

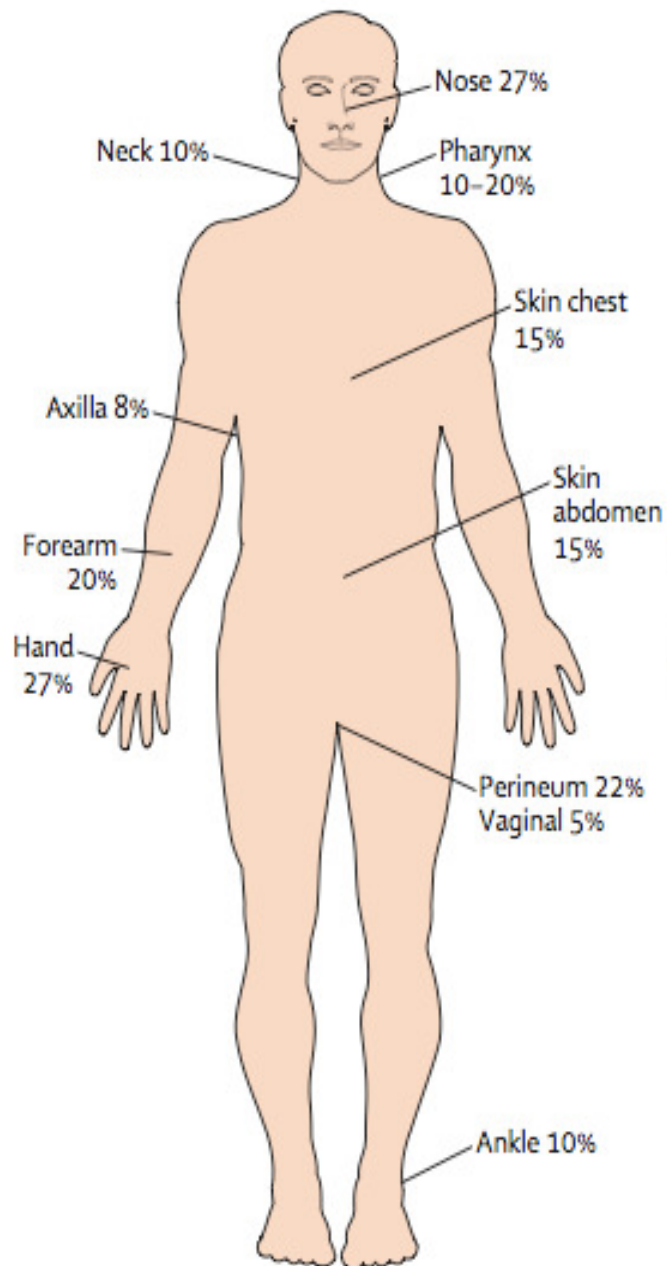
*S.aureus*

De la colonisation à  
l'infection

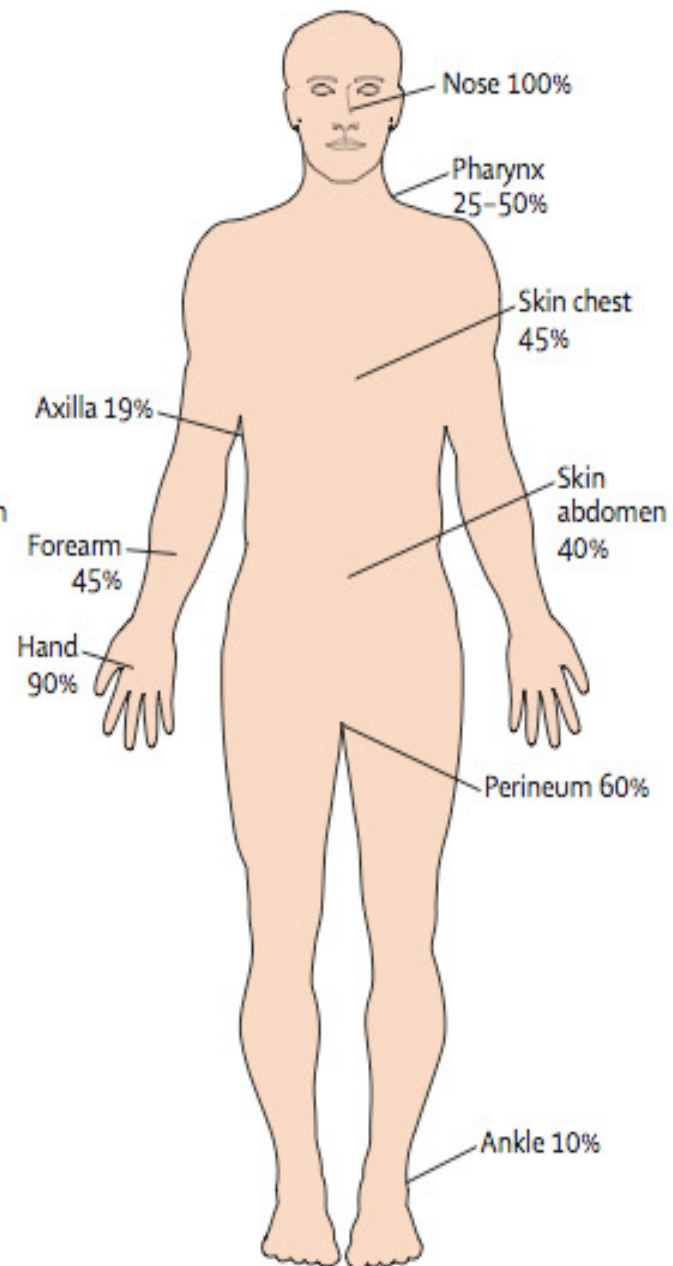
F. Vandenesch  
Lyon



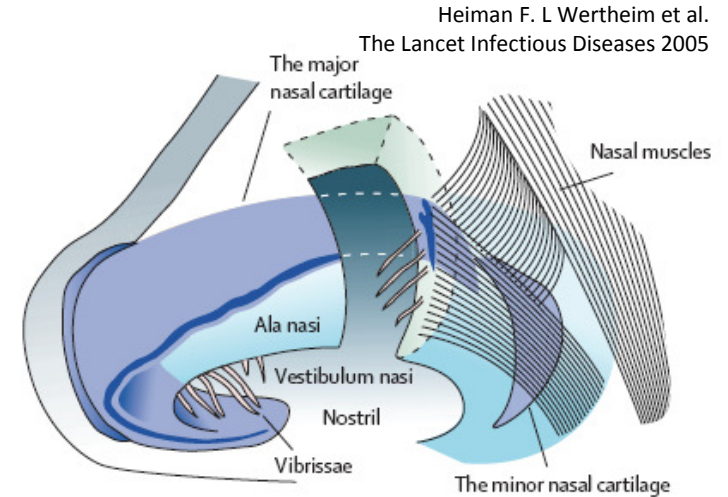
### General population



### *S aureus* nasal carriers



# nasal carriage of *S. aureus* and the development of staphylococcal infection are linked



- rates of infection are higher in carriers than in non-carriers
- individuals are usually infected with their own carriage isolate
- temporary eradication of carriage following the use of topical mupirocin has been shown to reduce nosocomial infection

# Outlines

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- The different categories of carriers
- The various sites of carriage
- Factor affecting carriage
- Interventions : decontamination, vaccination, bacterial interference

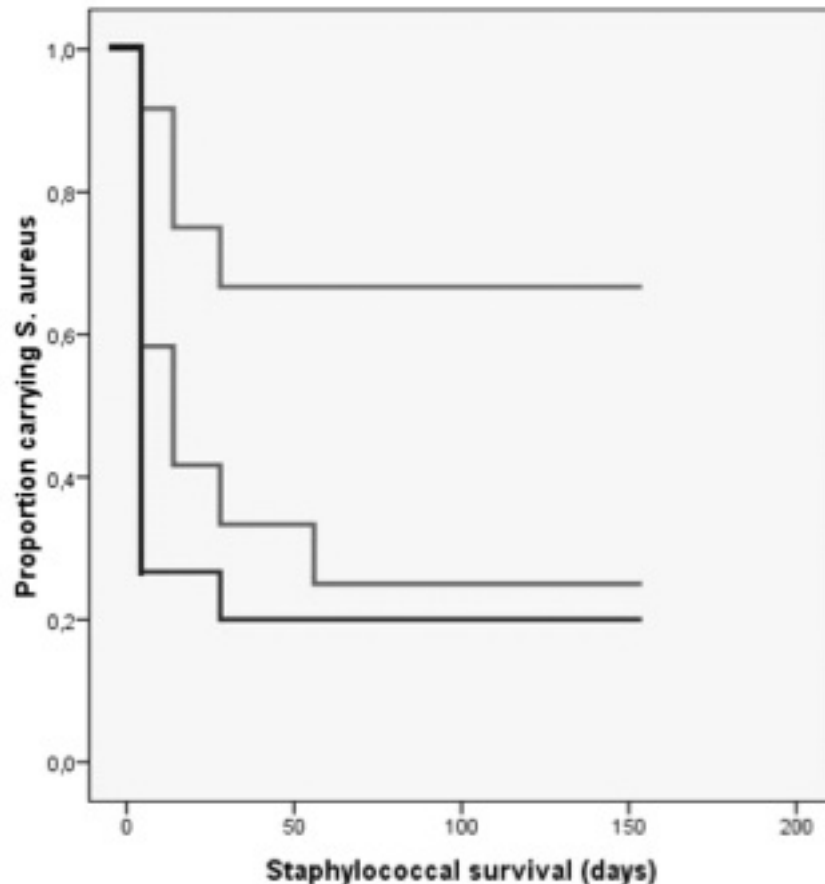
# Outlines

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# Colonisation study in human

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Pre-inoculation  
*S. aureus*  
carrier state

- Intermittent carriers behave as non carriers:
  - Eliminate the inoculum in few days
- Persistent carriers preferentially reselected their autologous strain from the inoculum mixture

# Colonisation study in human

**Table 1. Median fluorescence intensity (MFI) values reflecting antigen-specific immunoglobulin (Ig) G and IgA levels in persistent carriers (PC), intermittent carriers (IC), and noncarriers (NC).**

<i>S. aureus</i> protein (antibody isotype), carrier state	MFI value, median (range)	<i>P</i> <sup>a</sup>			
		PC vs. NC	PC vs. IC	IC vs. NC	PC vs. IC and NC
<b>TSST-1 (IgG)</b>					
PC	12,123 (100–18,322)	<.001	.003	NS	<.001
IC	5973 (57–18,136)				
NC	4714 (42–17,053)				
<b>TSST-1 (IgA)</b>					
PC	754 (87–3130)	.001	<.001	NS	<.001
IC	134 (10–3139)				
NC	110 (20–3506)				
<b>SasG (IgG)</b>					
PC	56 (29–485)	.042	.037	NS	.019
IC	127 (32–556)				
NC	110 (21–413)				
<b>SEA (IgA)</b>					
PC	48 (19–1070)	.017	.056	NS	.013
IC	31 (16–277)				
NC	29 (17–284)				
<b>ClfA (IgA)</b>					
PC	1197 (108–3997)	.008	.028	NS	.005
IC	524 (74–2430)				
NC	441 (87–3156)				
<b>CHIPS (IgA)</b>					
PC	5513 (1004–12,309)	.032	.006	NS	.006
IC	3445 (156–11,644)				
NC	2525 (27–11,532)				

**NOTE.** CHIPS, chemotaxis inhibitory protein of *Staphylococcus aureus*; ClfA, clumping factor A; NS, not statistically significant; SasG, surface protein G; SEA, staphylococcal enterotoxin A; TSST-1, toxic shock syndrome toxin 1.

<sup>a</sup> Differences in antigen-specific MFI values between groups were considered to be statistically significant at  $P < .05$  (Mann-Whitney *U* test).

- Intermittent carriers behave as non carriers:
  - Similar antibody profiles

# The paradigm to be changed

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- Only two categories of people :
  - persistent carrier
  - non persistent carriers (non carrier and intermitent carrier)
- Majority of people are non carriers

# Carrier vs autoinfection

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- Persistent carriers are at a higher risk for development of *S. aureus* infections
- intermittent carriers have a lower risk of autoinfections than persistent carriers

vonEiffC,BeckerK,MachkaK,StammerH,PetersG.Nasalcarriageas a source of *Staphylococcus aureus* bacteremia. *N Engl J Med* 2001; 344: 11– 6.

Wertheim HF, Vos MC, Ott A, et al. Risk and outcome of nosocomial *Staphylococcus aureus* bacteraemia in nasal carriers versus non-carriers. *Lancet* 2004; 364:703–5.

Nouwen JL, Fieren MW, Snijders S, Verbrugh HA, van Belkum A. Persistent (not intermittent) nasal carriage of *Staphylococcus aureus* is the determinant of CPD-related infections. *Kidney Int* 2005; 67:1084 –92.

# Outlines

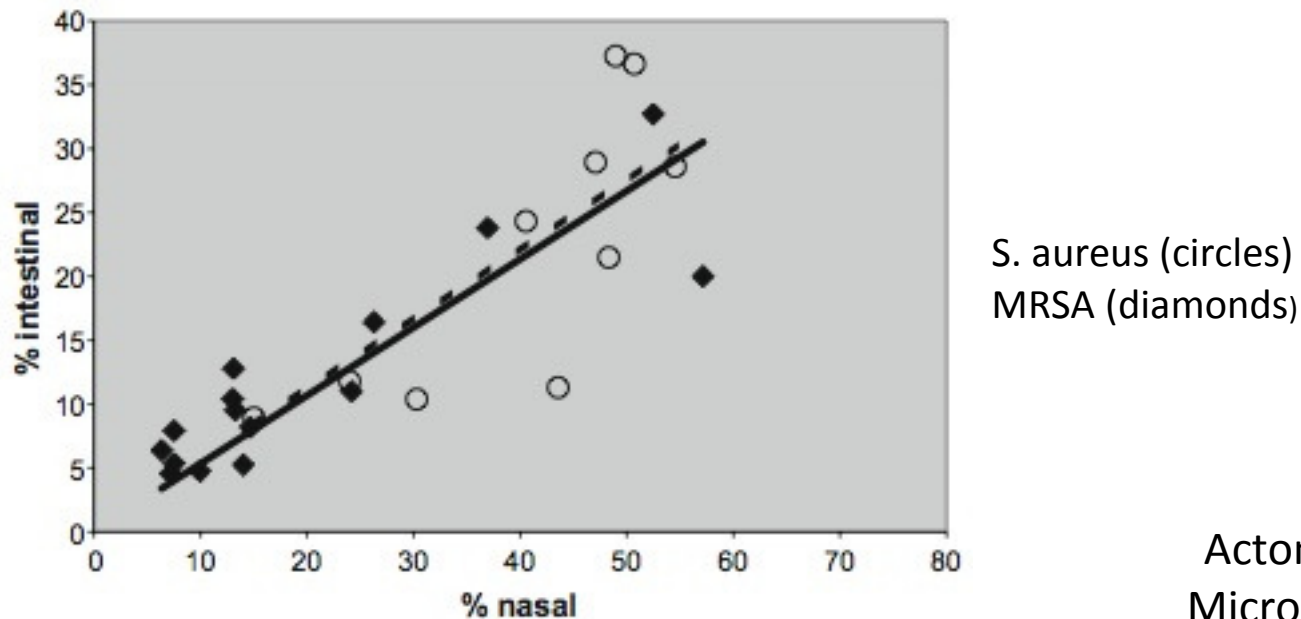
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- The different categories of carriers
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# Other sites of carriage : intestine

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- intestinal carriage in healthy individuals and patients is 20% for *S. aureus* and 9% for MRSA
- sole intestinal carriage is observed in 1 out of 3 intestinal carriers



# Other sites of carriage : throat

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- Sole throat carriage observed in 12.8% of 2966 individuals screened for *S. aureus* carriage with swabs of both nares and throat.
- independent risk factor for exclusive throat carriage:
  - age 30 years or younger (odds ratio, 1.66;  $p=0.001$ )
  - Protective effect : exposure to the HCS (odds ratio, 0.67;  $P = 0.001$ ).
  - Healthy blood donors were almost twice as likely to have exclusive throat carriage than in-hospital patients and HCWs (30.2% vs 18.4% of all carriers,  $P=0.001$ )

# Do the other sites of colonization play a role in infection ?

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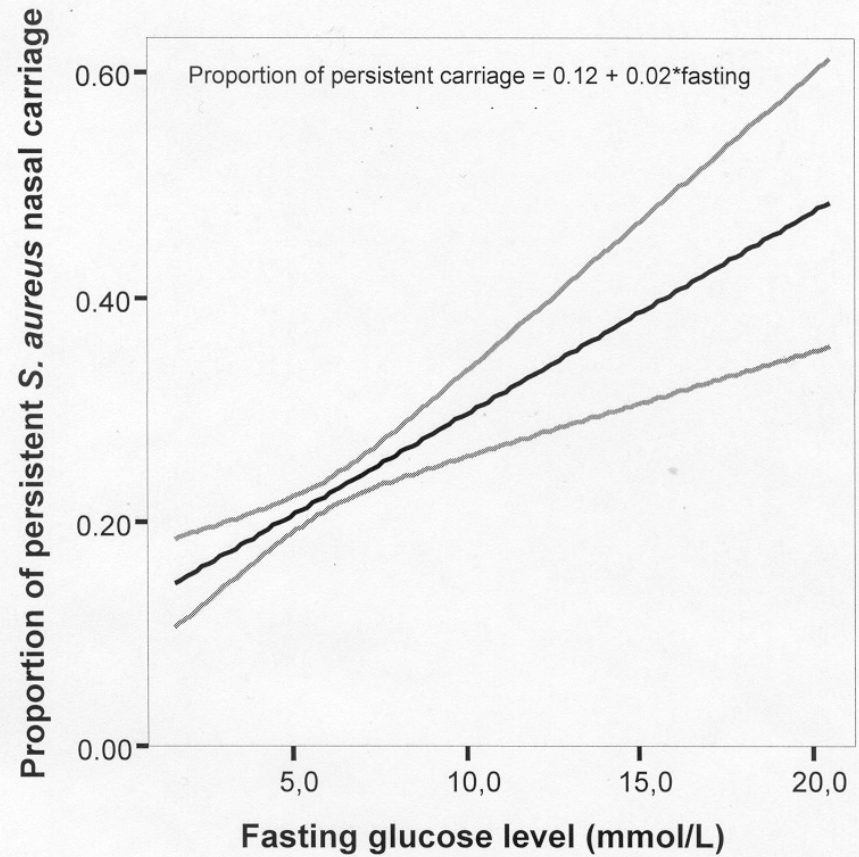
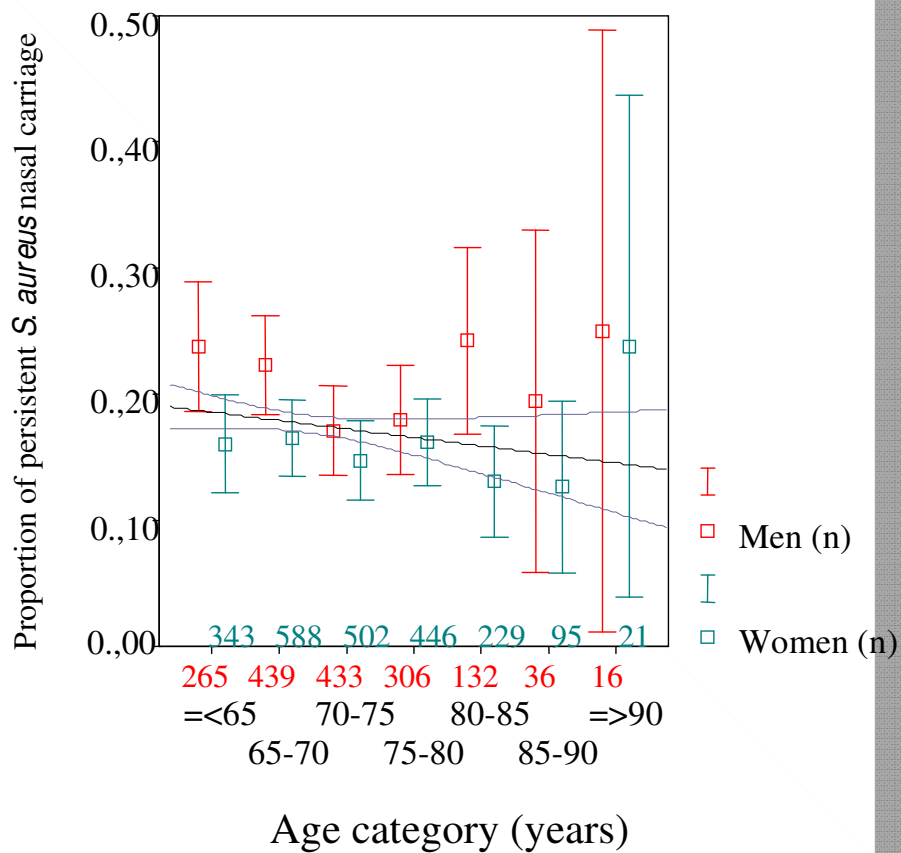
- Is nasal carriage of *Staphylococcus aureus* the main acquisition pathway for surgical-site infection in orthopaedic surgery? Berthelot et al. Eur J Clin Microbiol Infect Dis (2010)
- Intestinal carriage likely contribute to bacterial dissemination and subsequent risk of infections
- Whether intestinal rather than nasal *S. aureus* carriage is a primary predictor for infections is still ill-defined (Acton DS et al. Eur J Clin Microbiol Infect Dis 2009)

# Outlines

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# Host : age, gender and glucose level



# Host Genetic factors

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- Glucocorticoid Receptor Gene Polymorphisms
  - 2929 subject enrolled
  - GG homozygotes of the exon 9beta polymorphism were associated with a 68% reduced risk of persistent *S. aureus* nasal carriage,
  - Presence of the codon 23 lysine allele displayed an 80% increased risk
  - Hypothesis: cortisol resistance (lysine allele) leads to elevated levels of cortisol induces immune suppression and increases the risk of being a persistent carrier

# Host Genetic factors

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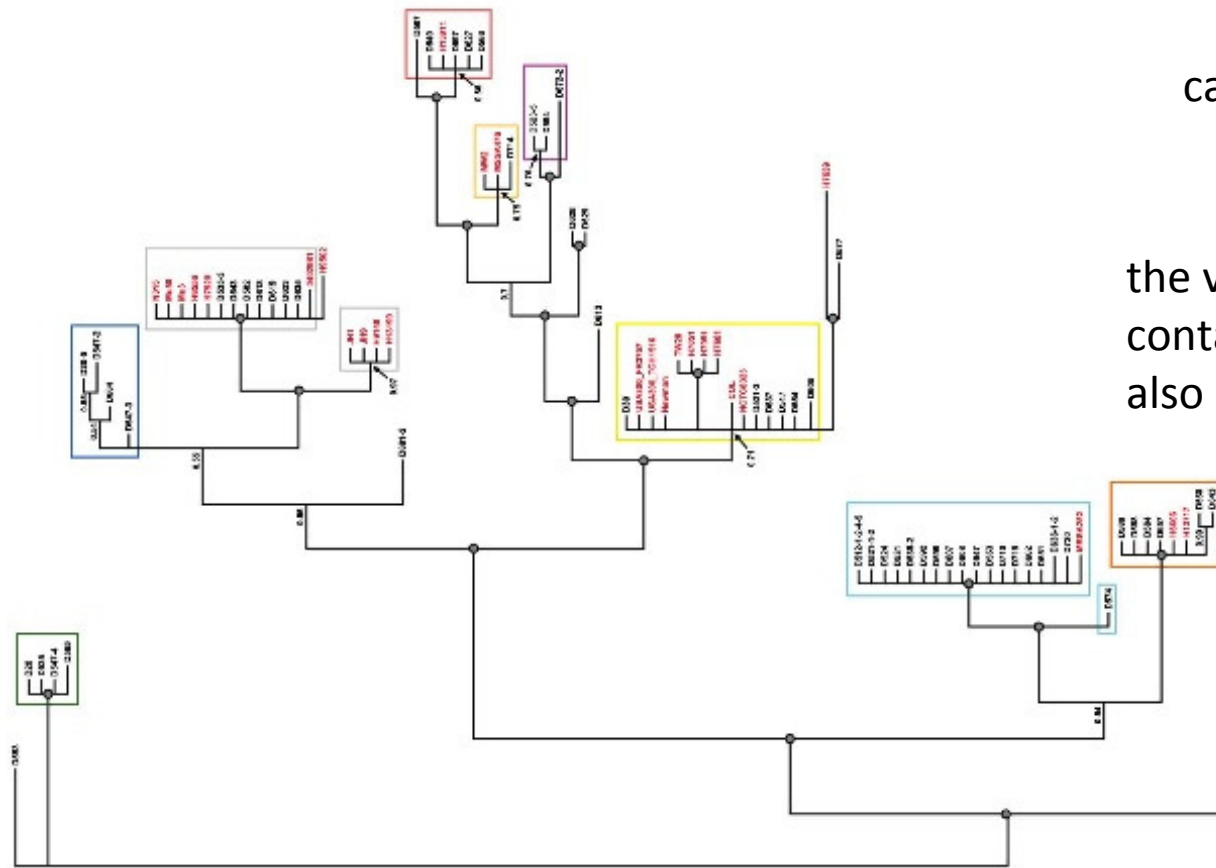
- Polymorphism in IL 4, complement factor H and CRP genes or promotor regions
- -> associated with nasal carriage of certain S.aureus strains

# The Bug

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- Core genome
- Core variable: factors with genetic variability
- Variable genome: includes PI
- -→ invasive isolates vs colonising isolates?

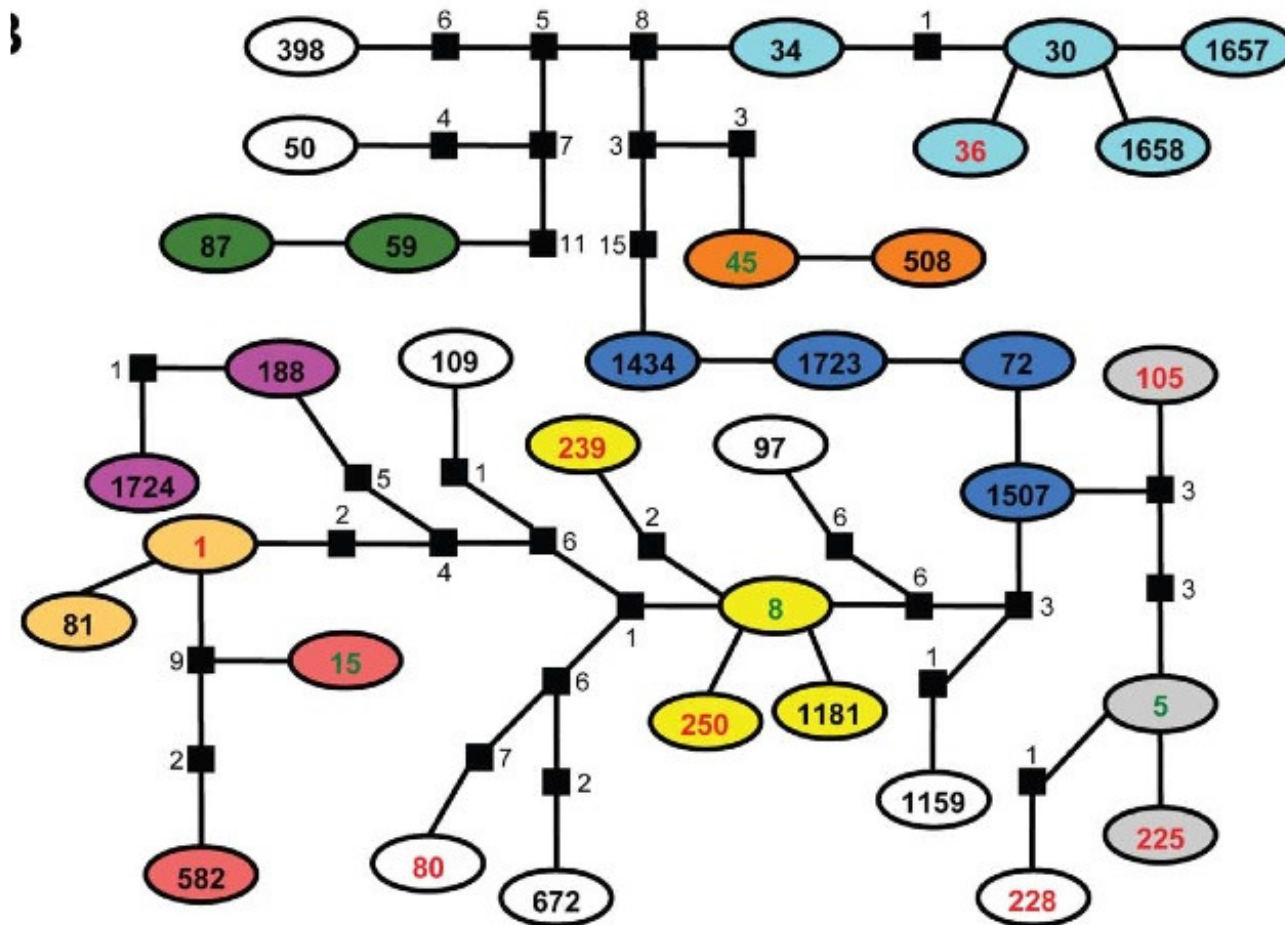
# MLST analysis reveals phylogenetic relationships between *S. aureus* nasal carriage and clinical strains



carriage strains in black  
clinical strains in red

the vast majority of clades containing clinical isolates also contain nasal carriage

# Nasal carriage and clinical isolates of *S. aureus* belong to the same genetic clusters



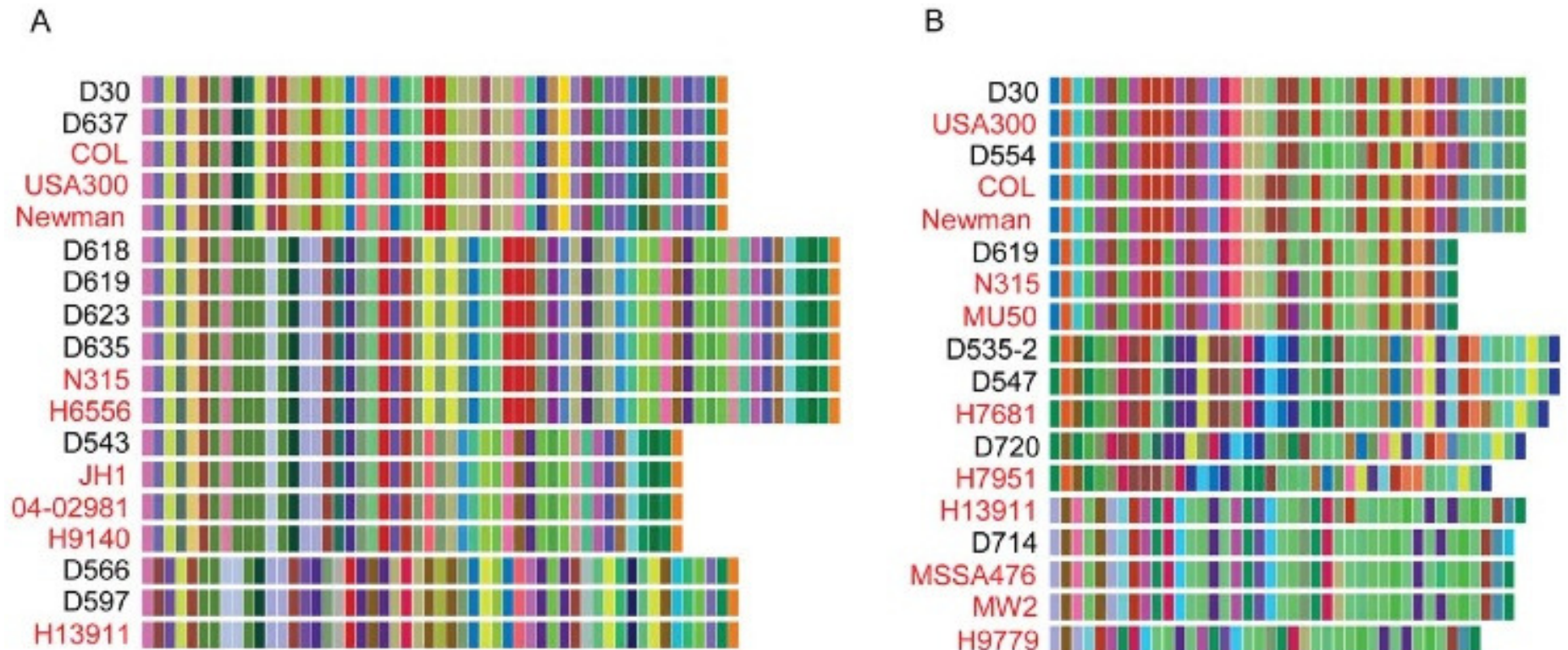
n° in black: carriage strains  
 n° in red: clinical strains  
 n° in green: clinical & carriage

# Virulence gene typing facilitates sub-sequence type strain resolution

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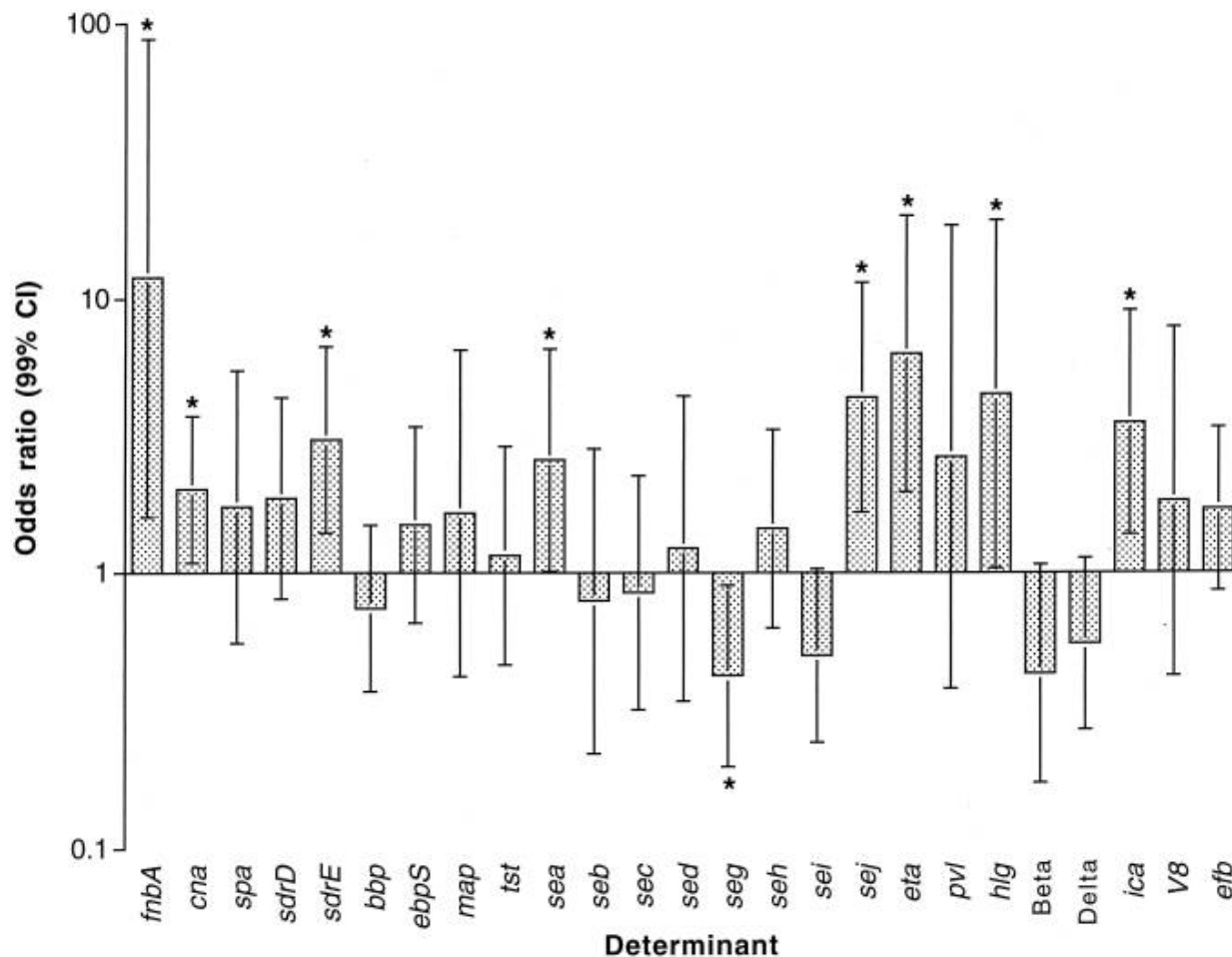
- Clf and fnb are putative determinants of nasal carriage
- Length differences within the repeat regions of the clf and fnb genes did not discriminate between colonizing and clinical isolates

# Nasal carriage and clinical isolates of *S. aureus* share (near-)identical clf repeat region sequences



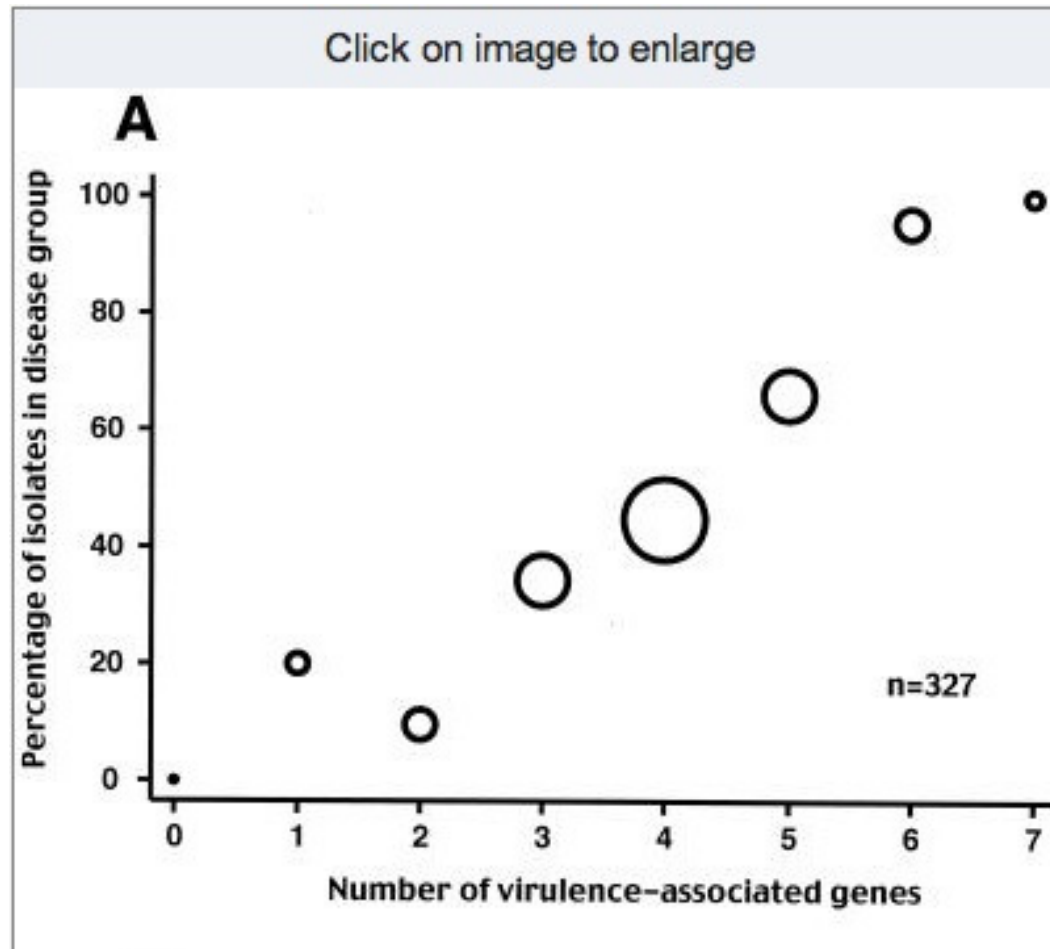
n° in black: carriage strains  
n° in red: clinical strains

Somes virulence determinants are positively associated with disease vs colonization across multiple *S. aureus* lineages



Peacock SJ et al. Virulent combinations of adhesin and toxin genes in natural populations of *Staphylococcus aureus*. *Infect Immun.* 2002 Sep;70(9):4987-96

# Cumulative effect of virulence genes for disease vs colonization



# The bug

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- Nasal carriage and clinical isolates of *S. aureus* belong to the same genetic clusters
- Some virulence determinants are positively associated with disease vs colonization
- Virtually any colonization isolate can cause invasive disease

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# Interventions

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- Nasal carriage eradication with mupirocin ointment generally considered to be highly effective, at least in the short term....
- Mupirocin treatment may only be marginally effective in the eradication of multi-site carriage
  - > chlorhexidine mouth wash, oral rifampin, oral vancomycin

# Impact of vaccination on nasal carriage

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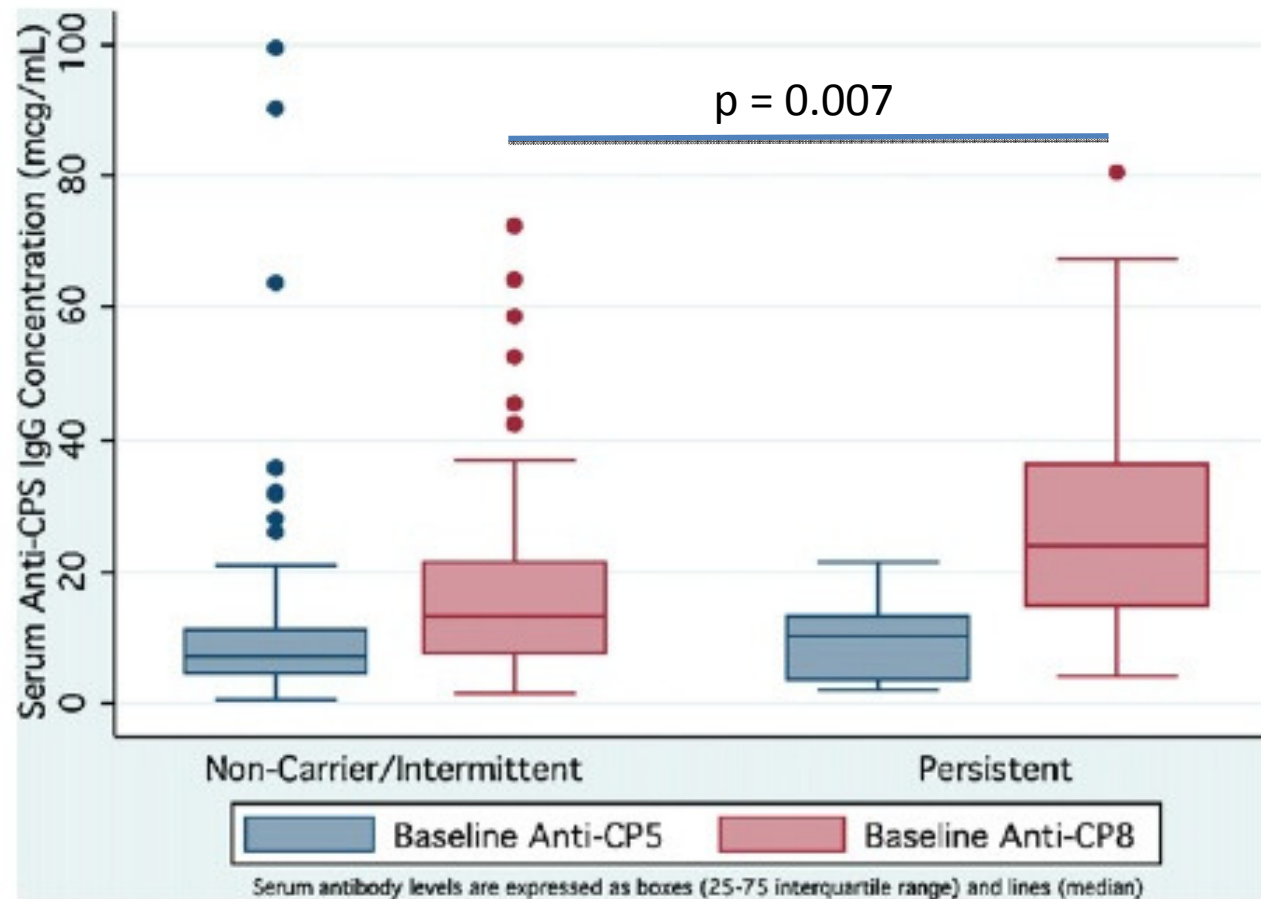
- *S. aureus* nasal colonization tested at two weekly points prior to vaccination and again at six weeks post immunization
- StaphVAX<sup>®</sup> (*S. aureus* capsular polysaccharide 5 and 8 conjugate vaccine)
- Serum anti-capsular antibody titers to CP5 and CP8 prior and 42 days post immunization

# Results

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- Statistically significant rises in serum antibody concentrations (CP5 and 8) were noted after vaccination
- No significant impact on colonisation of the vaccinated subjects

# Pre-immunization anti-CPS level stratified by pattern of colonization



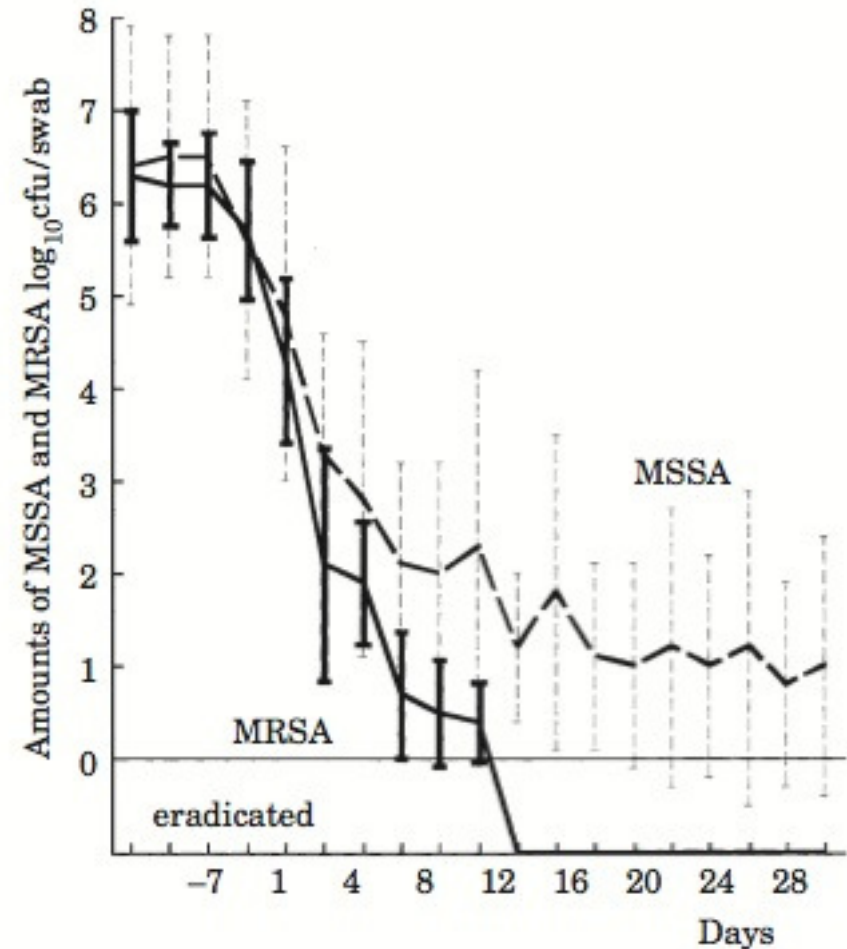
# limits

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- unimmunized control group was not included
- mucosal anti-capsular antibodies not measured
- Ab by ELISA and not by functional opsonophagocytic assays (OPA),
- Study underpowered to detect small changes in colonization after vaccination

# Bacterial interference

- Implantation of a corynebacterium sp in the nose of 17 *S. aureus* carriers
- 71% eradication of carriers by up to 15 inoculations (Fup: 3-35 months)
- similar doses of 0.9% NaCl or *S. epidermidis* : no effect



# Bacterial interference

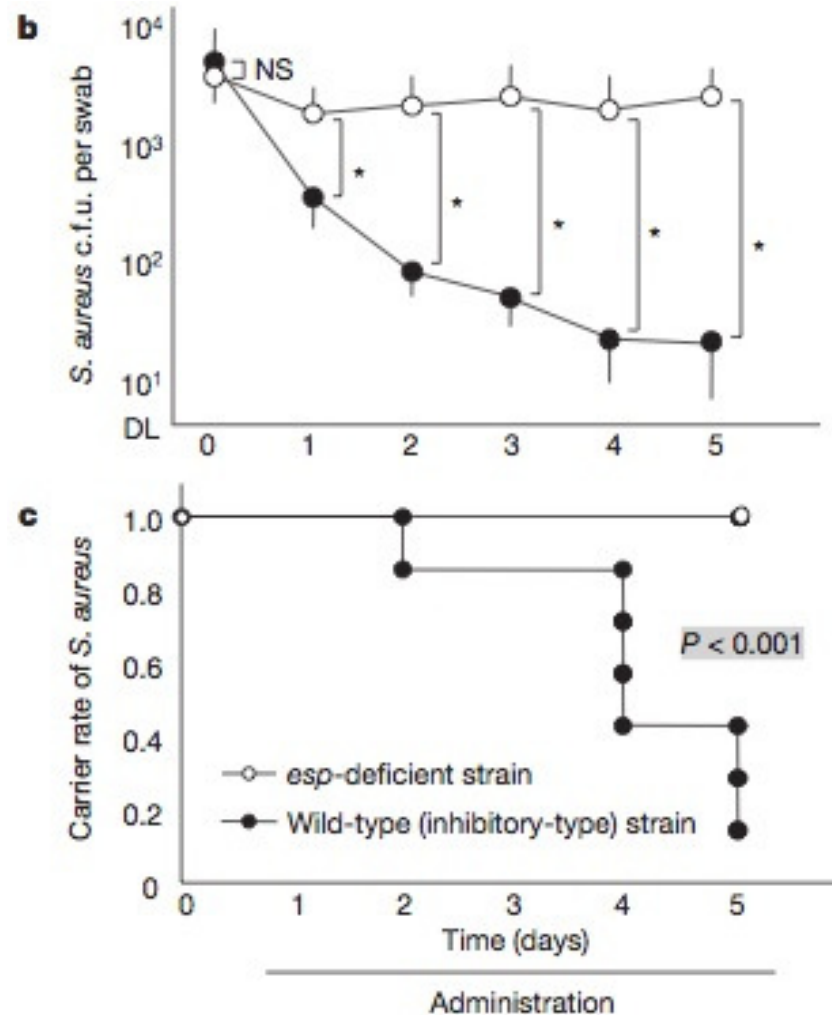
- Esp-secreting *S. epidermidis* in the nose of human volunteers correlates with the absence of *S. aureus*
- Purified Esp inhibits biofilm formation and destroys pre-existing *S. aureus* biofilms

**Table 1 | Odds ratios for *S. aureus* colonization in 88 volunteers (univariate analysis)**

Measurement	<i>S. aureus</i> colonization		Odds ratio (95% CI)	P-value
	Yes (n = 28)	No (n = 60)		
Age (years)	22.2* (1.2)†	21.7* (1.3)†	1.10 (0.78–1.55)	0.58
Sex			2.61 (0.93–7.40)	0.07
Male	22	35		
Female	6	25		
Active smoking			0.33 (0.04–2.91)	0.32
Yes	1	6		
No	27	54		
Passive smoking			0.69 (0.26–1.83)	0.46
Yes	8	22		
No	20	38		
Allergy in nose			1.21 (0.49–3.00)	0.69
Yes	12	23		
No	16	37		
Allergy in eye			1.08 (0.30–3.95)	0.90
Yes	4	8		
No	24	52		
Allergy in skin			1.49 (0.51–4.36)	0.47
Yes	7	11		
No	21	49		
Antibiotic treatment in last month			0.69 (0.13–3.67)	0.67
Yes	2	6		
No	26	54		
Colonization of <i>S. epidermidis</i>			0.45 (0.06–3.36)	0.43
Yes	26	58		
No	2	2		
Colonization of inhibitory <i>S. epidermidis</i>			0.29 (0.11–0.76)	0.01
Yes	8	35	0.30 (0.11–0.80)‡	
No	20	25		

\* Mean, † standard deviation, ‡ multivariate analysis (adjusted for age, sex or smoking habits).

# Elimination effect of inhibitory *S. epidermidis* cells on *S. aureus* nasal colonization



# De la colonisation à l'infection

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- Portage multifactoriel et multi-sites
- Portage = facteur de risque infectieux mais toutes les infections à *S.aureus* ne sont pas associées à un portage
- Combattre le portage ou susciter les défenses anti-infectieuses ?

