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Review
THE LANCET INFECTIOUS DISEASES

The role of nasal carriage in *Staphylococcus aureus* infections

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***Staphylococcus aureus* is a frequent cause of infections in both the community and hospital. Worldwide, the increasing resistance of this pathogen to various antibiotics complicates treatment of *S aureus* infections. Effective measures to prevent *S aureus* infections are therefore urgently needed. It has been shown that nasal carriers of *S aureus* have an increased risk of acquiring an infection with this pathogen. The nose is the main ecological niche where *S aureus* resides in human beings, but the determinants of the carrier state are incompletely understood. Eradication of *S aureus* from nasal carriers prevents infection in specific patient categories—eg, haemodialysis and general surgery patients. However, recent randomised clinical trials in orthopaedic and non-surgical patients failed to show the efficacy of eliminating *S aureus* from the nose to prevent subsequent infection. Thus we must elucidate the mechanisms behind *S aureus* nasal carriage and infection to be able to develop new preventive strategies. We present an overview of the current knowledge of the determinants (both human and bacterial) and risks of *S aureus* nasal carriage. Studies on the population dynamics of *S aureus* are also summarised.**

Lancet Infect Dis 2005; 5: 751–62

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Introduction

Staphylococcus aureus is both a human commensal and a frequent cause of clinically important infections (figure 1).[1] Although the prevalence of meticillin-resistant *S aureus* (MRSA) is still very low in northern European countries,[2] there is a worldwide increase in the number of infections caused by MRSA. Vancomycin is one of the last therapeutic options available for MRSA infections. The recent isolation of vancomycin-resistant MRSA strains in the USA is a major cause for concern.[3] Therefore, the prevention of staphylococcal infections and reduction of the spread and emergence of MRSA are essential.

The association between *S aureus* nasal carriage and staphylococcal disease was first reported by Danbolt in 1931, who studied furunculosis.[4] The increasing incidence of penicillin-resistant *S aureus* hospital infections since 1947 emphasised the need for a better understanding of the pathogenesis of staphylococcal disease. Subsequently, numerous studies confirmed Danbolt's finding.[5–9] A causal relation between *S aureus* nasal carriage and infection is supported by the fact that the nasal *S aureus* strain and the infecting strain share the same phage type or genotype.[8,10] Furthermore, nasal application of an antistaphylococcal drug temporarily decolonises the nose and other body sites, which prevents infection.[11]

Our knowledge of the mechanisms, risks, and treatment of *S aureus* nasal carriage has greatly expanded over the past decade. Table 1 presents an overview of major events in *S aureus* research. Here, we focus on the latest insights into the determinants of *S aureus* nasal carriage and the risks of infection associated with *S aureus* nasal carriage. Most studies were done in western countries, so conclusions drawn can not always be generalised.

Determinants of nasal carriage of *S aureus*

S aureus nasal carriage patterns

S aureus colonises the skin and mucosae of human beings and several animal species.[5] Although multiple body sites can be colonised in human beings, the anterior nares of the nose is the most frequent carriage site for *S aureus*.[5] Extra-nasal sites that typically harbour the organism include the skin, perineum, and pharynx.[5,23–25] Other carriage sites including the gastrointestinal tract,[5,26] vagina,[27] and axillae[5,25,28] harbour *S aureus* less frequently (figure 2).

Most studies on *S aureus* nasal carriage have used a cross-sectional design with a single nasal culture to

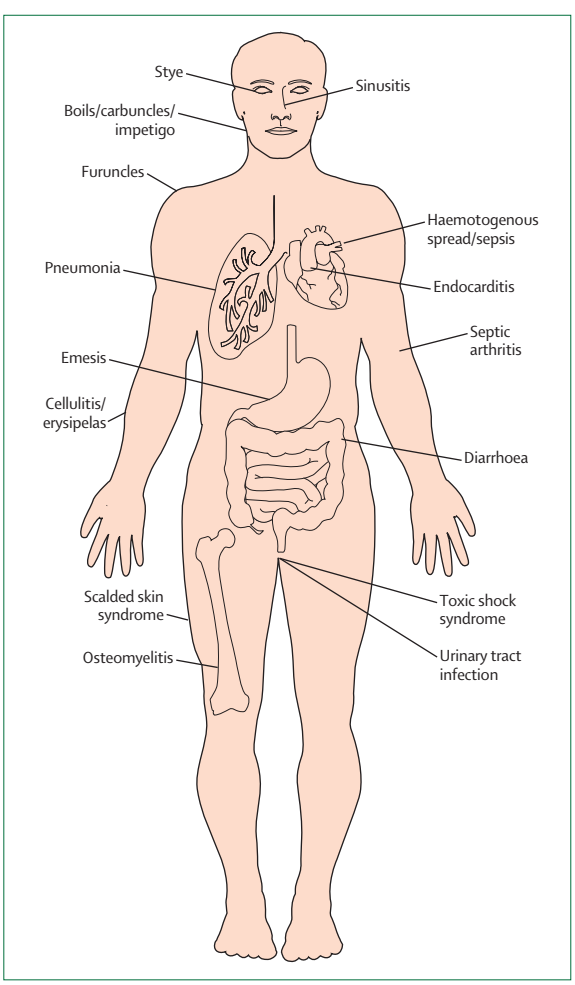

Figure 1: **Large diversity in *S aureus* infections**

Year	Event
1880	Alexander Ogston identifies micrococci in purulent infections[12]
1931	Association between nasal colonisation and furunculosis discovered[4]
1934	Popularisation of the coagulase test for the identification of *S aureus*[5]
1944	Introduction of phage typing[13]
1947	Penicillin-resistant *S aureus* reported[14]
1952	Association between nasal colonisation of *S aureus* and infection with the same strain determined by phage typing[10,15]
1961	Meticillin-resistant *S aureus* (MRSA) reported[16]
1991	Pulsed field gel electrophoresis used for genotyping *S aureus*[17]
1994	Identification of microbial surface components recognising adhesive matrix molecules (MSCRAMMs)[18]
2000	Multilocus sequence typing developed for studying clonality of *S aureus*[19]
2001	Whole genome of *S aureus* sequenced[20]
2001	80% of bacteraemic *S aureus* isolates are endogenous[8]
2001	Increase in community-onset MRSA infections[21]
2002	Vancomycin-resistant *S aureus* reported[22]

Table 1: **Major events in *S aureus* research**

classify an individual as a carrier or not. However, longitudinal studies distinguish at least three *S aureus* nasal carriage patterns in healthy individuals: persistent carriage, intermittent carriage, and non-carriage.[5,6,23,29,30] Some studies make a further distinction between occasional and intermittent carriers.[29,31] Therefore, a patient classified as a carrier in cross-sectional studies could either be a persistent or an intermittent carrier. This distinction is important because persistent carriers have higher *S aureus* loads and a higher risk of acquiring *S aureus* infection.[32,33] Likewise, non-carriers in a cross-sectional study may actually be intermittent carriers.

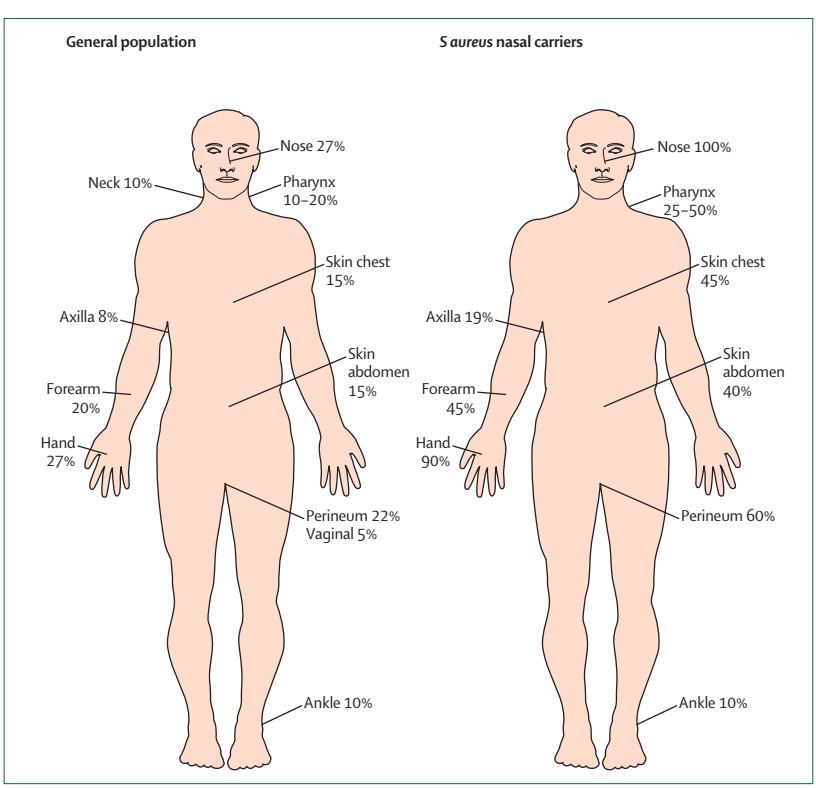

Figure 2: ***S aureus*** **carriage rates per body site in adults**
There is an increase in carriage rates at extra-nasal sites within nasal *S aureus* carriers. The mentioned rates are approximations using data from the literature cited in the text.

The definition of persistent carriage varies from study to study. There is no general consensus on how many cultures should be taken and how many cultures should be positive to define persistence. One study concludes that a "culture rule" that combines qualitative and quantitative results of two nasal swabs taken with a week interval can accurately classify *S aureus* nasal carriage.[34] Since adequate, internationally accepted definitions are needed, the so-called culture rule is an improvement for those studying determinants and risks of *S aureus* nasal carriage.

Longitudinal studies show that about 20% (range 12–30%) of individuals are persistent *S aureus* nasal carriers, approximately 30% are intermittent carriers (range 16–70%), and about 50% (range 16–69%) non-carriers.[6,29,34,35] The very wide ranges found in the proportions of intermittent and non-carriers are the result of the use of different culture techniques, different populations being studied, and the use of different interpretation guidelines.[30] Although at least seven nasal swab cultures are necessary to segregate non-carriers from intermittent carriers, the more nasal cultures are analysed, the higher the chance of identifying an intermittent carrier.[34]

Children have higher persistent carriage rates than adults.[23,36,37] Rates vary substantially with age, falling from approximately 45% during the first 8 weeks to 21% by 6 months.[38] More than 70% of newborn babies have at least one positive nasal culture with *S aureus*.[38] There is a transition from persistent carriage to intermittent or non-carriage states during adolescence (figure 3).[5,23] Cross-sectional surveys of healthy adult populations have reported *S aureus* nasal carriage rates of approximately 27% since 2000.[7,9,39–46] This rate is much lower than the earlier reported prevalence of 35%, which included studies since 1934.[6] Plotting the carriage rates of either healthy populations or a general hospital population clearly illustrates a substantial decline in the *S aureus* nasal carriage rate in time (figure 4, patient categories with known higher *S aureus* nasal carriage rates, like dialysis patients, were excluded). Explanations for this decline include improved personal hygiene, changes in socioeconomic class,[47] and smaller families.[48]

Determinants of *S aureus* nasal carriage

Although the reasons remain unknown, the basic determinants of persistent and intermittent carriage are thought to be different. Persistent carriers are often colonised by a single strain of *S aureus* over long time periods, whereas intermittent carriers may carry different strains over time.[29,30,35] Furthermore, the load of *S aureus* is higher in persistent carriers, resulting in increased dispersal and a higher risk of infection.[33,34] Nasal carriers who are also perineal carriers have higher *S aureus* loads and disperse more *S aureus*.[4,25,49]

The mechanisms leading to *S aureus* nasal carriage are multifactorial. A recent study in which volunteers (non-carriers and persistent carriers) were artificially inoculated with a mixture of *S aureus* strains showed that non-carriers quickly eliminated the inoculated *S aureus* strains, whereas most persistent carriers selected their original resident *S aureus* strain from the inoculation mixture.[50] The investigators concluded that host characteristics substantially co-determine the *S aureus* carrier state and that an optimal fit between host and bacteria seems to be essential.[50]

This view is further supported by the fact that *S aureus* carriage rates vary between different ethnic groups, with higher rates in white people[5,40] and in men,[5,29,51] and depend on age.[23,38,52] Patients with diabetes mellitus (both insulin dependent and non-insulin dependent),[53] patients undergoing haemodialysis[54,55] or continuous peritoneal dialysis for end stage renal disease,[56] patients with end stage liver disease,[57,58] patients with HIV,[59,60] patients with *S aureus* skin infections and skin disease (eg, eczema or psoriasis),[61–63] and obesity and a history of cerebrovascular accident[51] have been shown to have higher *S aureus* nasal carriage rates. Most studies are hospital or outpatient-clinic based and need confirmation from community-based surveys. In one community-based study, Boyko and co-workers[64] found similar *S aureus* carriage rates in diabetics and non-diabetics, by contrast with an earlier clinic-based study.[53]

Nasal colonisation of *S aureus* can be seen as the net result of repellent and attracting forces. There are four prerequisites to becoming a nasal carrier of *S aureus*. First, the nose has to come in contact with *S aureus*. Second, *S aureus* needs to adhere to certain receptors in the nasal niche. Third, *S aureus* needs to overcome the host defences. Finally, *S aureus* should be able to propagate in the nose. We will discuss these issues separately (table 2).

How does *S aureus* reach the nose?

S aureus cells can survive for months on any type of surface.[65] Hands are the main vector for transmitting *S aureus* from surfaces to the nasal niche—eg, nose picking.[66] *S aureus* cells are principally found in the anterior nares (vestibulum nasi or "nose picking area"), and *S aureus* nasal carriage and hand carriage are strongly correlated.[4] Some studies find higher carriage rates more proximal in the nose, but these studies are rare and probably reflect a chance finding.[67] *S aureus* may also reach the nose directly through the air, but this probably occurs less frequently.[68] However, airborne transmission is important for the dispersal of staphylococci to many different reservoirs, from where, via the hands, they can reach the nose. *S aureus* nasal carriers with rhinitis can disperse high loads of *S aureus* into the environment and may be the source of an outbreak of *S aureus* infections—the so called "cloud" individual.[69]

Environmental factors can also influence the *S aureus* nasal carriage state. Hospitalisation, for example, has been shown to be an important risk factor.[70] Furthermore, it seems that *S aureus* carriers can "impose" their carrier state upon other household members. Recently, Peacock and colleagues[38] found concordant carrier states between mothers and their children. Also, Bogaert and co-workers[48] found large households (≥five members) to be positively associated with *S aureus* nasal carriage. Most mothers carry the same strain as their children, indicating that carriage strains are transmitted to close contacts.[38] A study among an elderly population demonstrated that not only persistent but also non-carriage or intermittent *S aureus* nasal carrier states are shared among household members.[71] Up to 65% of people with positive cultures living within one household shared genotypically identical strains.[71] Intrafamilial spread of MRSA from and to health-care workers has also been shown to be an

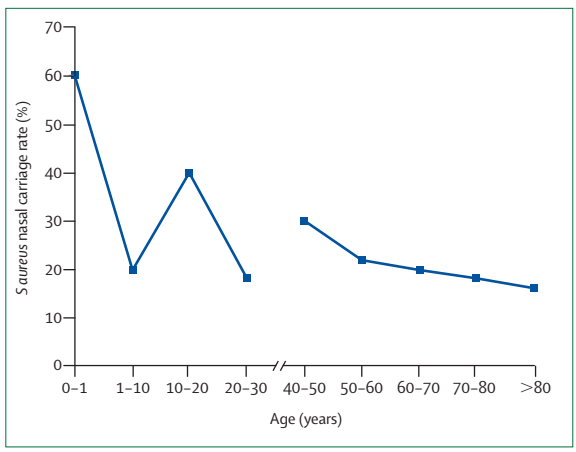

Figure 3: **Rates of *S aureus* nasal carriage according to age**

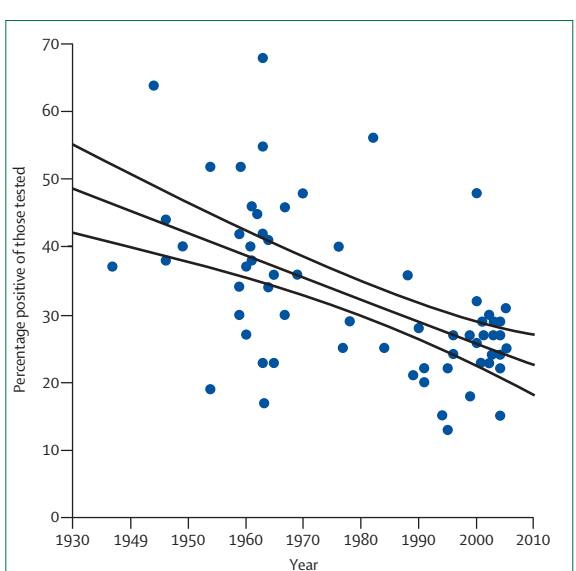

Figure 4: **Reported *S aureus* nasal carriage rates through the years**
There is a significant negative correlation between the year of reporting and the reported carriage rate (correlation coefficient −0·55; p<0·001).

Mechanism	Host	*S aureus*
General	Age, sex, ethnicity	Virulence
	Socioeconomic class	
	Antibiotic use	Antibiotic resistance
	Underlying disease (insulin-dependent diabetes mellitus, HIV, liver disease, eczema, nasal abnormalities, and others)	
	HLA type	
	Immune status	
Exposure	(Heavily) colonised partner	
	Hospital environment	
	Nose picking	
Adherence	Receptors	Adhesins
	(Extracellular) matrix proteins	MSCRAMMs
	Cytokeratin type 10	Clumping factor B
	Epithelial membrane	(Lipo)teichoic acid
		Capsule
	Mucins	Capsular polysaccharides
	Surface charge	Surface charge
	Hydrophobicity	Hydrophobicity
(Evading) immune response	Mucosal/skin barrier	Proteases, lipases
	Clearance in mucus by microvilli	Host cell internalisation
	Immunoglobulins	Protein A (binds Fc of IgG)
	Lysozyme, lactoferrin, antimicrobial peptides	Resistance to antimicrobial peptides
	Opsonisation	Capsule

MSCRAMMs=microbial surface components recognising adhesive matrix molecules

Table 2: **Overview of mechanisms associated with *S aureus* nasal carriage**

important risk factor for the re-introduction of MRSA into hospitals.[72] Furthermore, Herwaldt and colleagues[73] demonstrated that in 21% of patients receiving continuous peritoneal dialysis, the source of newly acquired nasal *S aureus* strains were their respective family members.

Activities leading to skin lesions are also correlated with higher *S aureus* nasal carriage rates. These include river rafting,[74] football,[75] and (pig-)farming.[76] Repeated skin punctures in drug users and diabetics were thought to explain higher *S aureus* nasal carriage rates.[6] However, recent studies do not support this theory: intravenous drug users have a lower prevalence of *S aureus* nasal carriage compared with drug users on an oral methadone programme,[77] and *S aureus* nasal carriage rates are not different between diabetic patients injecting insulin and those using oral glucose-lowering medication.[53,64]

There is no relation between carriage rate and seasonality, temperature, or relative humidity.[5,78,79] A population-based cohort of children and adolescents showed that active cigarette smoking is associated with a lower *S aureus* nasal carriage rate, whereas passive smoking is associated with a higher *S aureus* nasal carriage rate.[48] The aetiological basis of this observation is unknown.

How does *S aureus* withstand and evade the host immune response?

Nasal secretions have a prominent role in the innate host defence. Components of nasal secretions that contribute to the innate immune response include immunoglobulin A and G, lysozyme, lactoferrin, and antimicrobial peptides.[80] *S aureus* nasal carriers may have a dysregulation of these innate humoral factors in their nasal secretions.[81] Such people have raised concentrations of the alpha-defensins (eg, human neutrophil peptide [HNP] 1, 2, and 3) and human beta-defensin 2 (HBD2), indicative of the presence of both neutrophil-mediated and epithelial-mediated inflammation.[81] Lipoteichoic acid, present in the *S aureus* cell wall, is a strong stimulus for neutrophil recruitment.[82] Therefore, this inflammatory response could be induced by *S aureus* colonisation. However, studies have shown that HNP1, 2, and 3, and HBD2 are not microbicidal against *S aureus* in vitro, suggesting that the host response is ineffective and insufficient to prevent *S aureus* nasal carriage.[40] The role of the cellular response is unclear. The previously established relation between glycaemic control and *S aureus* carriage rate in diabetics[53] could be seen as the result of hyperglycaemia-related reduced phagocytic activation.[83]

Several studies have found that certain antimicrobial peptides have no or little activity against *S aureus* or that other peptides are needed to enhance their activity.[84,85] The inability of nasal antimicrobial peptides to clear *S aureus* from the nose may be explained by (1) the anatomy of the nose in relation to *S aureus* nasal carriage and (2) resistance of *S aureus* to many antimicrobial peptides.[40,86] *S aureus* predominantly colonises an area in the vestibulum nasi that is devoid of cilia and relatively free from nasal mucous secretions that contain antimicrobial peptides and immunoglobulins.[40] It is nevertheless possible that the innate immune response prevents *S aureus* from invading the mucosa and causing more extensive forms of colonisation or even infection.

In-vitro studies have shown that *S aureus* is able to resist certain cationic antimicrobial peptides by reducing the net negative charge of its cell wall and cell membrane, or perhaps by using efflux pumps or by releasing proteases.[86] *S aureus* has several mechanisms—including staphylokinase[87] and membrane lipid modification[88]—through which it can withstand an attack by cationic antimicrobial peptides, including defensins and cathelicidins, which are present in nasal secretions.[86,89] Whether the resistance of *S aureus* to defensins and other cationic antimicrobial peptides is a determinant of *S aureus* nasal carriage is currently not known. Cathelicidin can synergistically work with defensins to exert a bactericidal effect on *S aureus*.[84] Furthermore, all *S aureus* strains are lysozyme resistant since they possess the peptidoglycan-specific O-acetyltransferase.[90]

The presence of *S aureus* in the nose elicits a subclinical immune response, as shown in a study where seroconversion occurred after carriage was established.[91] *S aureus* produces protein A that binds the Fc region of immunoglobulins, thereby inactivating them.[65] It is clear that *S aureus* has a wide arsenal of strategies to evade the host immune response. Further studies are needed to

identify all the components of the immune response towards *S aureus* in the nose.

How does *S aureus* adhere to, and propagate in, the anterior nares?

The vestibulum nasi is limited laterally by the interior of the wing of a nostril and medially by a mucous fold (limen nasi), behind which the nasal cavity with mucosal lining begins (figure 5).[92] The epithelial inner wall of a nostril is fully keratinised and includes apocrine sweat glands, sebaceous glands, and hair follicles of the vibrissae.[92] Most studies on determinants of *S aureus* nasal carriage focus on mucosal and mucin binding.[93–95] Considering the anatomy of the vestibulum nasi, this focus should be changed.

Bibel and colleagues[96] demonstrated the importance of keratinised epithelial cells in binding *S aureus*. In addition to the nose, *S aureus* can also multiply independently in the area of the perineum.[97] Both the vestibulum nasi and the perineum contain large apocrine sweat glands, which is an important clue in studying determinants of *S aureus* nasal carriage, but has not been studied thoroughly.[25] Since *S aureus* binding to mucosa or mucin probably has a transient nature, we propose that: (1) intermittent carriers are actually "mucosal carriers" and (2) persistent carriers use a special niche, such as an apocrine gland, where *S aureus* cells can multiply to high numbers.

S aureus adherence may also be non-specifically mediated via physicochemical forces, including hydrophobic interactions.[6] Alternatively, adherence may be more specifically accomplished through binding of certain bacterial cell surface moieties (adhesins) to defined structural receptors in the membranes of the host cells.[6] *S aureus* has a greater affinity for nasal epithelial cells sampled from carriers than from non-carriers,[94] and the bacterium adheres better to nasal epithelial cells from patients with eczema than to cells from patients without eczema.[6]

Recent experiments have shown that clumping factor B (ClfB) and the *S aureus* surface protein G (SasG) bind to nasal epithelial cells.[98,99] ClfB specifically binds human cytokeratin type 10 and SasG to an unknown ligand of desquamated nasal epithelial cells.[98] Also, cell wall teichoic acid is essential for *S aureus* nasal carriage.[95,100] Microbial surface components recognising adhesive matrix molecules (MSCRAMMs) can bind to fibronectin, fibrinogen, and collagen related polysaccharides.[18] MSCRAMMs probably have a role in the binding of staphylococci to sites where the mucosal lining is breached, exposing these matrix molecules.[66] Differences in the expression of genes coding for these factors, depending on the ecological niche, and other putative adhesins and receptors may provide clues to the true determinants of *S aureus* nasal carriage or non-carriage.

Bacterial interference has been postulated to be a major determinant of the *S aureus* carrier state, or rather, non-carrier state. When an ecological niche is already occupied by certain bacteria, other bacteria do not seem to have the means to replace this resident bacterial population.[101] The resident flora must be reduced or eliminated before other bacteria can successfully "interfere" with the resident bacterial population.[102] Cross-inhibition of the expression of various virulence factors by the accessory gene regulator (*agr*) and staphylococcal accessory regulator (*sar*) may be one mechanism by which one strain excludes others from colonising sites including the anterior nares,[103] although a large *S aureus* population genetic analysis failed to confirm this suggestion.[104] Still, bacterial interference can be seen as a determinant of *S aureus* nasal carriage, although it does not appear to be the ultimate determinant.[38]

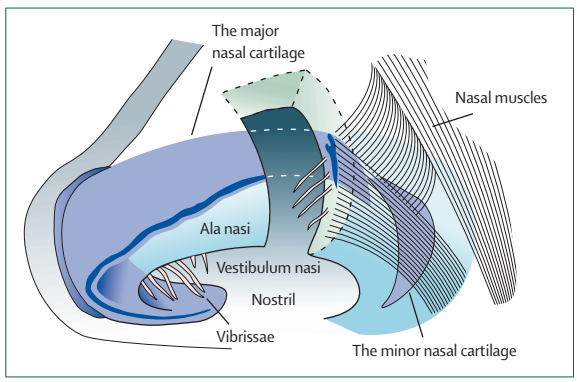

Figure 5: **Anatomy of the nostril**
Adapted from reference 92.

Bacterial interference by active colonisation using a non-pathogenic *S aureus* strain (502A) was successful in nurseries during outbreaks of *S aureus* infections in the 1960s and for treatment of patients with recurrent furunculosis.[102,105] The early practice of artificial inoculation with *S aureus* 502A was abandoned after alleged complications[106] and the advent of newer antistaphylococcal antibiotics in the early 1970s.

Bacterial population dynamics

To understand *S aureus* nasal carriage and the relation with subsequent disease, we need to define the population structure of *S aureus*. Several techniques have been used to describe the natural population structure of *S aureus*, including multilocus enzyme electrophoresis,[107] pulsed-field gel electrophoresis,[108] multilocus sequence typing (MLST),[19,109] and amplified fragment length polymorphism (AFLP).[110] These studies have revealed that *S aureus* is highly clonal, by contrast with other pathogenic species such as *Streptococcus pneumoniae*.[111] Most recent studies have assessed the population structure of *S aureus* using MLST.[19,109] This molecular typing method characterises bacterial isolates on the basis of the sequence of internal fragments of seven housekeeping genes that represent the stable "core" of the bacterial genome. These MLST studies have placed most *S aureus* isolates (colonising as well as invasive isolates of meticillin-sensitive *S aureus* [MSSA]

and MRSA) in five major clusters—clonal complex (CC) 8, CC30, CC5, CC22, and CC45.[109,112,113] MRSA isolates were found in several major clonal complexes, indicating that meticillin resistance has developed in most distinct phylogenetic sub-populations of *S aureus*.[110,114,115] The pandemic penicillin-resistant *S aureus* clone in the 1950s, now known as CC30, is currently re-emerging as a pandemic MRSA clone.[116,117]

Most population structure studies of *S aureus* were biased by the use of mostly clinical isolates and collections of nosocomial MRSA.[108,114] Recently, the population structure of *S aureus* isolated from the nose of people living in the community was analysed by AFLP.[110] AFLP is a whole genome typing method, documenting the contribution of "accessory genetic elements" as well as genome-core polymorphisms. This study revealed the existence of three major (I, II, III) and two minor (IVa and IVb) genetic clusters of *S aureus* (figure 6). AFLP clusters II and III—identical to MLST CC30 and CC45, respectively—account for almost half (47%) of all carriage isolates, suggesting that these two clonal complexes have evolved to be very successful in colonising human beings.[110] Melles and co-workers[110] identified the same major clusters as the MLST studies (Oxford database, UK; http://www.mlst.net). Apparently, these clonal clusters have spread successfully worldwide.[110]

There is controversy as to whether all *S aureus* strains have equal disease invoking potential or whether invasive disease is associated with particularly virulent genotypes. Feil and co-workers[109] found no significant differences in the distribution of genotypes between strains isolated from carriers and those from patients with invasive disease. There was, therefore, no evidence for the existence of hyper-virulent *S aureus* clones. By contrast, subclusters of strains with differential degrees of pathogenicity were observed in the study by Melles and colleagues,[110] who identified subclusters with an over-representation of bacteraemia isolates. Furthermore, expansion of multidrug-resistant clones or clones associated with skin disease (impetigo) were observed. Some clones have been shown to be more virulent than others; however, given the appropriate clinical conditions each and every strain of *S aureus* can become a life-threatening pathogen. Another study found that invasive *S aureus* strains belonging to a clonal complex are associated with a higher in-hospital mortality rate, indicating co-evolution of *S aureus* virulence and spread among human beings.[119] This study also concluded that (major) CC45 was significantly under-represented among invasive strains (odds ratio [OR] 0·2, 0·04–0·6), which corroborated earlier findings.[110,119] Furthermore, Peacock and colleagues[120] provided evidence of considerable horizontal transfer of virulence-associated genes in a clonal background. In summary, *S aureus* will remain an important clinical challenge and, apparently, some strains will present challenges that are more vigorous than others. It remains to be seen whether the possibility of identifying the more pathogenic clones of *S aureus* in the laboratory can be translated into a reliable diagnostic tool with clinical relevance in the future.

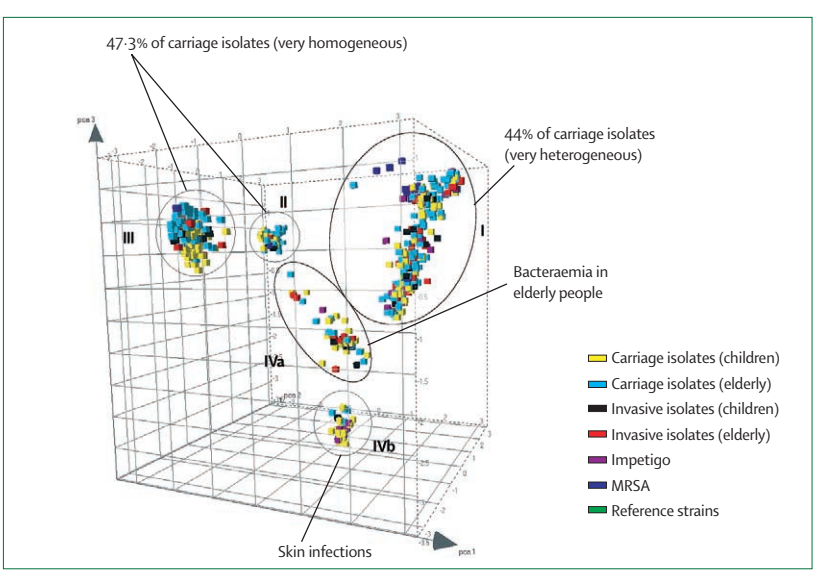

Figure 6: **Principal component analysis of 1056 *S aureus* strains reveals genetic clusters of hypervirulent clones[110,118]**

The different boxes, plotted here in a three-dimensional space and coloured according to their source, represent each *S aureus* strain analysed in the study. The five circles indicate the three major (I, II, and III) and two minor (IVa and IVb) different phylogenetic clusters identified by AFLP. Although strains from each of the genetic clusters are essentially able to cause invasive disease, some clusters contain proportionally more invasive isolates.

Risks of *S aureus* nasal carriage

Community-acquired infections

Most studies regarding the risks of acquiring *S aureus* infections in the community concern skin and soft tissue infections. Several, mostly older, studies investigated the relation between *S aureus* nasal carriage and skin infections,[121] including furunculosis,[122,123] impetigo,[124] sycosis barbae,[10,122,125] and stye.[126] On average, 80% (range 42–100%) of those with skin lesions were *S aureus* nasal carriers, and 65% (range 29–88%) had the same phage type in the nose and lesion.

In one large prospective population-based study among elderly people there was no relation between persistent *S aureus* nasal carriage and all-cause mortality, a surrogate end-point for serious staphylococcal disease.[71] Earlier retrospective cohort or case-control studies have demonstrated increasing age, male sex, alcoholism, lung disease, cancer, diabetes mellitus, end stage renal failure, and dialysis to be risk factors for community-acquired *S aureus* infections necessitating hospital admission.[127–129] These factors have also been identified earlier as determinants of *S aureus* nasal carriage in case-control or cross-sectional studies.[6]

The spectrum of community *S aureus* disease is rapidly changing with the advent and spread of community-onset MRSA strains.[75,116,130,131] Overall MRSA carriage rates in the community are still low,[2,42,132] but seem to be rising rapidly in certain parts of the world.[130,133] In the only prospective

study done so far on nasal carriage of community-onset MRSA and risk of infections in soldiers, Ellis and co-workers[134] found a relative risk of 3·1 (95% CI 1·5–6·5) for nasal MRSA carriers to acquire a MRSA infection (eg, cellulitis, abscesses) in the community. In a retrospective study concerning community-onset MRSA skin infections among professional football players, Kazakova and colleagues[75] did not find any MRSA in nasal swabs or environmental cultures, although 42% were nasal carriers of MSSA strains. Apart from these highly selected populations, it remains questionable whether the results from these studies can be extrapolated to the general population.[134] We need more community-based studies to better understand the ecology, pathophysiology, and epidemiology of *S aureus* nasal carriage and infections in the community and to develop and target preventive measures.

Nosocomial infections

S aureus (MSSA as well as MRSA) ranks as the second most common cause of hospital-acquired (nosocomial) bloodstream infections. About 20% of patients undergoing surgery acquire at least one nosocomial infection, leading to increased morbidity, mortality, hospital stay, and costs.[135–139] Hospital treatment usually requires that first line barriers for pathogens—of which the skin is an important one—are intentionally breached, resulting in an increased risk of infection. Most of these nosocomial *S aureus* infections are caused by the patient's own *S aureus* cells, which were already present on the skin or mucosal membranes before hospital admission in at least 80% of the cases.[7,8] It could well be that more infections are of endogenous origin, since 10% of the nasal *S aureus* carriers have more than one genotype or phage type in their nose.[5,140]

S aureus nasal carriage has been identified as a risk factor for the development of nosocomial infections in general hospital populations,[141] surgical patients (general,[5,6,9] orthopaedic,[142] thoracic surgery,[143] and children[144]), patients on haemodialysis or continuous peritoneal dialysis,[6,33,54,145,146] patients with liver cirrhosis and after liver transplantation,[58,147–149] HIV-infected patients,[59,60] and patients admitted to intensive care units.[150–152] In a recent study there was a threefold increased risk for non-surgical patients who were *S aureus* nasal carriers to acquire a nosocomial *S aureus* bacteraemia versus non-carriers.[7] Also nasal carriers among surgical patients have a higher risk (OR 4·0) for nosocomial *S aureus* bacteraemia compared with controls.[153]

Second to coagulase-negative staphylococci, *S aureus* is the most prevalent organism causing intravascular device-associated bacteraemia.[6,137,154] Pujol and colleagues[150] looked at bacteraemia in an intensive care unit. Most of the *S aureus* bacteraemias had an intravascular device as a source. In this study, carriers of *S aureus* had a relative risk of 12·4 for the development of *S aureus* bacteraemia.[150] In a study by Wertheim and co-workers,[7] the source of bacteraemia was device related in more than 50% of the cases. Interestingly, the mortality rate from *S aureus* bacteraemia is higher in non-carriers compared with carriers.[7] Since bacteraemia is usually endogenous in carriers, partial immunity may have an important role here. This finding needs confirmation and the underlying mechanism resolved.

In HIV-positive patients, increased rates of *S aureus* bacteraemia and deep soft tissue infections have been observed, which frequently recur. Even higher infection rates are found in patients with AIDS compared with HIV-positive asymptomatic patients. Nguyen and colleagues[59] found that nasal carriage is an important risk factor in this patient population (OR 5·1). Other risk factors for infection in this study were presence of a vascular catheter (OR 4·9), low CD4 cell count (<100 cells/μL; OR 3·5), and neutropenia. The risk for developing an *S aureus* infection was approximately 10% for every 6 months in patients who were nasal carriers of *S aureus* and had CD4 cell counts of less than 100 cells/μL. It should be noted that *S aureus* nasal carriage was more common in patients who were not receiving co-trimoxazole prophylaxis for prevention of *Pneumocystis jiroveci* pneumonia.

In haemodialysis patients, *S aureus* is the most frequently found pathogen in infections at the vascular access site and in bacteraemia. The infection rate is higher in carriers on haemodialysis, with relative risks varying from 1·8 to 4·7.[6,54,145,146,155] *S aureus* isolates are usually identical to the one previously isolated from the patient's nose.[156] In a study by Nielsen and colleagues,[155] the relative risk for *S aureus* bacteraemia was 26·2 (6·1–113) when *S aureus* was colonising the insertion site, and 3·3 (0·74–15·1), in the case of only *S aureus* nasal carriage. However, multiple studies have demonstrated that long-term eradication of *S aureus* nasal carriage by (repeated) application of mupirocin effectively prevents *S aureus* infections among patients who are receiving dialysis, thereby decreasing complications and costs.[157–160] Additional application of a local antibiotic ointment to exit sites is also important in preventing infections.[161]

In patients on continuous peritoneal dialysis, *S aureus* is the leading cause of continuous peritoneal dialysis-related infections, often leading to catheter loss. *S aureus* nasal carriage has been found to be a major risk factor for infections in patients on continuous peritoneal dialysis, mainly associated with exit site and tunnel infections.[33,56,162–166] Intervention studies consistently demonstrated a substantial reduction in the incidence of exit site infections, but not a consistent reduction in the incidence of continuous peritoneal dialysis-related peritonitis.[54,166–170] Two studies did not find a correlation between *S aureus* nasal carriage and the development of *S aureus* exit site infections.[171,172] In a recent study it was demonstrated that only continuous peritoneal dialysis patients who are persistent *S aureus* nasal carriers are at increased risk of acquiring continuous peritoneal dialysis-

Search strategy and selection criteria

We searched Pubmed with the following search terms: "*Staphylococcus aureus*", "colonisation", "carriage", "nose", "nasal", "vestibulum nasi", "mucosa", "nasal", "nosocomial", "epidemiology", "determinants", "risk factor", "treatment", and "infection". The following limits were used: English language, abstract, and human studies. We identified additional articles by searching the reference lists of existing articles.

related *S aureus* infections.[33] Intermittent nasal carriers of *S aureus* have the same risk of *S aureus* infection as non-carriers.[33] Targeting interventions to prevent continuous peritoneal dialysis-related infections is thus possible, thereby eliminating unnecessary prophylactic and therapeutic antibiotic use and resistance development.[173] The nasal strain and the infectious strain are clonally related in most patients on continuous peritoneal dialysis with *S aureus* infection.[6,33,56]

Studies in the 1950s and 1960s show that with increasing numbers of staphylococcal bacteria in the nose, as in persistent carriers, *S aureus* skin carriage rates increase proportionally, in parallel with a rise in risk of *S aureus* surgical site infections.[4,32,174,175] The more recent observation that patients carrying *S aureus* in their nose as well as perineal (or rectal) skin are at a higher risk for subsequent *S aureus* infections when compared with only perineal or nasal carriers can probably also be explained by a higher *S aureus* load.[49] Presumably people who carry *S aureus* in their nose contaminate their hands, then transferring the organism to other sites on their bodies.[66] The number of staphylococcal cells needed to cause infection decreases dramatically at the site of a suture, compared with healthy skin.[176]

Although *S aureus* nasal carriage is unanimously accepted as one of the most important risk factors for nosocomial and surgical site infections today and studies using historical controls have reported substantial reductions of surgical site infections among patients receiving mupirocin,[136,177–179] randomised controlled trials uniformly failed to confirm these results.[9,180,181] Perl and colleagues[9] could only demonstrate a significant effect (48% risk reduction, p=0·02) on the rate of nosocomial *S aureus* infections after surgery among *S aureus* nasal carriers before surgery. The 37% reduction in *S aureus* surgical site infections was not statistically significant (p=0·15).[9] Wertheim and colleagues[180] and Kalmeijer and co-workers[181] did not find a significant effect of eradication of *S aureus* nasal carriage in a general hospital and orthopaedic patient population, respectively. In the study of Perl and co-workers,[9] 53% of *S aureus* surgical site infections occurred in the non-carrier group, and 15% of the *S aureus* surgical infections in carriers was caused by a strain other than their resident strain. These infections probably result from exogenous transmissions from the hospital environment or undetected extra-nasal *S aureus* carriage sites. Health-care workers can be important sources of transmission of *S aureus* and cross-infection.[182]

Conclusions

Many studies have been published on *S aureus* nasal carriage—a Pubmed search with the terms "*Staphylococcus aureus*" and "nasal" gives 1383 hits. Based on these studies and the results of contradicting twin studies[183,184] a simple Mendelian trait probably does not explain the different *S aureus* nasal carrier states.[38,48] The repeated exposure to *S aureus* in the (household) environment is considered to be an important determinant of *S aureus* nasal carriage, probably more important than the genetic background of individuals. In general, a multifactorial genesis underlies *S aureus* nasal carriage.

We now need to identify which factors of *S aureus* and the nasal niche are of importance in adherence. Recent in-vitro and in-vivo studies in rats have begun to elucidate these factors, which is an important step forward.[98–100] Furthermore, we may need to change the focus from mucosal adherence to adherence to more prevalent epitopes present in the anterior nares. The real importance of these factors needs to be confirmed in a human colonisation model. Only then may we find new, effective ways of decolonising the nares and other body sites. So far there is limited evidence that decolonisation of the anterior nares to prevent staphylococcal disease is only effective in dialysis and surgical patients. Recent clinical trials in non-surgical and orthopaedic patients did not show any positive effect.[180,181] Focusing only on at-risk patients—eg, persistent carriers—may improve the outcome of an intervention. Also the decolonisation of extra-nasal sites needs to be improved.[24]

So far, there has been concern only for the increased risk of *S aureus* nasal carriers for acquiring *S aureus* infections. However, studies have shown that non-carriers who acquire exogenous *S aureus* bacteraemia have a fourfold increased mortality rate compared with *S aureus* nasal carriers.[7] Thus, the immunological mechanisms of *S aureus* nasal carriage need to be resolved. In non-carriers, preventing the acquisition of *S aureus* strains deserves more attention.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This work was made possible by grants from the Netherlands Organisation for Scientific Research, the Netherlands Organisation for Health Research and Development, Dutch Kidney Foundation, Dutch Ministry of Economic Affairs, and Trustfonds of the Erasmus University.

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