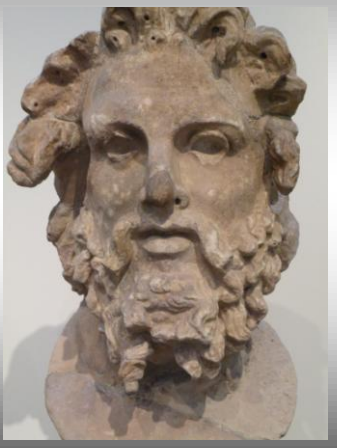
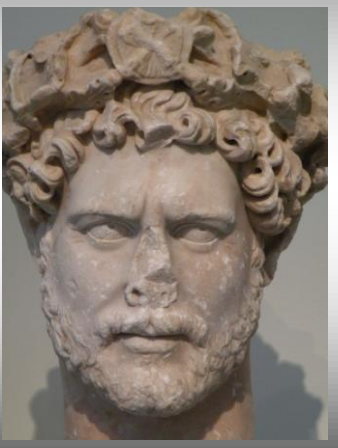
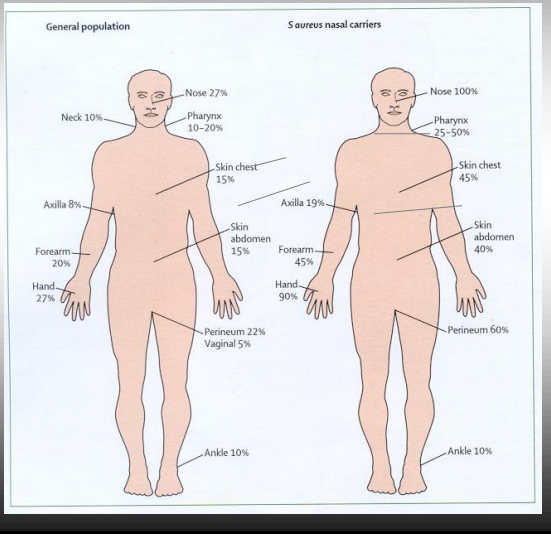
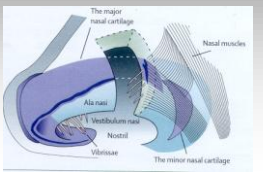
CAN NOSOCOMIAL INFECTIONS BY *STAPHYLOCOCCUS AUREUS* BE PREVENTED?





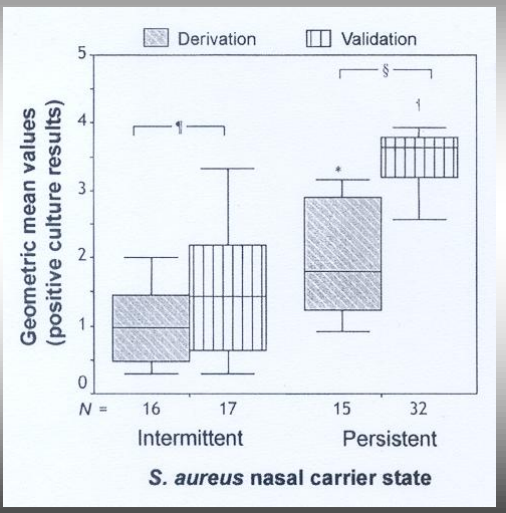
STAPHYLOCOCCUS AUREUS CARRIAGE SITES





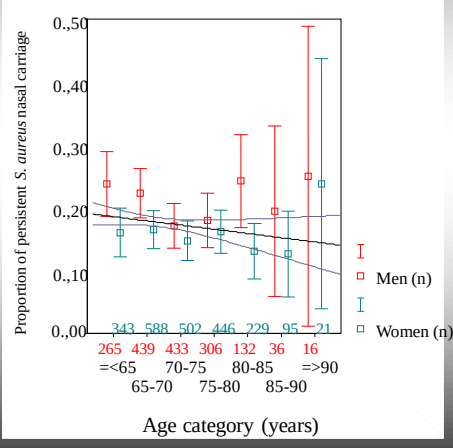
THE ANATOMICAL NICHES FROM WHICH **ALL (!!)** STRAINS CAN CAUSE INFECTIONS: AMONG WHICH 80% AUT0-INFECTIONS

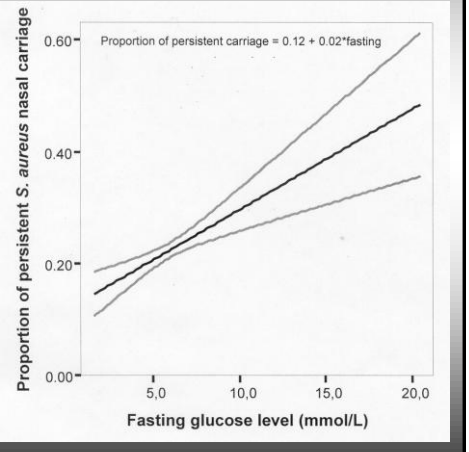
HOST FEATURES: QUANTITATIVE ASPECTS OF NASAL CARRIAGE



Nouwen *et al.*, CID 2004

HOST FEATURES: GENDER AND AGE AND BLOOD GLUCOSE LEVELS





HOST FEATURES: GLUCOCORTICOID RECEPTOR GENE POLYMORPHISM

Four polymorphisms determined for 3000 people for whom also the *S. aureus* carriagestatus is known

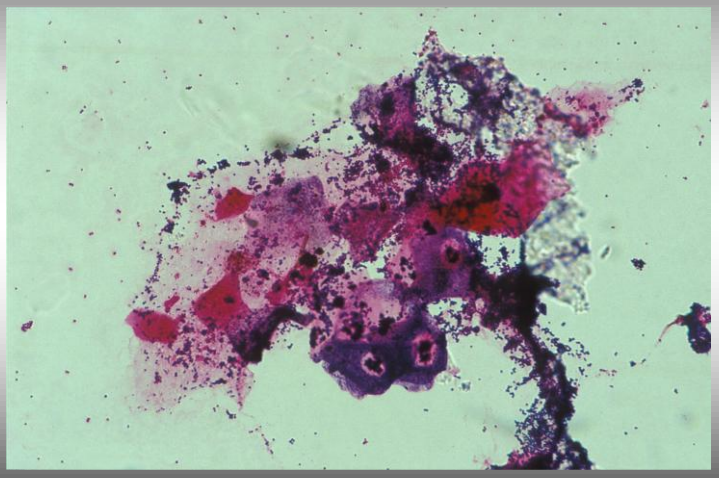
9-beta GG homozygotes have a 67% lower risk of being a persistent carrier (Odds ratio 0.33, 95% CI 0.15-0.74)

9-beta-ER22/23K genotypes stand an 80% increased risk of being a persistent carrier (Odds ratio 1.80, 95% CI 1.08-3.00)

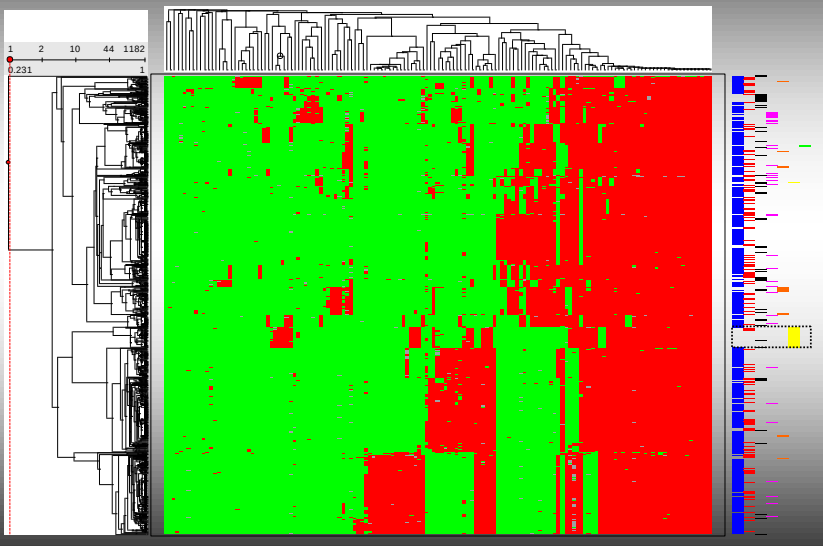
Data: the different mutations affect cortisol susceptibility

Hypothesis: cortisol resistance (9-beta-ER22/23K mutant) leads to elevated levels of cortisol, induces immune suppression, increases the chance of being a persistant carrier

THE ORGANISM AT HOME



STAPHYLOCOCCUS AUREUS DOES ITS POPULATION STRUCTURE PREDICT THE EXISTENCE OF HYPERVIRULENT CLONES?



Legend color-bar: blauw = carriage; rood = bacteraemia; zwart = animal; roze = impetigo; oranje = MRSA (Harmony); geel = varkens MRSA; groen = Mu50, N-315

CURRENT WORKING HYPOTHESIS

ESSENTIALLY ALL
STAPHYLOCOCCUS AUREUS STRAINS
HAVE THE CAPACITY
TO BECOME INVASIVE AND
ACCESORY GENEPRODUCTS
MIGHT VERY WELL BE
THE MOST RELEVANT FACTORS
IN STAPHYLOCOCCAL VIRULENCE

**ATTACHMENT – COLONISATION –
INVASION OR PENETRATION – EVASION OF HOST IMMUNITY
HUMORAL IMMUNE RESPONSES**

CLINICAL RELEVANCE OF NASAL CARRIAGE

	Nosocomial *S aureus* bacteraemia		
	Yes	No	Relative risk (95%CI)
S aureus carrier	40* (1·2%)	3380 (98·8%)	3·0 (2·0–4·7)
Non-carrier	41 (0·4%)	10 547 (99·6%)	1·0

*Nasal and subsequent bacteraemic *S aureus* isolates were clonally related in 80% of patients, measured by pulsed-field gel electrophoresis.

Table 1: Relative risk of nosocomial *S aureus* bacteraemia by nasal carrier status

	S aureus carrier (total=40)	Non-carrier (total=41)	p Univariate
Mean age (SD)*	53·7 (18·6)	64·6 (16·3)	0·007
Sex (male)†	23 (58%)	28 (68%)	0·32
Reason for admission			
Cardiac	9 (23%)	21 (51%)	0·001
Malignant disease	9 (23%)	4 (10%)	0·12
Infection	5 (13%)	3 (7%)	0·43
Vascular	2 (5%)	5 (12%)	0·25
Other	15 (38%)	8 (20%)	0·07
Underlying disease or risk factor			
Diabetes	10 (25%)	9 (22%)	0·75
Immunocompromised	14 (35%)	5 (12%)	0·02
Central venous access	18 (45%)	19 (46%)	0·90
Other indwelling device	13 (33%)	22 (54%)	0·05
Outcome (mean and SD, or number and percentage)			
Hospitalisation (days)	25 (72)	50 (64)	0·01
Time to bacteraemia (days)	11 (21)	16 (25)	0·22
In-hospital mortality (all causes)	7 (18%)‡	19 (46%)	0·005
In-hospital mortality (*S aureus*-related)	3 (8%)	13 (32%)	0·006
Source of bacteraemia			
Intravascular device-related	21 (53%)	23 (56%)	0·75
Wound	9 (22%)	3 (7%)	0·05
Other	6 (15%)	8 (20%)	0·59
Unknown	4 (10%)	7 (17%)	0·36

*Mean age of all carriers was 57·0 (SD 18·4) and of non-carriers 59·8 (17·4) years. †56% of all carriers and 53% of all non-carriers were male. ‡All bacteraemic strains of carriers who died were of endogenous origin.

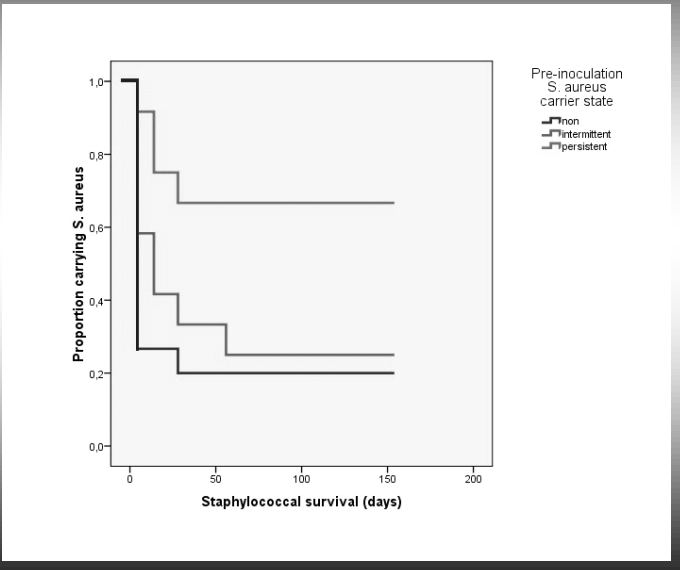
Table 2: Comparison of patients with nosocomial *S aureus* bacteraemia by nasal carrier status

Wertheim *et al*, Lancet 2004

ARTIFICIAL COLONISATION

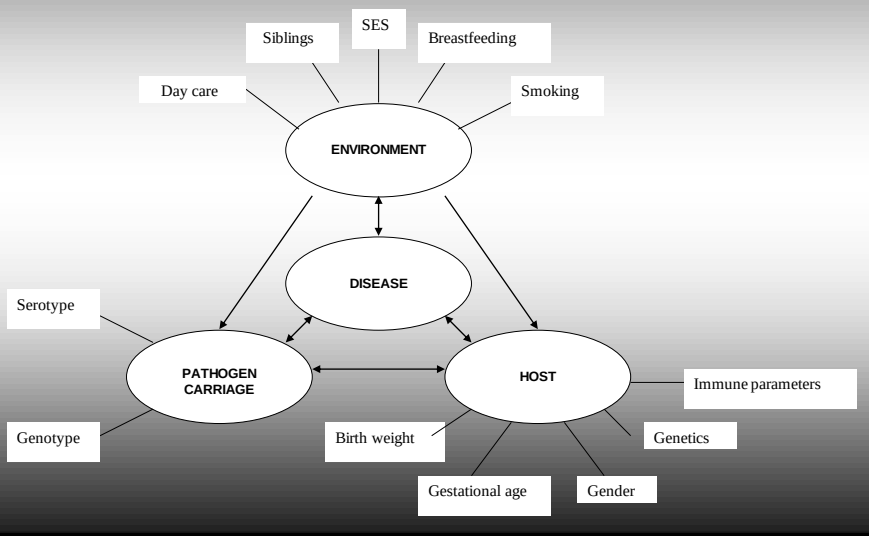
	Before mupurocin											Nasal culture results: After mupurocin, Before inoculation						After inoculation								
volenteer	w1	w2	w3	w4	w5	w6	w7	w8	w9	w10	status	n0	t0	p0	n5	t5	p5	n7	n8	n10	n14	n22	n28	typering	typering1	typering2
55	0	0	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0	1	ander	ander	
64	0	0	0	0	0	0					0	0	0	0	0	0	0	0		0	0	0	620	ander	ander	
74	0	0	0	0							0	0	0	0	0	0	0	68		0	90	0	18	ander	ander	
118	0	0	0								0	0	0	0	0	0	0	0	0	0	1	0	0	neg	ander	
135	0	0									0	0	0	0	0	0	0	800	2300	5800	6500	4500	84	n22 = n28	ander	
34	0	0	0	0	0						0	0	0	0	0	0	0		600	0	0	0	0	neg	interm	
38	0	0	0	0	0	0					0	0	0	0	0	0	0	330	900	326	26000		5500	interm	interm	
18	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0	0	0	0	0	0	0	neg	nvt	
26	0	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	neg	nvt	
73	0	0	0	0	0						0	0	0	0	0	0	0	0	0	0	0	0	0	neg	nvt	
97	0	0	0	0	0	0	0	0			0	0	0	0	0	0	0		0	0			0	neg	nvt	
102	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	neg	nvt	
132	0	0									0	0	0	0	0	0	0	0	0	0	0	0	0	neg	nvt	
155	0	0	0	0							0	0	0	0	0	0	0	0	0	0	0	0	0	neg	nvt	
158											0	0	0	0	0	0	0	0	0		0	0	0	neg	nvt	
150	0	0	0	0	0	0	0	0			1	16	0	0	0	0	0	2	0	0	610	1	0	neg	?	
42	0	0	0	0	0	0	0				1	1020	0	0	0	0	0,5	2500	12		0	0	0	p5 is niet n7	502a	
41	2	0,5	1	0	0	0					1	0	0	0	0	0	0	0	82	50	2	260	10000	ander	ander	
127	0,5	0	0,5	0	0						1	10	0	0,5	0	0	0	2	0	0	7000	1	0	n1=p28, n22=p28, n3 uniek	ander	
129	0	0									1	0	0	0	0	0	0	30		0	5700	16	1640	ander	ander	
154	0										1	0	0	0	0	0	0	0	0		0	4	0	neg	ander	
163											1	600	3	2	0	0	0	6	500		1100	0	800	ander	ander	
105	0,5	2	0,5	0	0	0	0,5	0	0	0	1	1	1	0,5	0	0	0	0	0	0	8	8000	10	eigen	eigen	
141	0	0									1	0	0	0	0	0	0	0	8		2	62	320	eigen	eigen	
156	0										1	16	2	0	0	1	0	434	0	0	4	0	0	n14=n0	eigen	
90	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	6	6	110	0	0	0	neg	interm	
101	0,5	0	0	0	0	0					1	0	0	0	0	0	0	0				0	0	neg	nvt	
144	0	0									1	0	0	0	0	0	0	0		0	0	0	0	neg	nvt	
157											1	0	0	0	0	0	0	0	0	0	0	0	0	neg	nvt	
160	0										1	4200	0,5	0	0	0	0	0	0	0				neg	nvt	
7	0	0	3	0	0	0					1	0	1	0	0	0	0	90	1	1	2	2	0	neg	p1	ander
37	0	0	0,5	0							1	0	0	0	0	0	0	0		0	2	0	0	n3 is niet n14	p1	
66	0	0	0	0	0	0	0				1	2	0	0	0	0	0	430	0	0	0	0	0	neg	p1	
100	0	0,5	0	0,5	0	0					1	0	2	0	0	0	0	0	0	0	0		1	p2 en ander	p2	ander
146	2	0	0								1	0	0	0	0	0	0	14		17000	50		0	neg	p2	
148	0,5	3	1	3							2	1300	0	0	0	0	0	0	44	300	88		1000	?	?	
56	2	2	1	2	3	3	3	0,5			2	0	0	0	0	0	0	2	0	0	830	50	280	2ander	ander	ander
48	2	0,5	2	0,5	3	0,5	1	0,5			2	26	0	0	0	0	0	0	1		290		2400	eigen	eigen	
106	2	2	2	1	3						2	64	0	0	0	1	0	320	1500000	480	4	1	0	op t14 ook p1 en 502a	eigen	
92	2	2	2	2	0	1	4				2	32	0	0	0	0	0	0	0	0	0	0	0	neg	nvt	
12	2	2	3	2							2	26	0	1	0	0	0	600	800	0	1800		0	neg	p1	
14	1	2	2	0,5	2	4					2	3500	0	0	0	0	0	9600	108	0	0	0	0	neg	p2	ander

THERE ARE ONLY PERSISTENT CARRIERS AND NON-CARRIERS!!!!!



NASAL AND NASOPHARYNGEAL BACTERIAL CARRIAGE STUDIES IN HEALTHY CHILDREN

THE OVERALL SOCIO-DEMOGRAPHIC, CLINICAL NETWORK PICTURE

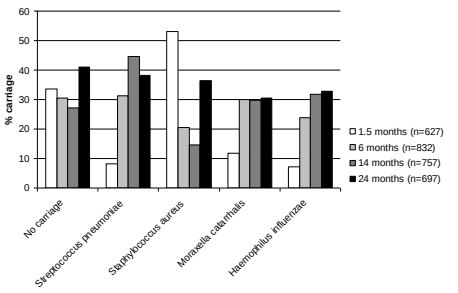


STUDY SET-UP

The bacterial carriage study is embedded in the Generation R Study, a prospective cohort study from fetal life onwards.

1. 10,000 pregnant women got enrolled.
2. 1,232 women were eligible to participate in the Generation R Focus Study
3. Complete follow up in Focus cohort of 1,079 infants
4. Visits at age 1.5, 6, 14 and 24 months of age (visit rate 82%)
5. Questionnaires at age 2, 6, 12, 24 months of age

OVERVIEW OF CARRIAGE PREVALENCES ACROSS THE FIRST TWO YEARS OF LIFE



	1.5 months (n=627)	6 months (n=832)	14 months (n=757)	24 months (n=697)
No carriage	33,7	30,4	27,1	41
Streptococcus pneumoniae	8,3	31,3	44,5	38,2
Staphylococcus aureus	53	20,4	14,5	36,3
Moraxella catarrhalis	11,8	29,9	29,7	30,6
Haemophilus influenzae	7,2	23,8	31,7	32,9

Carriage in %

RISK FACTORS

TABLE 1. Determinants of *Staphylococcus aureus* carriage in the first year of life

Parameter	Value for infants[a]: Not colonized (0–1) (n = 354)	Colonized (≥2) (n = 89)	OR (95% CI)	aOR (95% CI)
Gender				
Female	184 (52.0)	34 (38.2)	1.00	1.00
Male	170 (48.0)	55 (61.8)	1.75 (1.09–2.82)	2.09 (1.17–3.72)
Gestational age (mo)	40.3 (37.7–42.0)	40.3 (37.0–42.4)	0.91 (0.78–1.06)	0.94 (0.76–1.17)
Birth wt (g)	3,580 (2,751–4,305)	3,520 (2,385–4,605)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Breast-feeding at 6 mo				
No	237 (69.1)	56 (63.6)	1.00	1.00
Yes	106 (30.9)	32 (36.4)	1.28 (0.78–2.09)	1.36 (0.75–2.47)
Mother's educational level				
Higher education	223 (63.9)	63 (70.8)	1.00	1.00
Lower/intermediate education	126 (36.1)	26 (29.2)	0.73 (0.44–1.21)	0.52 (0.26–1.05)
Mother's prenatal smoking				
No	319 (94.4)	79 (94)	1.00	1.00
Yes	19 (5.6)	5 (6)	1.06 (0.34–2.93)	5.35 (0.86–33.40)
Mother's postnatal smoking				
No	260 (87.8)	70 (88.6)	1.00	1.00
Yes	36 (12.2)	9 (11.4)	0.93 (0.43–2.02)	0.25 (0.05–1.33)
Siblings				
No	201 (60.5)	52 (59.1)	1.00	1.00
Yes	131 (39.5)	36 (40.9)	1.06 (0.66–1.71)	1.03 (0.57–1.87)
Day-care attendance				
No	67 (22.5)	25 (31.6)	1.00	1.00
Yes	231 (77.5)	54 (68.4)	0.63 (0.36–1.08)	0.53 (0.27–1.01)

[a] Values are given as number (%) of infants unless indicated otherwise. Values are means or medians (5 to 95% range) for variables with skewed distribution. A total of 443 infants provided nasal swabs at all three collection moments. Data were missing on breast-feeding (n = 12), mother's educational level (n = 5), mother's prenatal smoking (n = 21), mother's postnatal smoking (n = 68), siblings (n = 23), and day-care attendance (n = 66).

POPULATION BASED SCREENING STUDIES

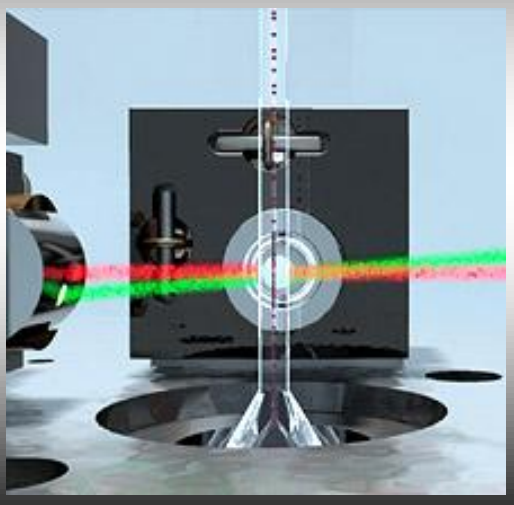
	Positive once		*Positive twice or more*	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
No atopic dermatitis	1.00	1.00	1.00	1.00
Atopic dermatitis 0-6 months**	0.67 (0.32 – 1.44)	0.64 (0.30 – 1.34)	1.61 (0.82 – 3.13)	1.67 (0.85 – 3.27)
Atopic dermatitis 6-12 months	1.23 (0.59 – 2.54)	1.24 (0.60 – 2.56)	1.47 (0.59 – 3.64)	1.46 (0.59 – 3.63)
Long-term atopic dermatitis ***	2.15 (1.10 – 4.19) *	2.16 (1.11 – 4.22) *	3.43 (1.60 – 7.35) *	3.48 (1.62 – 7.49) *

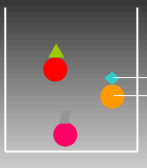
PRESS	*Positive once*		*Positive twice or more*	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
No atopic dermatitis	1.00	1.00	1.00	1.00
Mild atopic dermatitis	1.11 (0.68 - 1.81)	1.12 (0.69 – 1.83)	1.56 (0.85 – 2.85)	1.59 (0.87 – 2.92)
Moderate atopic dermatitis	1.77 (0.83 – 3.75)	1.81 (0.85 – 3.86)	1.84 (0.72 – 4.71)	1.92 (0.75 – 4.95)
Severe atopic dermatitis	2.15 (0.79 – 5.82)	2.12 (0.78 – 5.75)	5.71 (2.04 – 15.97) *	5.58 (1.99 – 15.64) *

* p value <0.05
** 14-month swab was not taken into account.

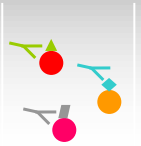
Adjusted for gestational age, birth weight.

HUMORAL IMMUNITY AND STAPHYLOCOCCAL CARRIAGE: CORRELATIONS AND PROTECTIVITY



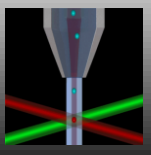


S. aureus proteins are coupled to different fluorescently-coloured beads and the beads are mixed in one well



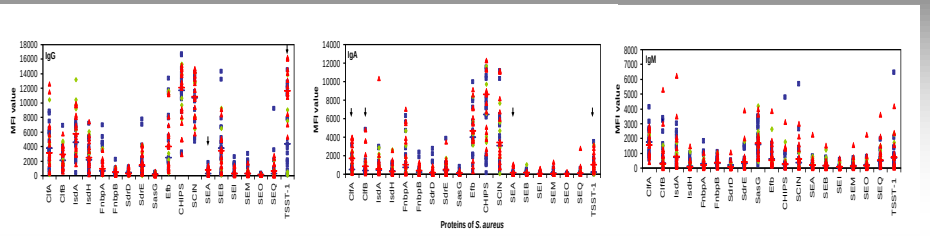
Serum is added and, when present, antigen-specific antibodies will bind to the proteins

A reporter molecule, labelled with a fluorescent dye, is introduced



Assays are read using a compact analyser. The beads pass through a red laser, to distinguish the bead set, and a green laser, to determine the assay result.

PERSISTENT VERSUS NON CARRIERS



MFI values reflecting antigen-specific IgG, IgA and IgM. Each dot represents a single volunteer; red triangles represent persistent carriers, green diamonds: intermittent carriers and blue squares non-carriers. Median levels of antistaphylococcal antibodies are indicated by horizontal lines. Statistically significant differences are indicated by black arrows (Mann Withney U test; persistent vs. non-carriers; IgG: TSST-1, 11554 vs. 429 ($p<0.001$) and SEA, 742 vs. 218 ($p<0.05$); IgA: TSST-1, 973 vs. 155 ($p<0.01$), SEA 127 vs. 32 ($p<0.05$); ClfA, 1661 vs. 441 ($p<0.05$) and ClfB, 792 vs. 356 ($p<0.05$).

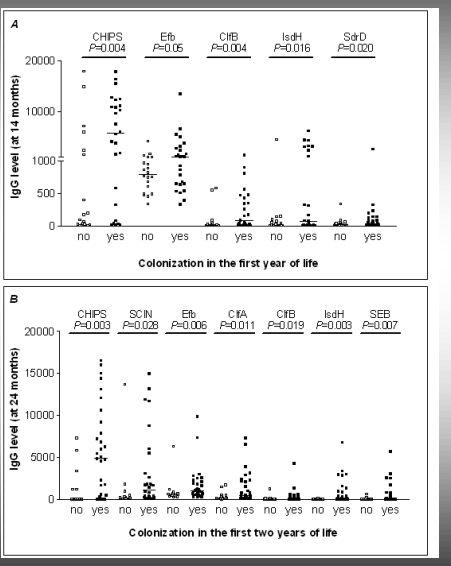
PERSISTENT VERSUS NON CARRIERS

Antistaphylococcal antibody levels in serum are highly variable, stable over time and correlate well with antibody levels in nasal secretions. Median antibody levels to TSST-1, SEA, ClfA and ClfB are higher in persistent than in non-carriers and antibodies to TSST-1 have neutralizing capacity. These antibodies might be associated with the difference in risk and outcome of *S. aureus* infections in nasal carriers versus non-carriers.

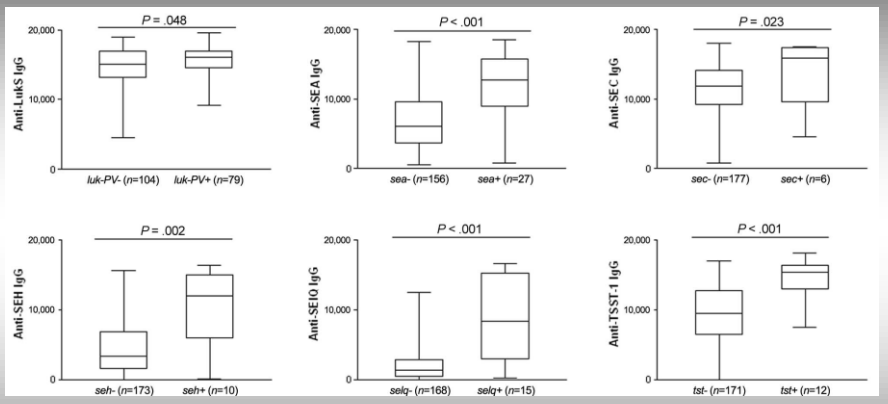
Dryla et al. 2005 presented similar data!
and Luminex data are in agreement with the novel persistent versus non carrier dogma

IMMUNE MATURATION AT YOUNG AGE

A. Relation between *S. aureus* colonization in the first two years of life and the level of IgG at 24 months. Each dot represents a serum sample. Median values are indicated by horizontal lines.
B. Relation between *S. aureus* colonization in the first year of life and level of anti-staphylococcal IgG, reflected by Median Fluorescence Intensity value, at 14 months.

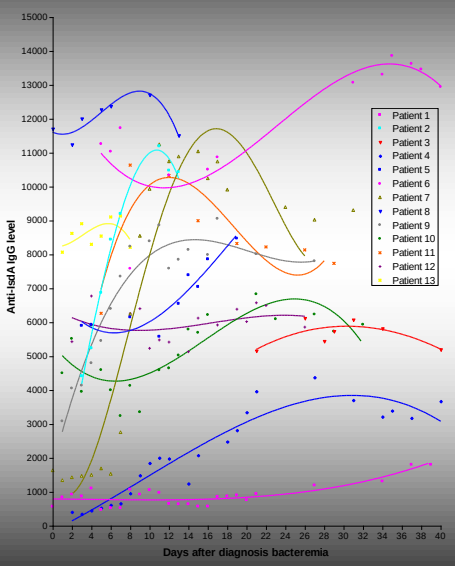


IN BLOOD



Immunogenicity of Toxins during *Staphylococcus aureus* Infection
Verkaik, Dauwalder, Antri, Boubekri, de Vogel, Badiou, Bes, Vandenesch, Tazir, Hooijkaas, Verbrugh, van Belkum, Etienne, Lina, Ramdani-Bouguessa, van Wamel

LONGITUDINAL FOLLOW UP DURING BACTERAEMIA



Course of anti-IsdA IgG levels during bacteremia and its follow-up in different adult patients

PREVENTING *Staphylococcus aureus* INFECTIONS BY SCREENING AND DECOLONIZATION OF CARRIERS

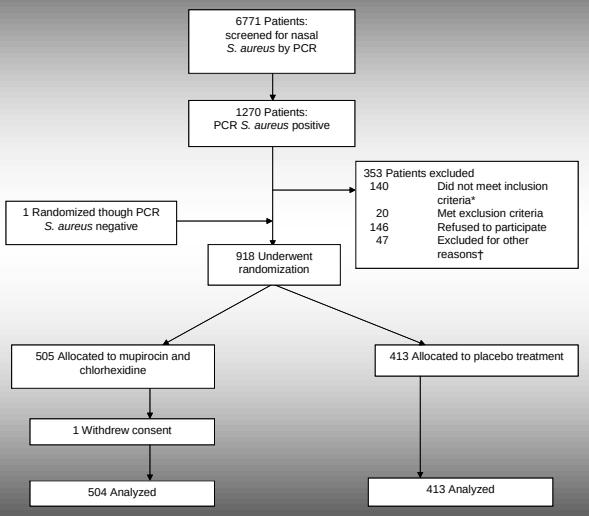
Lonneke G.M. Bode, Jan A.J.W. Kluytmans, Heiman F.L. Wertheim, Diana Bogaers, Christina M.J.E. Vandenbroucke-Grauls, Robert Roosendaal, Annet Troelstra, Adrienne T.A. Box, Andreas Voss, Ingeborg van der Tweel, Alex van Belkum, Henri A. Verbrugh, Margreet C. Vos

SET UP

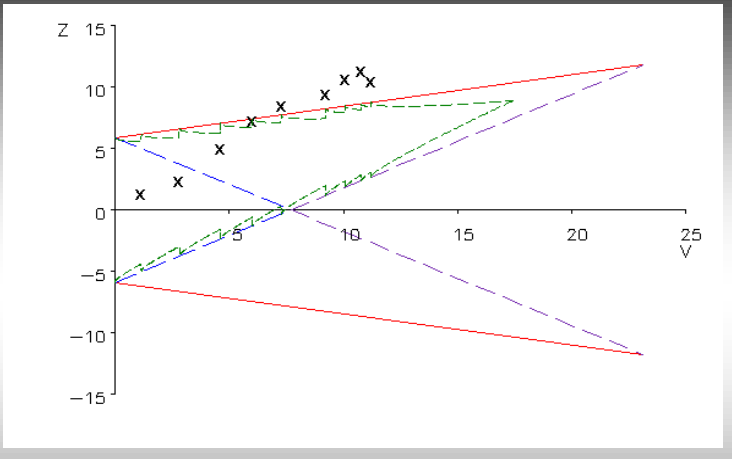
A LARGE SCALE MULTI CENTER RANDOMISED PLACEBO CONTROLLED STUDY INTO THE PROPHYLACTIC EFFECT OF WITHIN-EIGHT-HOURS-MOLECULAR-DIAGNOSTICS, MUPIROCIN TREATMENT AND CHLORHEXIDIN WASHINGS UPON STAPHYLOCOCCAL AUTO-INFECTION

(NEJM JANUARI 2010)

BASELINE CHARACTERISTICS OF THE ENTIRE STUDY

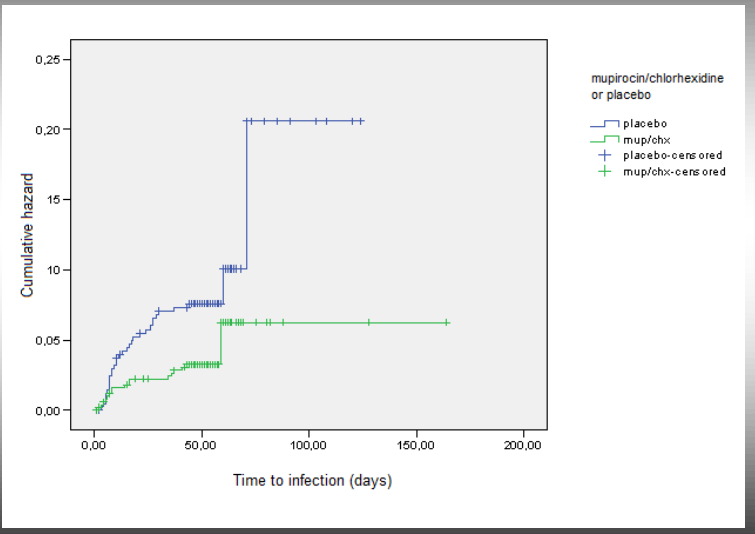


GROUP SEQUENTIAL ANALYSIS



V represents the cumulative information available, Z the cumulative effect size. Every (Z.V) x point represents 100 patients. Crossing of the upper red boundary indicates A significant reduction by mup/chlor of the cumulative incidence of nosocomial *S. aureus* infections (p = 0.0076).

KAPLAN-MEIER CURVE SHOWING CUMULATIVE HAZARD OF ACQUIRING HEALTHCARE ASSOCIATED *S. aureus* INFECTIONS



INFECTION PREVENTION

Healthcare-associated infections with *Staphylococcus aureus*, especially those in surgical patients, can largely be prevented by rapid screening of patients for nasal carriage of *S. aureus* and immediate decolonization of carriers after hospital admission. This is associated with a significantly shorter duration of hospitalization.

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