. Similarly, if reduced susceptibility to daptomycin is observed alongside reduced vancomycin susceptibility, then a combination of or use of a single agent among the following is recommended: quinupristin–dalfopristin, trimethoprim–sulfamethoxazole, linezolid or telavancin[161].

Vancomycin-resistant *S. aureus* (VRSA), which was first detected in the United States in 2002 (REF.[220]), has a very high vancomycin MIC (≥32 micrograms per millilitre). Vancomycin resistance in VRSA is mediated by the *vanA* gene, which is believed to have been transferred from *Enterococcus faecalis* on the plasmid-borne transposon Tn*1546* (REF.[221]). VRSA strains are mostly found in diabetic wounds infected by both vancomycin-resistant enterococci and *S. aureus*, where there is opportunity for horizontal gene transfer of Tn*1546* harbouring *vanA*. VRSA has remained extremely rare, possibly owing to the fitness costs associated with acquisition of vancomycin resistance[222].

For direct phenotypic detection of MRSA from positive blood cultures, there is renewed interest in refining bacteriophage-based assays. The KeyPath MRSA/MSSA blood culture test (MicroPhage Inc, Longmont, Colorado, USA) is a US FDA-approved, non-genotypic, rapid test for the identification of *S. aureus* and the detection of methicillin resistance directly from positive blood cultures. The assay detects the amplification of *S. aureus*-specific bacteriophages in the presence of methicillin with a turnaround time of 5 hours. Multicentre evaluation of this assay on 1,116 blood cultures showed 91.8% sensitivity, 98.3% specificity, 96.3% positive predictive value and 96.1% negative predictive value, with a median turnaround time of 16.9 hours versus 46.9 hours calculated for conventional tests for the identification of *S. aureus* and differentiating between MRSA and MSSA in positive blood cultures[117].

Non-phenotypic methods. One of the most promising non-genotypic techniques for direct identification of pathogens from positive blood cultures is matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS)[118]. Identification is based on the comparison of the protein profile obtained by mass spectrometry from a bacterial or fungal sample with a database of profiles obtained from several characterized microorganisms. However, as the performance of MALDI-TOF MS largely depends on a microorganism's purity and quantity, bacterial enrichment and purification procedures are required from positive blood cultures, which contain high concentrations of interfering non-microbial material[118]. A retrospective study of 227 cases of *S. aureus* bacteraemia comparing turnaround time and therapy adjustment before and after the introduction of MALDI-TOF MS plus real-time PCR to detect *mecA* showed a decrease in turnaround time of MRSA identification by nearly 50% compared with *S. aureus* identification and β-lactam susceptibility testing by conventional methods. Although the length of hospitalization and rates of adequate empirical antibacterial therapy were similar in the two groups, optimization of therapy occurred more frequently in the group assessed by MALDI-TOF MS[119].

Current DNA-based methods for direct MRSA detection from clinical samples are multiplex real-time PCR assays to detect *S. aureus* and the presence of *mecA*[120] and are well-validated assays[121]. Results are obtained in approximately 1.5 hours. The FilmArray (Idaho Technology, Salt Lake City, Utah, USA) is a multiplex PCR-based system designed to detect 25 microorganisms (90–95% of the pathogens involved in blood cultures) along with *mecA*, as well as the presence of genes encoding resistance to vancomycin (*vanA* and *vanB*) and carbapenems (bla_{KPC})[122]. This assay has higher sensitivity than MALDI-TOF MS in identifying microorganisms from blood culture bottles before positivity, with an average turnaround time of 2.5 hours[123].

The application of WGS to bacterial pathogens heralded the single most important advance in diagnostic microbiology and surveillance since in vitro culture. However, direct applications of WGS in diagnostic

microbiology remain limited, primarily because of the technological constraints in obtaining results within a time frame that can influence patient care and the need for standardized protocols and automated data interpretation. The introduction of the third generation of sequencers (such as the Oxford Nanopore MinION by Pacific BioSciences and Oxford Nanopore, Oxford, UK) has resulted in longer reads (obtained sequence lengths) that can span repeat regions in the bacterial sequence and enable complete bacterial genome assembly, as well as an increased portability of the machinery and a potential reduction in error rates. An important benefit afforded by the Oxford Nanopore MinION sequencer is that sequencing data can be analysed in real time and could lead to strain identification within 30 min and an antibiotic-resistance profile prediction within 10 hours after the start of a run[124], making this assay potentially useful for clinical diagnostics. The utility of WGS has been well demonstrated for studying antibiotic resistance and the population biology of MRSA[125] and has also led to many useful insights regarding transmission of MRSA during hospital outbreaks[126] and in community settings[127].

Screening methods

Screening measures and their effectiveness are discussed in the Prevention section below. Since the introduction of the first MRSA chromogenic medium (that is, a medium containing synthetic chromogenic enzyme substrates; in the presence of the specific target enzyme, the chromogenic substrate is processed and results in a corresponding bacterial colony of a specific colour, thereby enabling pathogen recognition)[128], these media have undergone rapid improvements in terms of sensitivity of the chromogen and the antibiotics used[120,129]. They have become the primary rapid diagnostic assays utilized for active surveillance for MRSA colonization as well as for patient diagnostics since they were introduced in the 2000s[129]. In 2005, an external quality assessment in 23 European countries and Israel found that 88% of the participating laboratories utilized a chromogenic medium alone to screen for MRSA[130]. The combination of chromogenic media with MALDI-TOF MS, which enables the species identification of multiple colonies in <1 hour, has further improved the specificity and turnaround time[131]. Development of automated colony scoring that could further increase specificity and reduce turnaround time is also being attempted[132].

Application of real-time PCR-based assays for MRSA screening from nasal swabs can decrease turnaround time to 1–2 hours, whereas the results of chromogenic media-based tests can take a minimum of 14–18 hours without confirmatory testing and, therefore, might not always be useful to guide clinical decisions. An observational cohort study demonstrated a significant reduction in MRSA transmission upon screening with a same-day commercial real-time PCR assay compared with screening with conventional culture (swabs incubated overnight in 7% NaCl and subcultured on mannitol salt agar with 2 milligrams per litre oxacillin for 48 hours): MRSA transmission was 4.9 new acquisitions per 1,000 patient bed days with real-time PCR compared with 13.9 new acquisitions per 1,000 patient bed days with culture[133]. (A patient bed day represents a unit of time during which a patient occupies a bed and stays overnight in a health-care facility; thus, 50 patients in a hospital over a period of 1 day would represent 50 patient bed days.) However, a major study in 13 ICUs in eight European countries did not find any positive effect of screening using PCR-based tests versus chromogenic media in the acquisition and transmission rates of multidrug-resistant bacteria (including MRSA, vancomycin-resistant enterococci and highly-resistant Enterobacteriaceae)[134]. Similarly, a UK-based study assessing screening by real-time PCR-based tests versus slower laboratory-based methods (MRSA-selective broth and chromogenic medium) reported a significant reduction in turnaround times (from 40.4 to 3.7 hours) but again no effect on MRSA acquisition rates[135], thereby rendering the utility of the more-expensive albeit faster PCR-based screening questionable.

Prevention

MRSA control interventions have been widely implemented across health-care facilities. These interventions aim to limit the emergence of MRSA by facilitating judicious use of antimicrobial agents (including introducing restrictions on their prescription), control the reservoir of patients who are carriers, prevent MRSA transmission between patients and prevent the development of infection in carriers. Several measures are usually required to successfully prevent transmission and infection with MRSA[136]. Decolonization, an important control intervention for which there is growing evidence, is discussed in the Management section.

Hand hygiene. By contact with patients with MRSA colonization or handling MRSA-contaminated equipment, health-care workers can acquire MRSA on their hands, and by this means, MRSA can be transmitted between patients[137]. Hand hygiene, with alcohol-based hand rub or soap and water, aims to reduce MRSA spread via this route. Indeed, the WHO has identified hand hygiene as an important factor in providing safe patient care and has issued detailed instructions regarding appropriate hand hygiene practices among health-care workers[137,138]. The effectiveness of improving compliance with hand hygiene among health-care workers in MRSA control has been demonstrated at local as well as national levels[139,140]. For example, the roll out of a national hand hygiene programme in England and Wales from late 2004 was associated with a fall in the incidence of MRSA bacteraemia from 1.88 to 0.91 per 10,000 patient bed days[140]. Although the hand hygiene campaign was implemented with other national infection control initiatives, the higher procurement of alcohol hand rub during the campaign was independently associated with reduction in the incidence of MRSA bacteraemia after adjustment for all other interventions[140].

Active surveillance. Most patients with MRSA colonization are asymptomatic, and, therefore, relying on culture of clinical samples (which are collected only when an individual develops symptoms or signs of infection) alone

to identify carriers of MRSA may fail to identify up to 85% of individuals with MRSA colonization[141]. Through screening methods, active surveillance programmes can identify this large asymptomatic reservoir of carriers and direct interventions (such as topical decolonization) to reduce transmission or infection risk. MRSA screening may be universal (applied to all patients) or targeted (limited to patients at increased risk of MRSA carriage). Universal MRSA screening has been one of the most controversial areas in infection control since the 2000s, with some studies showing that it is effective in reducing MRSA-associated disease[142], whereas other studies found it ineffective[143,144]. Importantly, recent data also show that universal screening is unlikely to be cost-effective, particularly in settings with low or decreasing MRSA prevalence[145]. On the basis of this accumulating evidence, many health-care facilities have now abandoned universal MRSA screening. We suggest, however, that changes in practices should be based on careful consideration of local MRSA epidemiology and the vulnerability of the patient population.

Randomized trials in ICUs have questioned the utility of routine MRSA screening in this high-risk setting[146,147]. However, a long turnaround time for screening results (a mean of 5.2 days with a culture-based method using a pre-enrichment step at a central laboratory)[146] or established good hand hygiene practices coupled with universal chlorhexidine bathing[147] might have contributed to the observed lack of effect of screening. It is argued that 'horizontal' strategies (that is, strategies aimed at preventing all health-care-associated infections, including MRSA, such as hand hygiene and universal bathing with antiseptics) are a better use of limited resources.

Contact precautions and isolation. In many facilities, health-care workers use contact precautions (use of disposable gowns and gloves) when caring for patients with MRSA colonization to reduce MRSA transmission associated with contamination of hands and clothing. Although the evidence for this intervention has previously been of low quality, there is now more robust data suggesting that this practice is associated with reduction in MRSA acquisition[148]. It is also widely recommended that patients with MRSA colonization are isolated in single rooms. However, in a prospective study in an ICU setting where MRSA was endemic and hand hygiene compliance was low, single-room isolation was not effective in reducing MRSA transmission[149]. Experts have called for a review of this practice and for guidelines to highlight the uncertainties regarding its value[150].

Management

The approach to the management of MRSA varies in different geographical regions depending on local MRSA prevalence and availability of antimicrobials, particularly the newer agents.

Decolonization of carriers

MRSA colonization is associated with an increased risk of infection and contributes to transmission. Both MRSA colonization on admission as well as acquisition during hospitalization are associated with an approximately tenfold increased risk of subsequent infection[107]. Thus, decolonization can contribute to MRSA control by reducing transmission and infection risk. Most decolonization strategies use topical agents applied to the nostrils, the principal site of colonization[47]. Mupirocin (pseudomonic acid A, which inhibits bacterial isoleucyl tRNA synthetase, preventing protein synthesis) is the principal agent and is often combined with chlorhexidine bathing[151]. Although mupirocin is the cornerstone for eradication of *S. aureus*, resistance is increasing, with some studies reporting resistance rates of up to 80% in MRSA[152]. Alternative agents are being studied, but to date, experience with these agents is limited[153]. Thus, it is recommended that mupirocin is used judiciously and that the emergence of resistance is monitored[152]. Ongoing research into the development and evaluation of new agents that can be effectively used for decolonization is also needed.

Short-term decolonization. Decolonization is most commonly used as a protective strategy during relatively short periods of increased risk of infection, for example, during the peri-operative period or ICU stays. Topical mupirocin to the nares and chlorhexidine body washing before surgery for known *S. aureus* carriers reduced the risk of post-surgical *S. aureus* infection by ~50% in a placebo-controlled study[154]. A subsequent cost-effectiveness analysis using these data showed that the mean cost saved per treated carrier was €1,911 (REF.[155]). However, this study was performed in the Netherlands, a country with low MRSA prevalence, and the effects of this short-term decolonization strategy might be different in settings with high MRSA prevalence.

The results of short-term decolonization interventions in the ICU setting have been variable. A large cluster-randomized trial compared three strategies[156]: screening and isolation of MRSA carriers (no decolonization); a combination of screening, isolation and decolonization (with mupirocin and chlorhexidine bathing) of MRSA carriers (targeted decolonization); and decolonization of all patients (universal decolonization). No significant differences in MRSA colonization and infection rates were found with the three strategies. However, bloodstream infections from any pathogen were significantly lower in the universal decolonization group. This may have been the result of universal chlorhexidine bathing rather than mupirocin. The authors concluded that universal decolonization was the best approach, as it reduced infections overall without the need for screening. However, as widespread use of topical antibiotics might lead to an increase in drug resistance, their use should be coupled with monitoring for resistance[152].

Permanent decolonization. In some situations, permanent MRSA eradication is pursued. Permanent decolonization is a component of the 'search and destroy strategy' in countries with a low MRSA prevalence[157]. For example, the Dutch protocol distinguishes between uncomplicated and complicated carriers on the basis of

MRSA strain and host characteristics, as well as colonization site, as treatment failure is three times more likely in individuals with throat colonization than in those without throat colonization[158]. Of 613 MRSA carriers, 80% were ultimately successfully decolonized, with a median time to decolonization of 10 days; of note, adherence to the protocol was crucial for success. Many other clinical trials evaluating permanent decolonization strategies have been conducted under real-life conditions, with rather disappointing results because of a high rate of endogenous recolonization[151].

Treatment of symptomatic infection

Empirical treatment and SSTIs. We recommend that an antibiotic effective against MRSA should be considered for empirical treatment of infection for patients with several risk factors for HA-MRSA infection or those with presumed severe staphylococcal infections in settings where MRSA prevalence is >20%, although precise thresholds have not been established. The choice, route of administration and duration of antibiotic therapy are determined by the site and severity of infection. Treatment should then be adjusted on the basis of subsequent results of cultures and susceptibility testing.

Intravenous vancomycin, daptomycin or linezolid can be used for severe SSTIs. Oral therapy as a rule should be avoided in the initial treatment of severe infections. Clindamycin, trimethoprim–sulfamethoxazole and doxycycline are alternative choices for the treatment of mild to moderate SSTIs, depending upon the antibiotic susceptibility testing. For uncomplicated skin abscesses, the use of clindamycin or trimethoprim–sulfamethoxazole in conjunction with incision and drainage has been shown to improve clinical cure rates in the emergency department and other outpatient settings[159,160].

Systemic and severe infections. The current recommendations for clinical management of severe MRSA infections include intravenous vancomycin or daptomycin for bacteraemia and intravenous vancomycin or linezolid for hospital-acquired pneumonia[161]. For severe infections, oral linezolid should not be used for initial therapy. However, when the patient has become stable and can tolerate the oral route, a switch to oral linezolid is recommended. In the setting of infection related to the presence of a medical device (such as central venous catheters), successful treatment usually requires removal of the device when possible[161].

Glycopeptides (such as vancomycin and teicoplanin) have been the mainstay of intravenous treatment for MRSA infections. Vancomycin remains the cornerstone of empirical treatment for systemic infections potentially caused by MRSA, first because of its safety profile and second owing to lack of other fully approved alternatives[161,162]. Teicoplanin is also commonly used in Europe and has been found to be non-inferior to vancomycin in terms of all-cause mortality, with an improved safety profile, although few patients with serious infections were studied[163] (TABLE 3). Of note, glycopeptides have slower bactericidal activity than β-lactam agents, and penetration into tissues is poor.

Recommendations have been made to increase vancomycin administration to achieve an appropriate 'trough' concentration (lowest concentration reached by the drug before the next dose is administered) and, in this way, to maximize the chances of microbiological and clinical cure (eradication of the organism as demonstrated by negative cultures and resolution of signs and symptoms of infection, respectively)[161,164]. Also, optimization of vancomycin therapy on the basis of pharmacokinetic and pharmacodynamic targets is becoming increasingly relevant, particularly as reports of the incidence of MRSA clinical isolates with minimum inhibitory concentrations (MICs) >1 microgram per millilitre (which is just below the breakpoint) are increasing in several settings. However, higher trough concentrations are associated with an increased risk of nephrotoxicity[165] and no clear improvement in outcome. Finally, vancomycin is administered in a continuous infusion instead of intermittent injections in some European countries[166]. However, there are insufficient data to make recommendations regarding this protocol[166]. In the presence of infections caused by MRSA strains with an MIC higher than the current breakpoint (>2 micrograms per millilitre), vancomycin is not effective, and an alternative agent should be administered[167]. Switching to daptomycin therapy, on the basis of the daptomycin MIC, should be done as early as possible once an elevated vancomycin MIC is confirmed. Alternative anti-MRSA antibiotics are increasingly being used, but it is important to note that they can have adverse effects, particularly linezolid[168] (TABLE 3). Of note, although reports of vancomycin failure have emerged for vancomycin intermediate-resistant *S. aureus* (VISA) and/or heterogeneous VISA (hVISA) infections, no data demonstrate superior outcomes with alternative antimicrobials agents (BOX 1).

Combination therapy. The duration of bacteraemia in patients with MRSA is twice as long as that in patients with MSSA infection[169]. The increased duration of bacteraemia is associated with complications (such as attributable mortality, complicated infection, embolic stroke or recurrent *S. aureus* infection)[170]. Combination therapy to treat *S. aureus* (including MRSA) bacteraemia has been used in an attempt to increase bacterial killing, particularly for endocarditis therapy[171]. However, evidence that combination therapy improves outcomes is lacking[171]. Several studies have demonstrated in vitro synergy between vancomycin and gentamicin against many MRSA isolates[172,173]. However, this combination seemed to be numerically inferior to daptomycin alone in the treatment of MRSA bacteraemia and endocarditis in a randomized trial[174]. Thus, because even low dose gentamicin (1 milligram per kilogram every 8 hours) for a short duration has been associated with substantial nephrotoxicity[175] and because the clinical effectiveness of vancomycin plus gentamicin is not confirmed, combination therapy with aminoglycosides is difficult to justify[176].

Vancomycin and rifampicin combinations have also been studied, particularly in the context of biofilm infections[177]. However, the addition of rifampicin

to vancomycin is not recommended for MRSA bacteraemia or native valve endocarditis[161]. In addition, a randomized controlled trial evaluating adjunctive rifampicin in *S. aureus* (including MRSA) bacteraemia found no overall benefit[178].

The combination of vancomycin and β-lactam antibiotics has shown synergistic bacterial killing in vitro[179]. However, sufficient clinical evidence in favour of this combination is lacking. In the CAMERA-1 trial (comparing vancomycin versus vancomycin plus

Table 3 | **Alternatives to vancomycin to treat invasive MRSA infections**

Indications	Resistance	Monitoring	Advantages	Disadvantages	Refs
Trimethoprim–sulfamethoxazole (folic acid inhibitor–sulfonamide combination), intravenous or oral					
• Second-line agent if patient unable to tolerate more active drugs, for example, glycopeptides or linezolid • Avoid in intravascular infection, abscesses or high degree of necrotic tissue • Better suited for low bacterial burden infections (for example, chronic osteomyelitis) and where there is no risk of death in case of clinical failure	• In vivo, thymidine release may inhibit folate antagonists • Avoid in high-burden infections (for example, intravascular infections and abscesses); availability of exogenous thymidine (folates) may inactivate this antibiotic, as it bypasses double thymidine biosynthetic blockade	• Therapeutic drug monitoring not required	• Inexpensive	• Inferior to vancomycin in a randomized study in *S. aureus* endovascular infections (47% MRSA)[231] • Caution required with angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or spironolactone (owing to hyperkalaemia)	231
Teicoplanin (glycopeptide), intravenous or intramuscular					
• Used in several European countries as main glycopeptide • More appropriate for long-term therapy (for example, bone infection) than acute severe infections owing to delay in reaching therapeutic levels	• MIC90 of teicoplanin greater than that of vancomycin • Teicoplanin-intermediate-resistant *S. aureus* may now be more common than VISA, but the clinical impact is not well studied	• Loading dose required • Often under-dosed, which can be particularly problematic for severe MRSA infections	• Efficacy comparable to that of vancomycin in various conditions[163], with improved safety profile including less renal toxicity and red man syndrome • Superior to vancomycin regarding bone diffusion[232] • Daily intramuscular injection an option for outpatient parenteral antimicrobial therapy	• Less suitable for acute severe infection, as 2–3 days required to reach therapeutic levels, even with loading dose	163, 232
Daptomycin (cyclic lipopeptide), intravenous					
• Restricted to treatment of serious infections where standard therapy with vancomycin not possible owing to resistance and/or patient intolerance • Use when elevated vancomycin MIC confirmed, on the basis of daptomycin MIC	• Associated with changes in structure and function of the bacterial cell membrane • Potential nonsusceptibility after vancomycin exposure[233]	• Muscle pain or weakness • CPK monitoring at baseline and weekly during therapy (more frequently for patients with renal insufficiency, those who have been treated with 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor or those who have had a previously elevated CPK)	• Non-inferior to standard therapy for *S. aureus* bacteraemia with or without right-sided endocarditis	• Not effective for pneumonia, as it is inactivated by lung surfactants[234], or for central nervous system infections, as it has poor cerebrospinal fluid penetration[235]	233–235
Linezolid (oxazolidinone), intravenous or oral					
• Superiority to vancomycin controversial • Acute SSTIs and VAP	• Resistance rare and due to target site mutations in the 23S ribosomal RNA gene (associated with long-term use) or to acquisition of or mutations in the *cfr* mobile resistance determinant • Outbreaks of plasmid-mediated linezolid-resistant MRSA reported in ICU setting	• No therapeutic drug monitoring required, except for with long-term treatment (especially in renal failure)[236]	• Excellent tissue penetration • High oral bioavailability (~100%) avoids need for intravenous access, potentially off-setting high costs • Shorter hospital stays and treatment durations compared with vancomycin, especially in MRSA-complicated SSTIs[237]	• Bone marrow suppression is the most common serious adverse effect (especially in renal failure) • Peripheral and optic neuropathy with long-term use (>28 days) • As it is a weak monoamine oxidase inhibitor, patients may develop serotonin syndrome when given with serotonin re-uptake inhibitors	236, 237

CPK, creatine phosphokinase; ICU, intensive care unit; MIC90, minimum inhibitory concentration required to inhibit growth of 90% of organisms; MRSA, methicillin-resistant *Staphylococcus aureus*; *S. aureus*, *Staphylococcus aureus*; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumonia; VISA, vancomycin intermediate-resistant *Staphylococcus aureus*.

Table 4 | **New agents and antibiotics in the pipeline for MRSA therapy**

Antibiotic (class)	Spectrum of activity				Indications	Adverse reactions	Notes
	MRSA	hVISA	VISA	VRSA			
New approved agents							
Ceftaroline (β-lactam)	Yes	Yes	Yes	Yes	• SSTI • CAP	• Cutaneous • Myelotoxicity (for use >7 days)	• Effective against daptomycin-nonsusceptible MRSA • Non-inferior to vancomycin plus aztreonam[238–240] for complicated SSTI • Growing evidence also supports the use of ceftaroline for severe MRSA infections (including endocarditis, bacteraemia and orthopaedic infections) • Salvage therapy for MRSA bacteraemia has demonstrated an overall success rate of ~80%[182]
Ceftobiprole (β-lactam)	Yes	Yes	Yes	Yes	• CAP (in Europe and Canada) • HAP	• Taste disturbance • Myelotoxicity	• Effective against daptomycin-nonsusceptible MRSA • In complicated SSTIs, no difference in clinical cure was reported in the patients treated with ceftobiprole and in the patients treated with vancomycin plus ceftazidime[241] • In clinical trials, inferior to linezolid plus ceftazidime for VAP
Telavancin (lipoglyco-peptide)	Yes	Yes	Yes	No	• SSTI • HAP • VAP	• Taste disturbance • New onset or worsening renal impairment and prolonged QTc[242] • Should be avoided during pregnancy, as adverse developmental outcomes have been demonstrated in animal studies[242]	• Non-inferior to vancomycin for HAP, with higher cure rates for infections caused by *S. aureus* (and comparable cure rates in patients with MRSA infection) and in patients with isolates with a high vancomycin MIC[243] • Similar efficacy to standard therapy (vancomycin or anti-staphylococcal penicillin) in a phase II trial of uncomplicated *S. aureus* bacteraemia including MRSA[244]
Dalbavancin (lipoglyco-peptide)	Yes	Yes	Yes	No	SSTI	• Measurable concentrations in the faeces after a single dose for up to 14 days, resulting in an ecological effect on intestinal flora[245]	• Long half-life (10 days); weekly dosing; suitable for outpatient treatment of complicated infections • As effective as vancomycin followed by linezolid in clinical trials of SSTI[246]
Oritavancin (lipoglyco-peptide)	Yes	Yes	Yes	Yes	SSTI	• Bleeding risk with warfarin	• Long half-life; suitable for outpatient parenteral treatment for those who do not otherwise need to be hospitalized • Single intravenous dose for SSTI was non-inferior to 7–10 days of vancomycin; response rates were equivalent for MSSA and MRSA[247] • Extended activity against MRSA (*mecA* and *mecC*) and *vanA*-encoded, *vanB*-encoded and *vanC*-encoded resistance[248]
Tedizolid (oxazolidinone)	Yes	Yes	Yes	Yes	SSTI	Thrombocytopenia (less common than with linezolid)	• Effective against linezolid-resistant MRSA • Non-inferior to linezolid and similar adverse events in clinical trials for SSTI[249,250]
Delafloxacin (fluoroquinolone)	Yes	NA[a]	NA[a]	NA[a]	SSTI	• Antibiotic class effects, including tendinitis and central nervous system toxicity • Other adverse effects not yet reported	• Very low potential for mutant selection • Potent activity against MRSA and also against biofilms[251] • Similar cure rates compared with linezolid and greater cure rates than vancomycin in a phase II trial (complete resolution of clinical signs and symptoms of SSTI as the primary end point)[252] • Non-inferior to vancomycin plus aztreonam for treatment of SSTI[253]

Table 4 (cont.) | **New agents and antibiotics in the pipeline for MRSA therapy**

Antibiotic (class)	Spectrum of activity				Indications	Adverse reactions	Notes
	MRSA	hVISA	VISA	VRSA			
In the pipeline							
Radezolid (oxazolidinone)	Yes	NA[a]	NA[a]	NA[a]	• SSTI (phase II completed; phase III ongoing) • CAP (phase II completed; phase III ongoing)	NA[a]	Effective against linezolid-resistant MRSA
Eravacycline (tetracycline; synthetic fluorocycline)	Yes	NA[a]	NA[a]	NA[a]	• Intra-abdominal infection (phase II and phase III completed) • UTI (phase II and phase III completed)	NA[a]	Two to four times more active against Gram-positive organisms than tigecycline
Omadacycline (tetracycline; aminomethylcycline)	Yes	NA[a]	NA[a]	Yes	• SSTI (phase II completed; phase III ongoing) • CAP (phase II completed; phase III ongoing)	NA[a]	Maintains activity in the presence of tetracycline-resistance genes that confer ribosomal protection (*tetM* in *S. aureus*) and tetracycline efflux (*tetK* in *S. aureus*)
Lefamulin (also known as BC-3781) (pleuromutilin)	Yes	NA[a]	NA[a]	NA[a]	• SSTI (phase II completed; phase III ongoing) • CAP (phase II completed; phase III ongoing)	NA[a]	• First drug of its class for systemic use in humans • No significant cross-resistance with other antibiotic classes • Affected by ribosomal RNA large subunit methyltransferase Cfr-mediated resistance

CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; hVISA, heterogeneous vancomycin intermediate-resistant *Staphylococcus aureus*; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; NA, not applicable; QTc, correct QT interval; *S. aureus*, *Staphylococcus aureus*; SSTI, skin and soft tissue infection; VAP, ventilator-associated pneumonia; VISA, vancomycin intermediate-resistant *Staphylococcus aureus*; VRSA, vancomycin-resistant *Staphylococcus aureus*; UTI, urinary tract infection. [a]Absent or limited clinical data. The main data sources for this table were www.clinicaltrials.gov, www.fda.gov and www.EMEA.eu; for the latest updates visit these websites. Note that not all compounds currently under development are listed in this table.

flucloxacillin), the mean time to resolution of bacteraemia (primary outcome) in the combination group was 1.94 days, compared with 3.00 days in the vancomycin alone group. According to a negative binomial model, the mean time to resolution of bacteraemia in the combination group was 65% (95% CI 41–102%; $P = 0.06$) of that in the group that received intravenous vancomycin alone (that is, it was 35% lower), and there was no difference between the two groups in relation to the secondary end points[179].

Ceftaroline plus daptomycin could be another option for refractory staphylococcal bacteraemia. Ceftaroline offers dual benefit via synergy with daptomycin and sensitization to cathelicidin antimicrobial peptide-derived LL-37, a peptide of the host innate immune response; sensitization to cathelicidin could attenuate the virulence of the pathogen[180] (see New drugs and current pipeline). Other combinations (for example, daptomycin and rifampicin) might be promising options in biofilm-related infections[181].

Other considerations. In contrast to many other bacterial infections, *S. aureus* (including MRSA) infections often require a lengthy course of treatment because of the risk of late-onset complications such as abscesses, osteoarticular infection and other secondary foci caused by haematogenous or direct seeding. In cases of documented bacteraemia, the recommended minimum duration of treatment is 14 days[161], as short-course therapy is currently not considered to be safe and effective.

Options for salvage therapy, based on low-quality data, include linezolid, trimethoprim–sulfamethoxazole, ceftaroline, quinupristin–dalfopristin and telavancin. Tigecycline should be avoided, as it is bacteriostatic against MRSA and has a large volume of distribution with high concentrations in tissues but low concentrations in serum[161]. No data in MRSA bacteraemia are yet available for other recently approved agents (for example, ceftobiprole, dalbavancin, oritavancin or tedizolid).

New drugs and current pipeline

Several new agents have been approved for the treatment of SSTIs and in some cases for pneumonia (FIG. 5; TABLE 4). However, the efficacy and safety of these antibiotics for invasive infections, for which there is a real need, have largely not been demonstrated. The new treatment options have some advantages over older agents and will probably play a part in the therapy of severe MRSA infections in the near future.

Ceftaroline and ceftobiprole are the first β-lactams with anti-MRSA activity. Use of the combination of daptomycin with an anti-staphylococcal β-lactam for refractory MRSA infections has been increasing. Multiple case reports have now documented success of the daptomycin–ceftaroline combination for MRSA bacteraemia and endocarditis[182]. Ceftobiprole for endocarditis has been studied in animal models only, with promising results[183], with a single human case report of ceftobiprole plus daptomycin for MRSA endocarditis[184]. However, resistance to ceftaroline has been observed in

Box 2 | **Future research needs**

- Life cycle and survival fitness of successful methicillin-resistant *Staphylococcus aureus* (MRSA) clones: prediction modelling and simulation of future introduction of successful community-associated MRSA strains into the health-care environment
- Virulence mechanisms: development of new inhibition strategies targeted to prevention and treatment of invasive MRSA infections
- Interplay between the host, *S. aureus* and competing nasal microbiota: microbiome studies on the competition between *S. aureus* and other commensal microbiota
- New decolonization regimens and approaches to decrease risk of MRSA infection: development and clinical evaluation of new drugs, vaccines and other preventive strategies
- Novel treatment approaches: discovery of inhibitors of the *S. aureus* stringent stress response or other *S. aureus* factors that can sensitize MRSA to β-lactam antibiotics[103]
- Whole-genome sequencing (WGS): effectiveness studies on WGS usefulness for clinical diagnostics and rapid antibiotic susceptibility testing
- Biomarkers: rapid molecular diagnostic tools and biomarkers for individual risk-profiling and treatment approaches
- MRSA reservoirs in animals: determinants of MRSA host tropism and host jumps

MRSA strains[185,186]. Of particular concern are reports of resistance in clinical MRSA isolates from patients in geographical regions never exposed to the drug[187].

Teicoplanin, introduced in Europe in 1988, was the first natural agent of the lipoglycopeptides class. Synthetic and semisynthetic derivatives of lipoglycopeptides have been produced, including telavancin in 2009 and dalbavancin and oritavancin in 2014 (REF.[188]). In 10 years of dalbavancin surveillance testing, only 0.35% of *S. aureus* isolates exceeded the FDA susceptibility breakpoint and, therefore, were dalbavancin nonsusceptible[189]. However, the long half-life of dalbavancin could lead to prolonged periods of low-level drug exposure at the end of therapy, potentially increasing the risk of resistance selection[190].

Possible advantages of tedizolid over linezolid include once-daily dosing, better adverse effects profile and lower risk of development of spontaneous resistance and susceptibility to the ribosomal RNA large subunit methyltransferase Cfr mobile resistance mechanism. As experience increases, tedizolid may be an attractive alternative for long-term treatment of osteoarticular and central nervous system infections. Trials in pneumonia are underway.

Ceftaroline, ceftobiprole, telavancin, dalbavancin and delafloxacin all require renal dose adjustment (that is, the antibiotic dose requires modification in individuals with impaired renal function).

Quality of life

Clinical effect

MRSA infections frequently complicate medical care and cause important treatment challenges. Most experts agree that β-lactam antibiotics are the optimal choice for treating invasive staphylococcal infections[171]. Thus, MRSA treatment relies on less efficacious (vancomycin) or more expensive (daptomycin or linezolid) therapeutic options. Owing to important prognostic cofactors such as potentially inadequate treatment, patient comorbidities and underlying illness, MRSA infections tend to have higher morbidity and mortality than MSSA infections[191].

However, the true clinical effect of methicillin resistance in *S. aureus* infection has been overestimated owing to methodological shortcomings of studies[192]. More-recent studies using advanced analytical approaches accounting for potential confounders and competing events confirm a non-negligible effect, which is, however, less pronounced than previously hypothesized[193,194]. For instance, a large international retrospective cohort study in ten European hospitals with endemic MRSA reported that methicillin resistance in *S. aureus* bacteraemia was not significantly associated with increased probability of in-hospital mortality (adjusted HR 1.26; 95% CI 0.82–1.94) after adjusting for potential confounders and accounting for the timing of events[195]. In this study, both MSSA and MRSA bacteraemia led to prolonged length of hospital stay, with a nonsignificant difference of 2.5 days (95% CI –3.2 to 8.3) longer for patients with MRSA infection.

Among patients with bacteraemia caused by *S. aureus*, methicillin resistance is associated with adverse health outcomes. Several studies show that patients with invasive MRSA infection might have diminished probability of long-term survival, regardless of the adequacy of initial treatment[191,196]. Furthermore, patients with MRSA infection can experience post-infection sequelae (such as the requirement for amputation owing to the higher risk of treatment failure for MRSA infections of prosthetic joints) and harmful adverse effects related to MRSA treatment[197,198]. Family members might be overwhelmed with caring for patients with MRSA infection in the community[199]. By contrast, MRSA carriage may not cause major concern per se, as shown in a Dutch study in which health-related quality of life was not decreased in otherwise healthy pig farmers carrying LA-MRSA[200].

Burden of disease

MRSA infections add to the global burden of antibiotic resistance. Several studies have shown that increased incidence of HA-MRSA infection occurs in addition to infections caused by MSSA, increasing the total burden of disease[201]. Furthermore, once endemic levels of MRSA are reached in a clinical setting, physicians are required to treat patients empirically for MRSA in cases of severe nosocomial infection[161]. This probabilistic approach of adding vancomycin or linezolid to empiric antibiotic coverage might be continued for years, even after MRSA incidence has substantially declined[202]. Finally, MRSA control requires substantial infrastructure and productivity costs of surveillance, screening and isolation of MRSA carriers[203]. However, these MRSA control expenditures (for example, universal, nation-wide MRSA screening) may no longer be justified once MRSA prevalence has declined below specific thresholds[145].

Outlook

Vaccines

The development of a vaccine could have an enormous effect on the incidence and outcome of MRSA infections. Indeed, *S. aureus* carriers have more frequent infections, but the infections are less severe than those developed by non-carriers[204], indicating that long-term exposure to *S. aureus* antigens can lead to protective

immunity. A vaccine could prevent infections at the onset and would ideally also impair *S. aureus* colonization, thereby strongly reducing the need for antibiotic treatment and extensive infection control measures[205]. Therapeutic monoclonal antibodies such as the passive vaccine against α-haemolysin by Medimmune (Gaithersburg, Maryland, USA) could provide new treatment opportunities, either alone or in combination with antibiotics. However, despite extensive research and development efforts, a protective vaccine against *S. aureus* will not become available in the next few years.

Two monovalent vaccine candidates have previously been tested but failed to induce protective immunity in late clinical development. The StaphVax vaccine (Nabi Biopharmaceuticals, Rockville, Maryland, USA), containing the capsular polysaccharide 5 (CP5) and CP8 antigens, and the V710 (Merck, Kenilworth, New Jersey, USA) vaccine, containing the iron-regulated surface determinant protein B (IsdB) antigen, have been protective in animal models but not in placebo-controlled phase III trials[206,207]. The reasons for failure remain unclear but may be related to the fact that several important *S. aureus* clones, including the major MRSA clone USA300, do not express any CPs, that the antigen preparations lacked adjuvants and that immune responses to the antigens used were not consistent enough. Moreover, there is a general concern that the extensive set of *S. aureus* immune evasion factors, such as immunoglobulin G (IgG)-binding protein A, could compromise the efficacy of antibodies, that opsonizing antibodies might not be sufficient to promote protection, whereas toxin-neutralizing antibodies might be equally or even more important, and that appropriate T cell-mediated immunity might be more crucial than previously thought[208].

Advances from basic science provide cues for new and hopefully more-successful vaccination approaches. Immunoproteomics studies have helped to elucidate the most immunogenic and protective *S. aureus* antigens[209], and the cell wall glycopolymer wall teichoic acid (WTA) has been identified as a dominant surface antigen[210]. Several new toxins, whose neutralization by antibodies might contribute to protection, have been identified[64]. Moreover, it has become clearer which T cell subsets are required for anti-*S. aureus* immunity[211]. Pharmaceutical companies continue to develop polyvalent anti-*S. aureus* vaccines based on surface proteins (ClfA) and polysaccharides (CP5 and CP8), secreted toxins (α-toxin, LukS-PV, ESAT-6 secretion system extracellular protein A (EsxA) and EsxB) and membrane-bound lipoproteins involved in nutrient uptake (manganese transport system membrane protein MntC and ferric hydroxamate receptor 2 (Fhud2))[205]. An innovative WTA-targeting monoclonal antibody conjugated to a rifampicin-related antibiotic showed protection in preclinical infection models[212]. There is hope that some of the ongoing vaccine development efforts may lead to successful completion of clinical trials.

Research needs and priorities

MRSA will probably always coexist with humanity. Despite the current focus on multidrug-resistant Gram-negative bacteria and the decline of HA-MRSA infections in some regions, the biomedical research community would be well advised not to abandon its diverse activities in the field of MRSA research. As highlighted by a 2017 WHO report[213], MRSA remains among the high-priority multidrug-resistant organisms that need renewed efforts for the research and development of new antibiotics and innovative preventive approaches. In addition to protective vaccines, bacteriophages or bacteriophage-derived lytic proteins could be used for new protective strategies, for instance, for nasal MRSA decolonization in an era of increasing mupirocin resistance[214]. Overall, there are still many knowledge gaps and important challenges to tackle (BOX 2), which require ongoing attention from researchers, policy makers and funders as well as those responsible for MRSA treatment and control.

MRSA has demonstrated its remarkable ability to evolve and disseminate widely in the 60 years since it was first recognized. Several factors, including a better understanding of the pathogenesis of infection, accurate and rapid diagnostics, ensuring the availability of effective treatment options and optimization of the prevention of transmission and infection, will ultimately facilitate control of this highly successful pathogen.

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Competing interests
J.G. has acted as a consultant for Roche, Nabriva, Paratek and Menarini. J.K. acts as a consultant for Pfizer, 3M and Destiny Pharma. S.M.-K. has received grants from Abbott and Agfa Health. She is receiving research grants from Pfizer and Huvepharma and has a service agreement with AiCuris. A.P. receives a consultant fee from Crucell and research grants from Crucell, Medimmune, MorphoSys and Roche; he has a patent pending for lugdunin. S.H. was a temporary member of the speakers' bureau for Takeda; has participated in the scientific advisory boards of DNA Electronics, Sandoz, GlaxoSmithKline and Bayer; and has received financial support for research activities from Pfizer and B. Braun. A.S.L. and H.d.L. declare no conflicts of interest.

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