ROLE OF NASAL / ORAL CARRIAGE IN SPREAD OF MDR

THE ROLE OF NASOPHARYNGEAL CARRIAGE IN THE SPREAD OF *STAPHYLOCOCCUS AUREUS*

WHAT DEFINES CARRIAGE?
WHAT DEFINES SUCCESSFUL SPREAD?
WHAT DEFINES EPIDEMICITY?

- **THE HOST**
- **THE BUG**
- **THE (A-)BIOTIC ENVIRONMENT**

- **??????**

MANY MICROORGANISMS MAINTAIN THEMSELVES IN THEIR HOSTS WITHOUT CAUSING TOO MUCH HARM

- ADAPTATION
- RESERVOIRS
- SUSCEPTIBILITY TO DISEASE
- MULTIPLE GENES (HOST AND MICROBE)

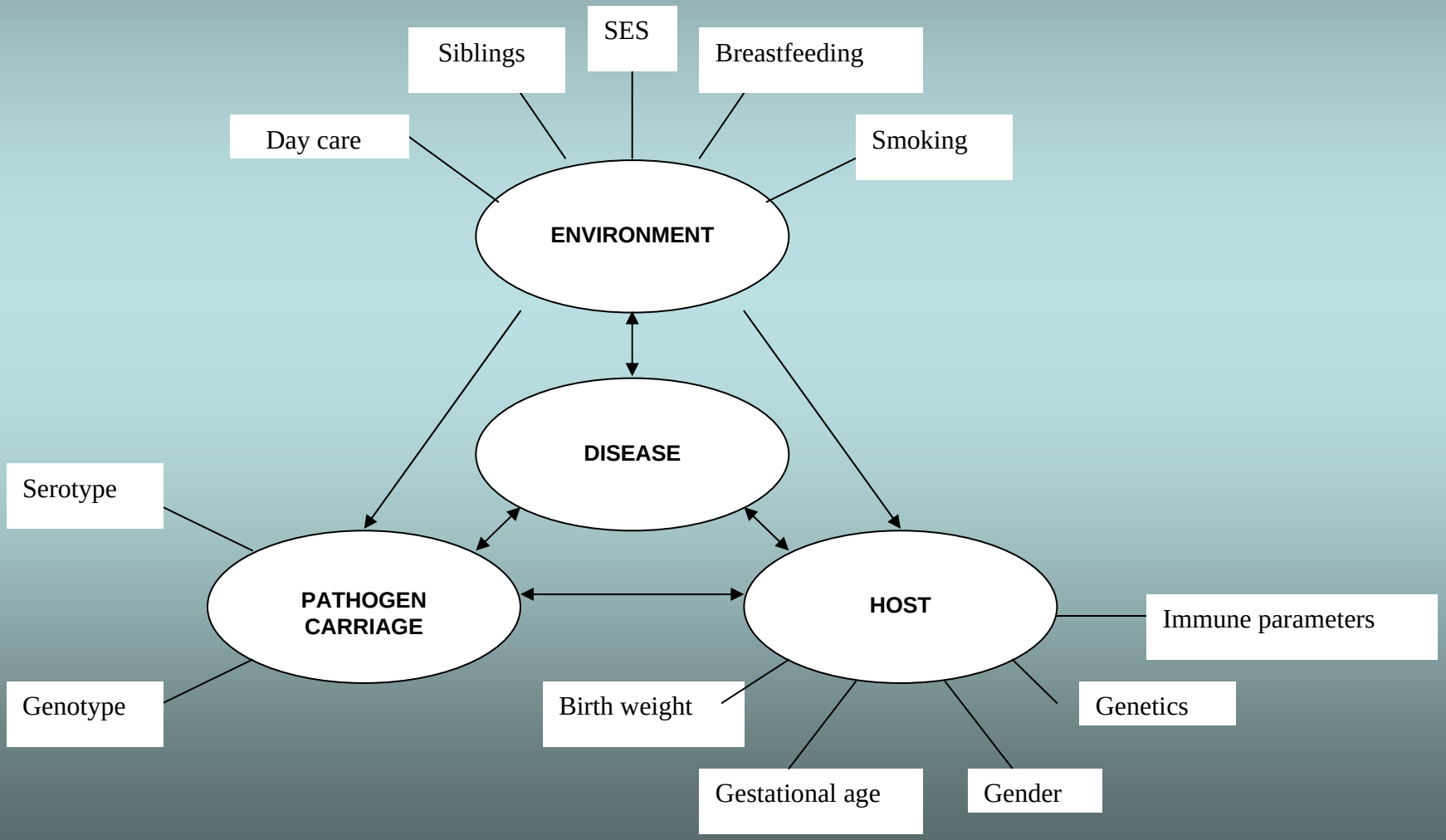
PEACEFUL COEXISTENCE

- MICROBE AND HOST SURVIVAL
- MICROBE TRANSMISSION
- INTERACTION BETWEEN HOST AND MICROBIAL MOLECULES
- WHAT IS VIRULENCE?

“BALANCED PATHOGENICITY”

COMPLEX ECOSYSTEMS

NASOPHARYNGEAL COLONISATION IN VERY YOUNG CHILDREN: what defines epidemicity??



THE GENERATION R MICROBIOLOGY STUDY

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

10,000 pregnant women got enrolled.

1,232 women were eligible to participate in the Generation R Focus Study

Complete follow up in Focus cohort of 1,079 infants

THE GENERATION R MICROBIOLOGY STUDY

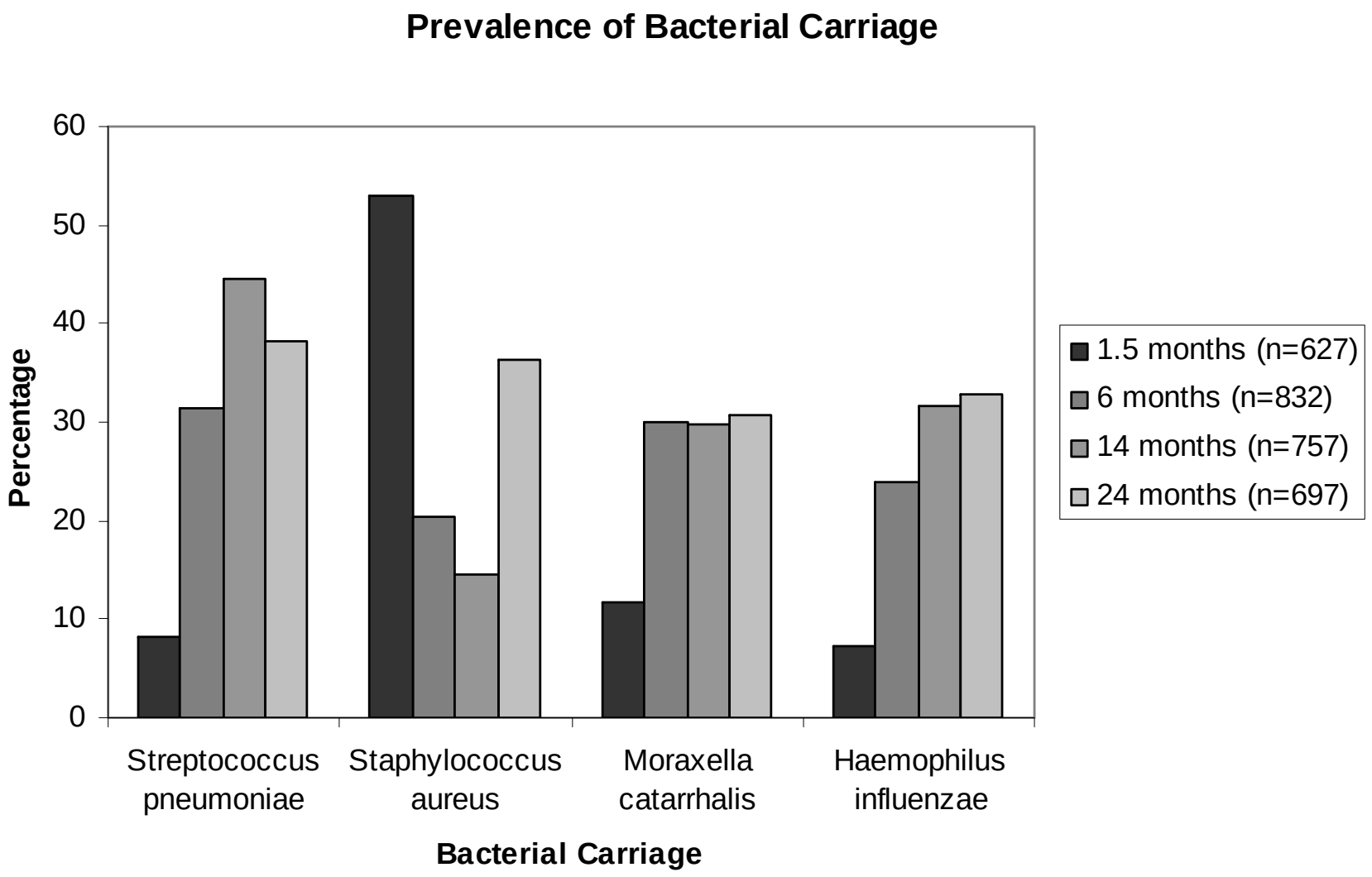
- N = 1,079
- Nasal and nasopharyngeal swabs were taken at age 1.5 (n=), 6 (n=), 14 (n=) and 24 months (n=)
- Blood samples were taken at age

- Microbiological and serological testing
- Immunophenotyping of lymphocyte subsets
- Respiratory tract infections

THE GENERATION R MICROBIOLOGY STUDY

- Bacterial cultures (n=750)
  - S. aureus (53 to 14.5%)
  - S. pneumoniae (8.3 to 44.5%)
  - M. catarrhalis (11.8 to 29.7%)
  - H. influenzae (7.2 to 31.7%)
- Mean number of respiratory infections 4-12 (SD2)

Prevalence of carriage



PREVALENCE OF CARRIAGE

- *S. pneumoniae* and *S. aureus* are known to interact.
- *S. pneumoniae* and *H. influenzae*
- *S. aureus* and *M. catarrhalis* are found significantly associated with each other.

Host and pathogen must have co-evolved to a state where the pathogen does not harm the host (too much)

POPULATION BASED SCREENING STUDIES

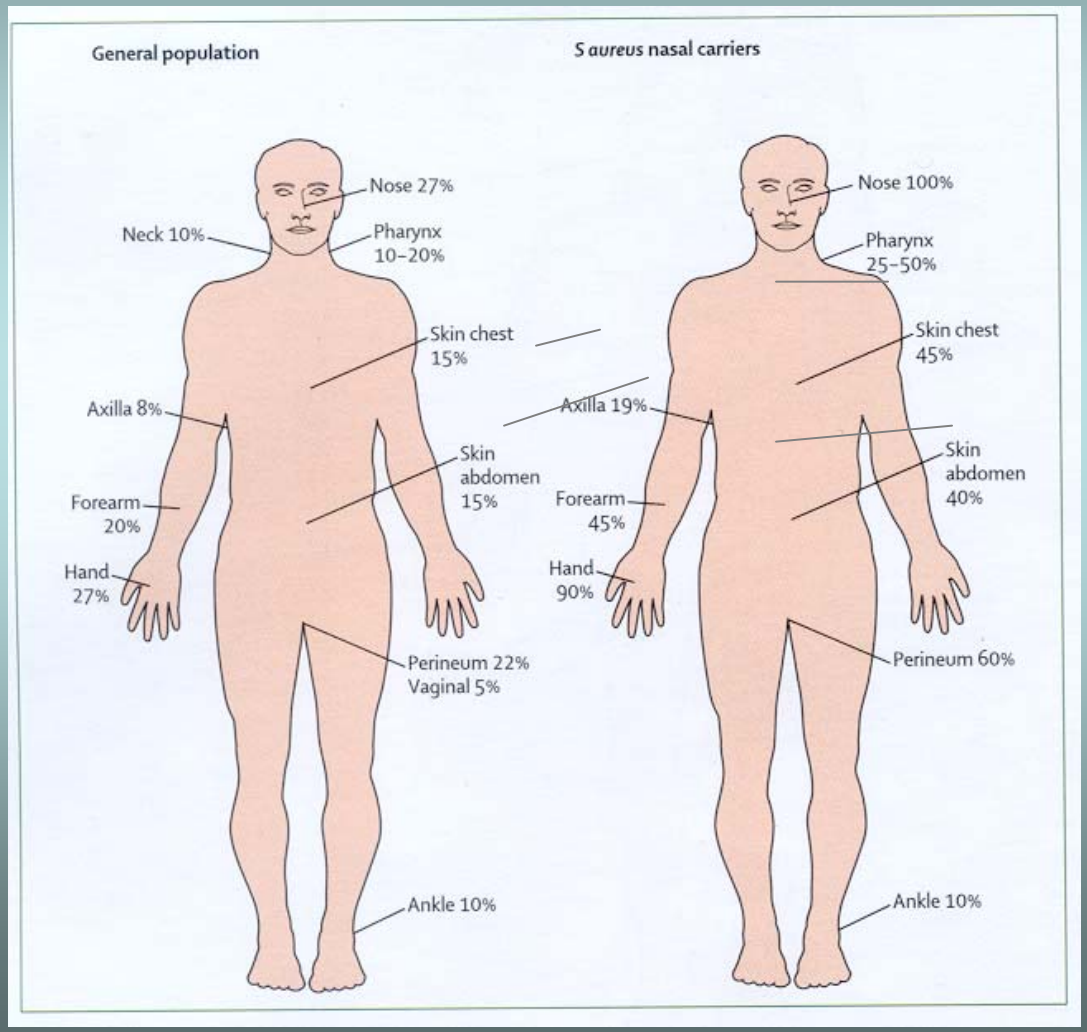
	Positive once		*Positive twice or more*	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
No atopic dermatitis	1.00	1.00	1.00	1.00
Atopic dermatitis 0-6 months**	0.67 (0.32 – 1.44)	0.64 (0.30 – 1.34)	1.61 (0.82 – 3.13)	1.67 (0.85 – 3.27)
Atopic dermatitis 6-12 months	1.23 (0.59 – 2.54)	1.24 (0.60 – 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) *

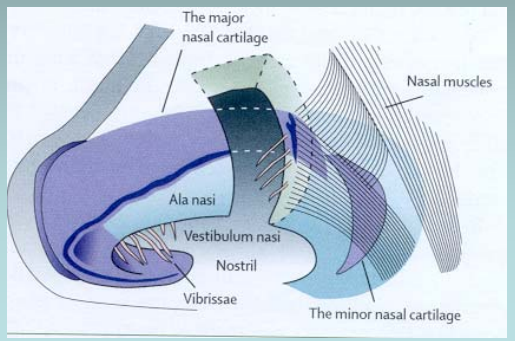
PRESS	*Positive once*		*Positive twice or more*	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
No atopic dermatitis	1.00	1.00	1.00	1.00
Mild atopic dermatitis	1.11 (0.68 - 1.81)	1.12 (0.69 – 1.83)	1.56 (0.85 – 2.85)	1.59 (0.87 – 2.92)
Moderate atopic dermatitis	1.77 (0.83 – 3.75)	1.81 (0.85 – 3.86)	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.

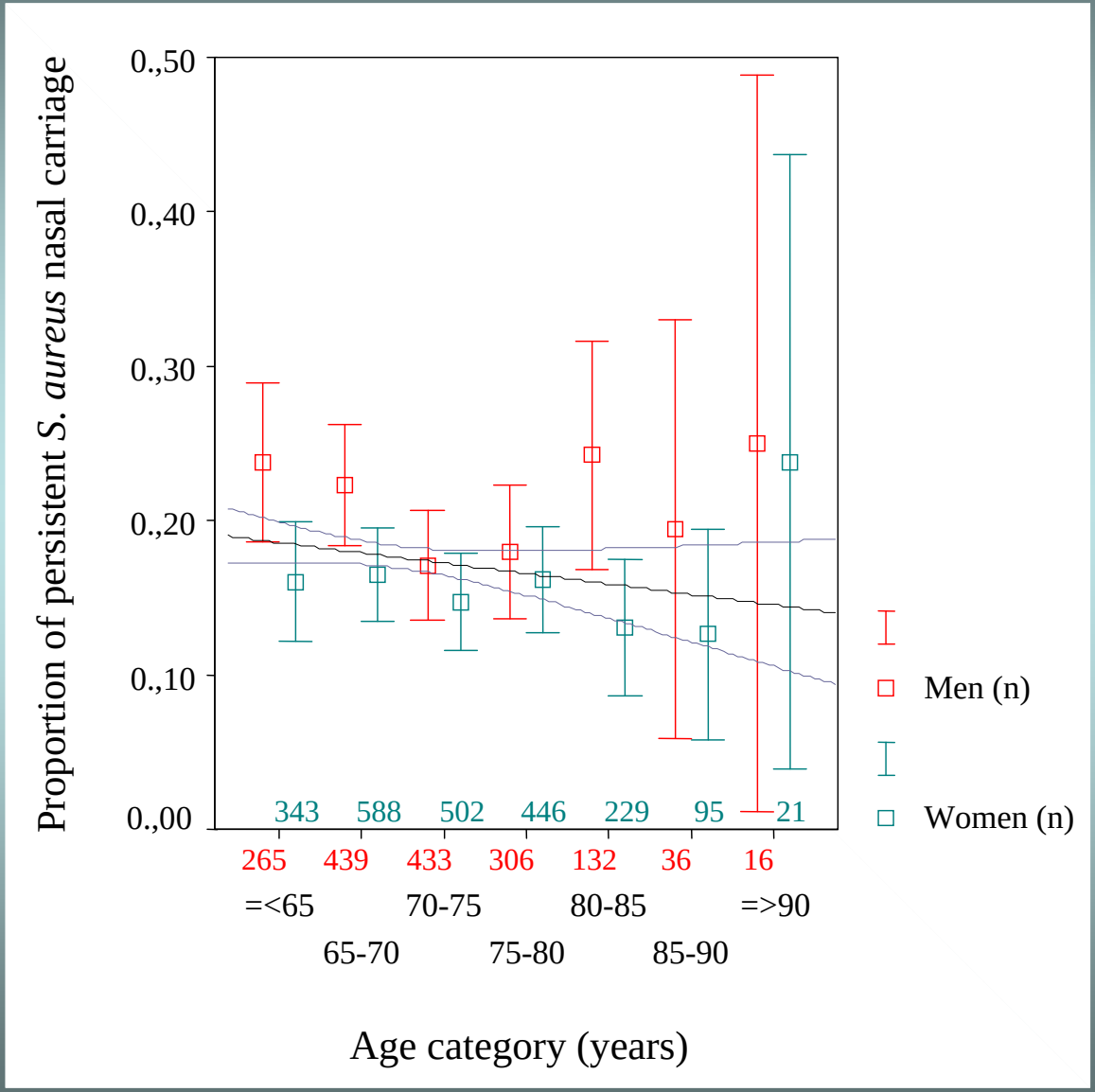
STAPHYLOCOCCUS AUREUS CARRIAGE SITES: HOST PATHOGEN INTERACTION!!



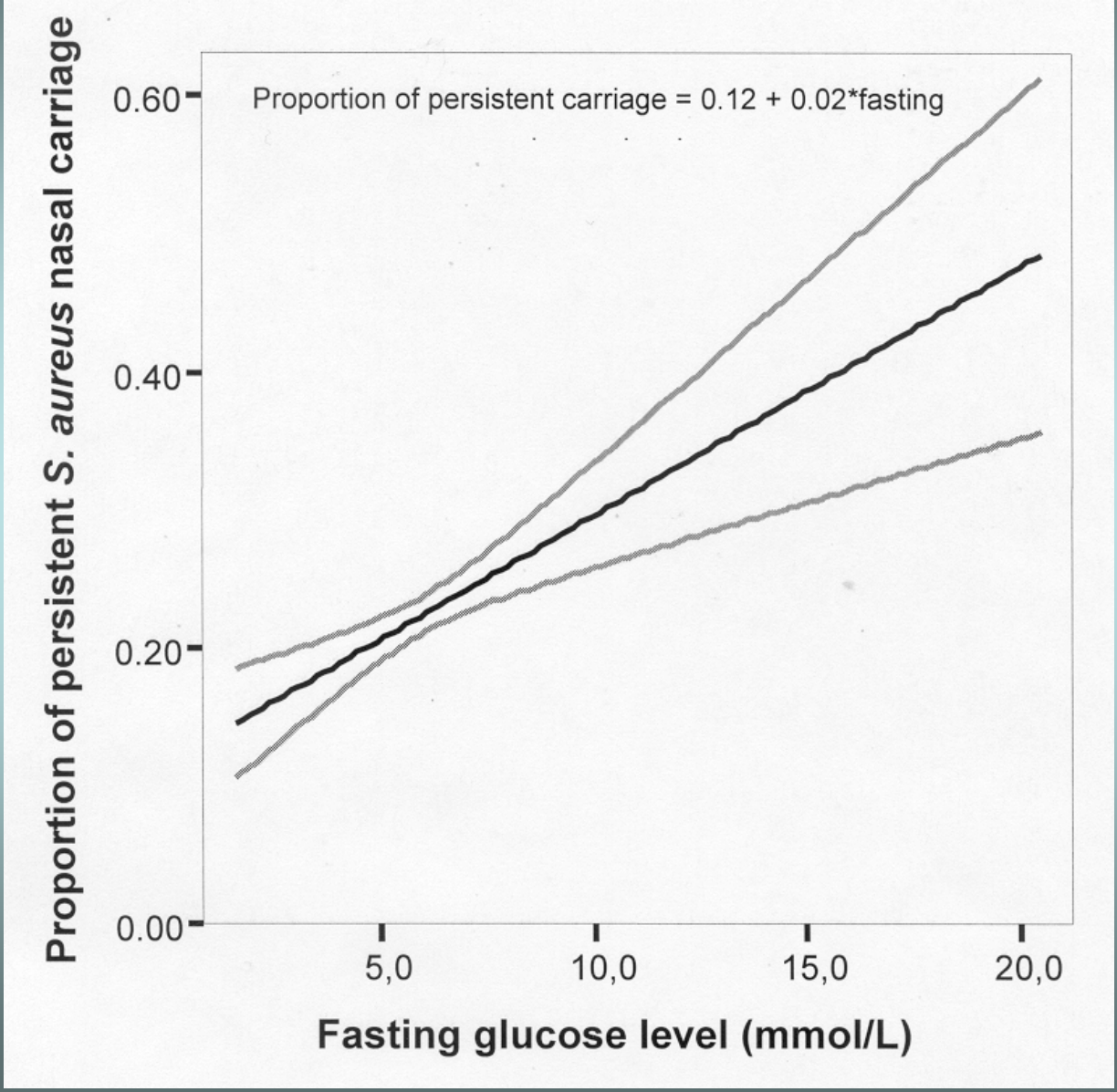


THE ANATOMICAL NICHES

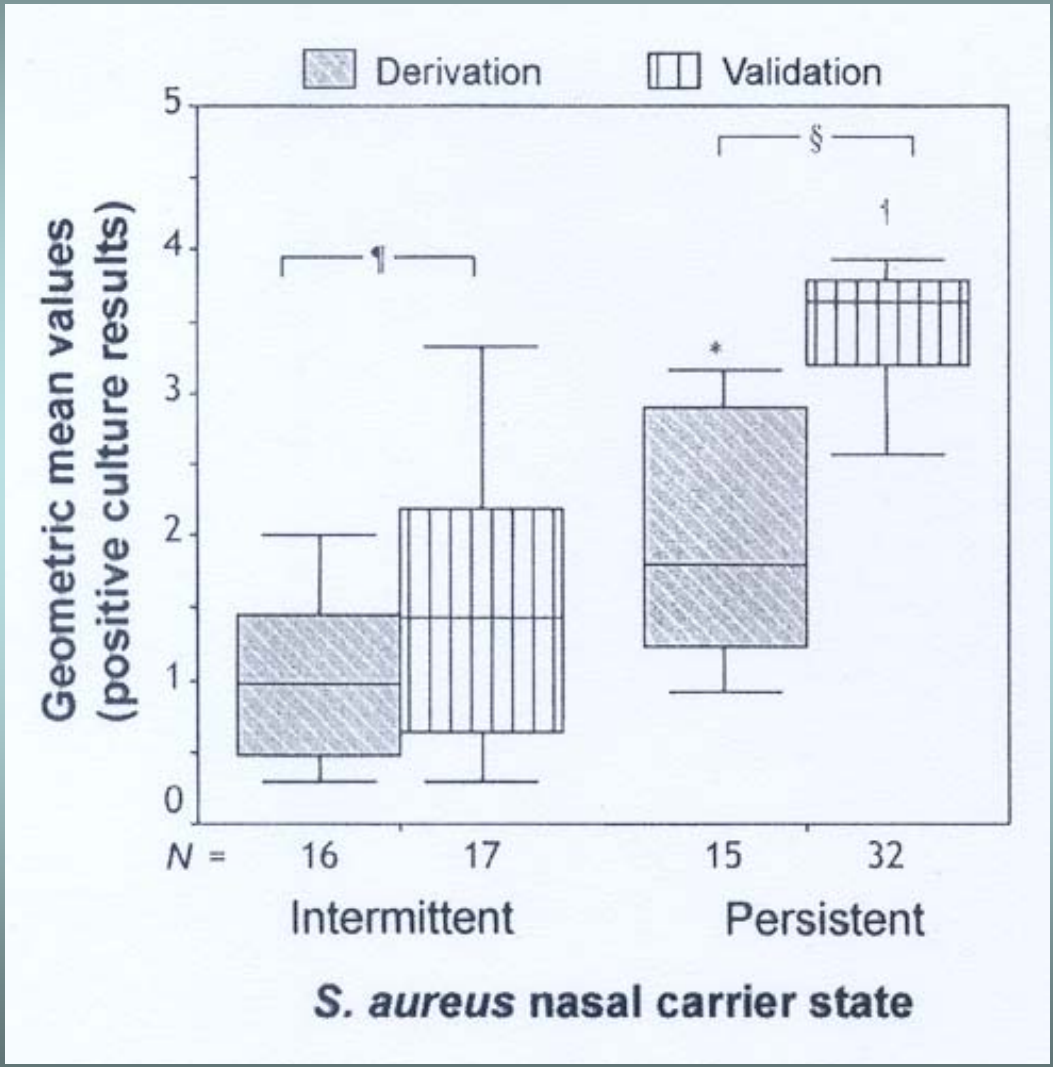
SEX AND AGE


Proportion of persistent S. aureus nasal carriage
0.,50
0.,40
0.,30
0.,20
0.,10
0.,00
343
588
502
446
229
95
21
265
439
433
306
132
36
16
=<65
65-70
70-75
75-80
80-85
85-90
=>90
Age category (years)
Men (n)
Women (n)

BLOOD GLUCOSE LEVELS

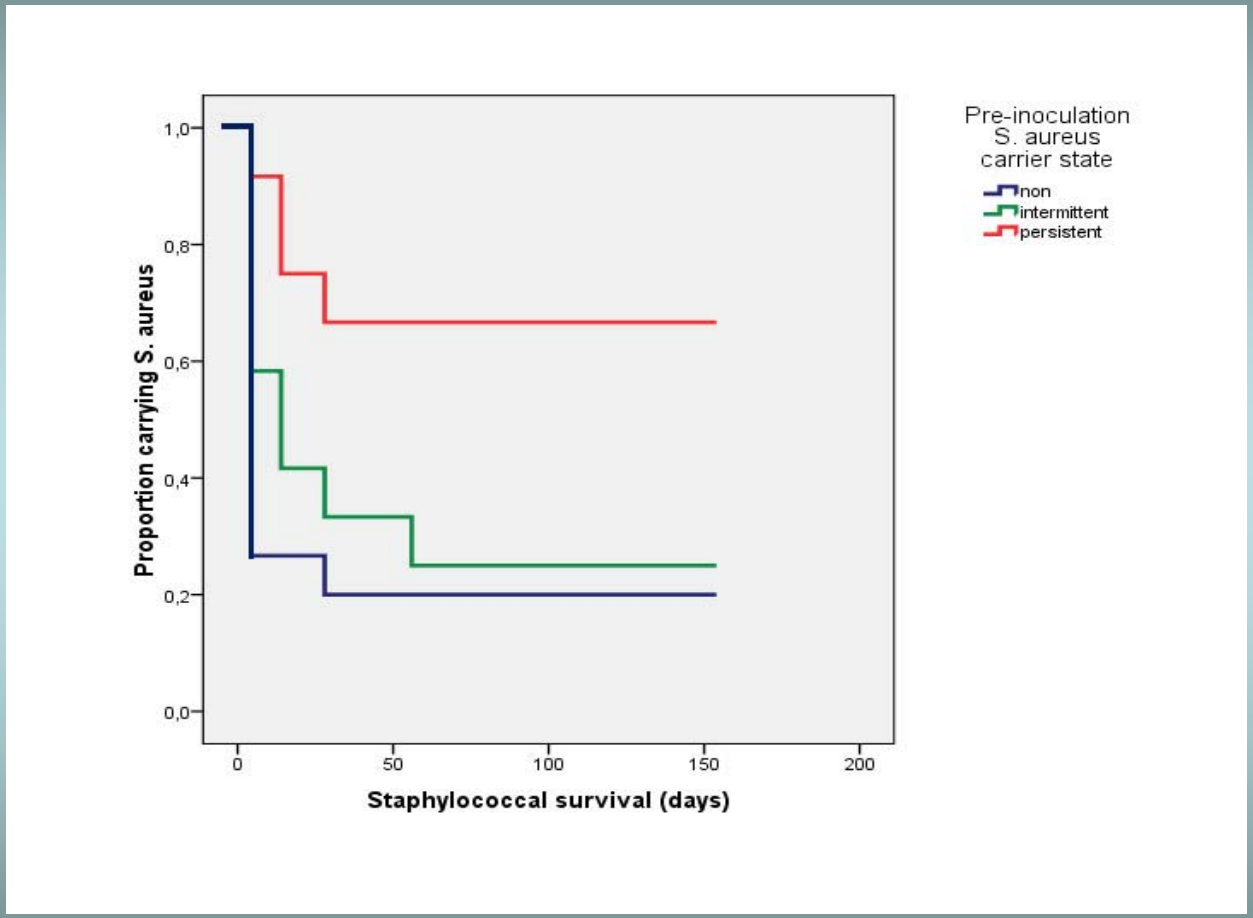


QUANTITATIVE ASPECTS OF NASAL CARRIAGE: VARIATION IN HOST SUSCEPTIBILITY



Nouwen *et al.*, CID 2004

ARTIFICIAL COLONISATION *in vivo*



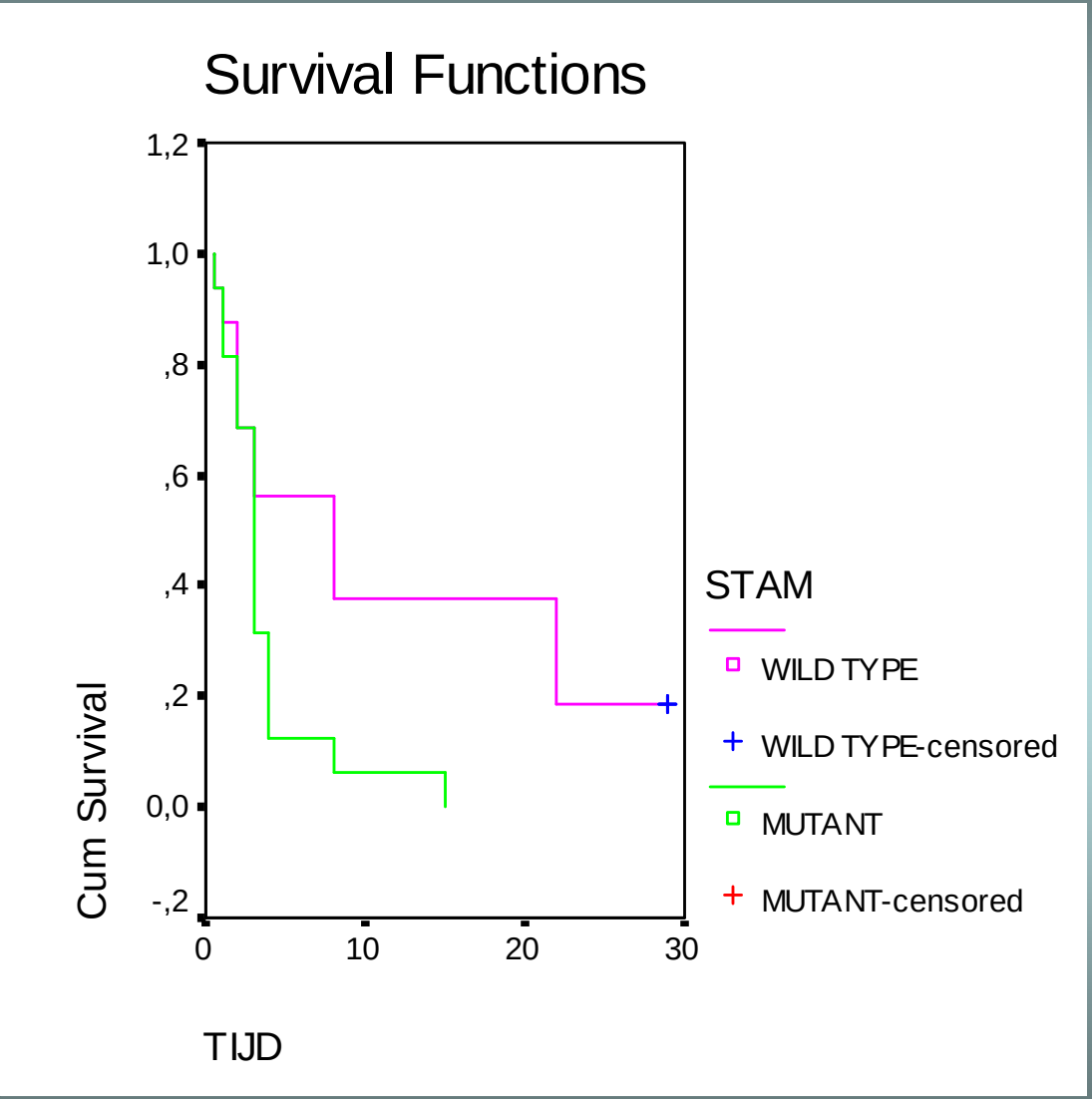
Log rank test: p=0.017 (own strain 0.04!!!

GENERAL DEMOGRAPHIC AND CLINICAL FEATURES

Table 2 Univariate analysis of the association of skin diseases, living condition, diabetes mellitus and smoking pattern with persistent *S. aureus* nasal carriage.

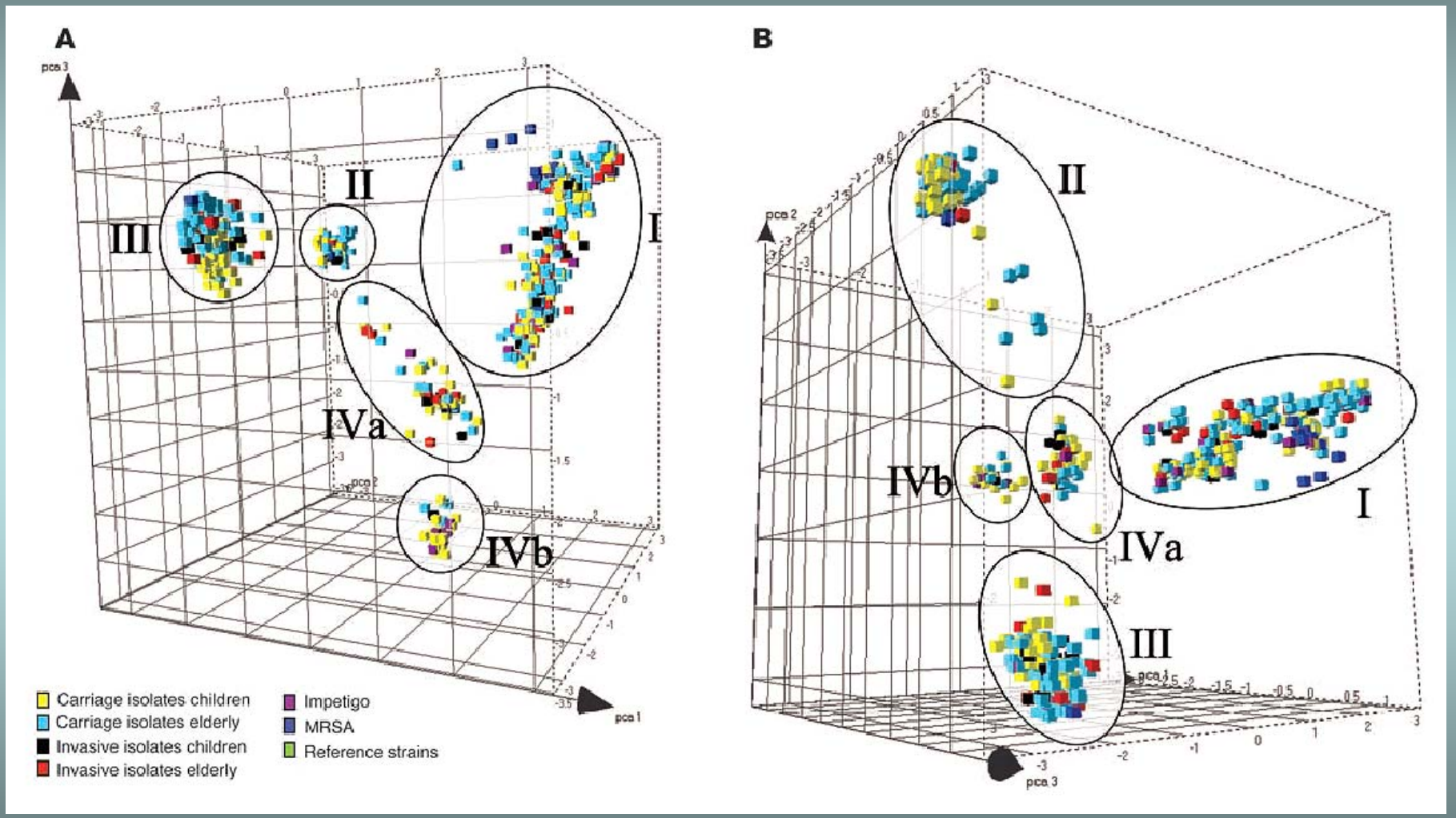
Determinant		SNC state		Total	p-value	Odds ratio (OR)	95% CI of OR	
		persistent	non or intermittent				lower bound	higher bound
Skin infections in the past 3 months	Yes	76	195	271	0.019	1.40	1.07	1.85
	No	772	2781	3553				
	Total	848	2976	3824				
Eczema in the past 12 months	Yes	111	253	364	<0.001	1.63	1.29	2.07
	No	728	2710	3438				
	Total	839	2963	3802				
Boils ever	Yes	315	955	1270	0.007	1.25	1.06	1.46
	No	533	2012	2545				
	Total	848	2967	3815				
Living condition	Institutionalized	77	361	438	0.014	1.38	1.07	1.79
	Independent	772	2621	3393				
	Total	849	2982	3831				
Diabetes mellitus	Yes	112	288	400	0.005	1.41*	1.11	1.78
	Impaired	145	458	603				
	No	583	2173	2756				
	Total	840	2919	3759				
Cigarette smoking pattern	Current	119	551	670	0.002	0.67¶	0.53	0.84
	Past	450	1415	1865				
	Non	280	1012	1292				
	Total	849	2978	3827				

ARTIFICIAL COLONISATION WITH MSCRAMM MUTANTS



Log rank test: p=0.017

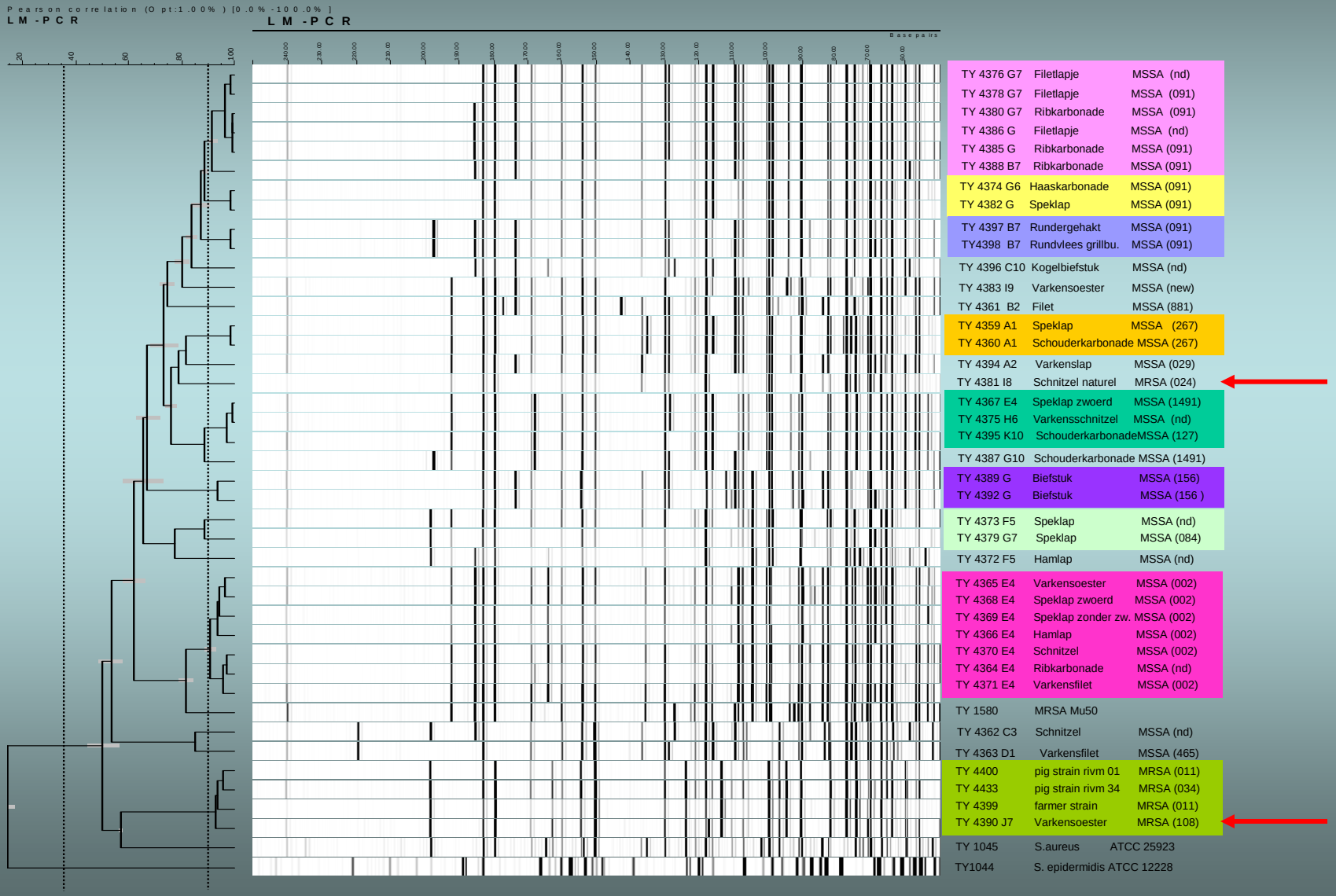
S. aureus population structure



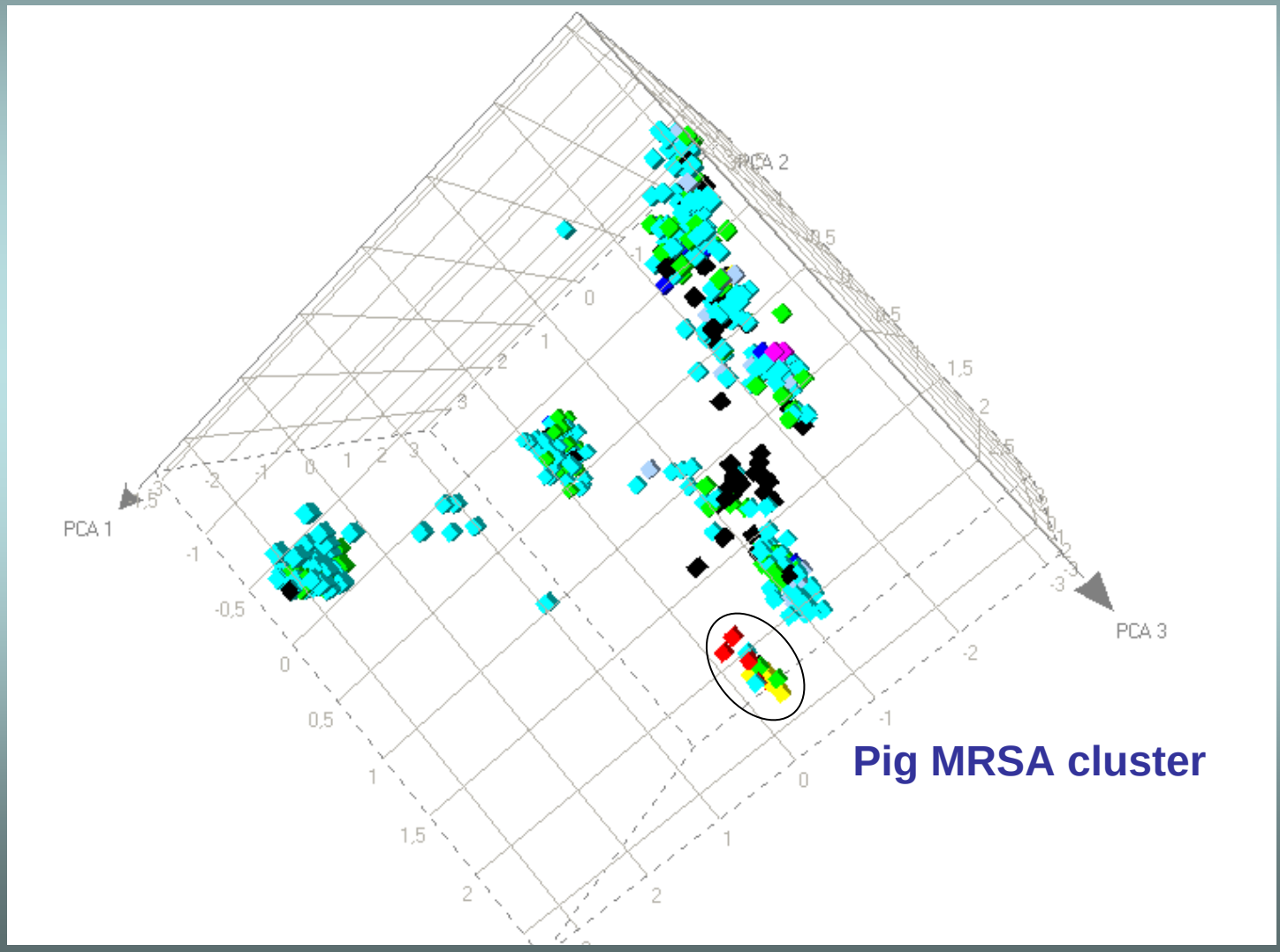
*principal component analysis

Melles *et al.*, JCI, 2004

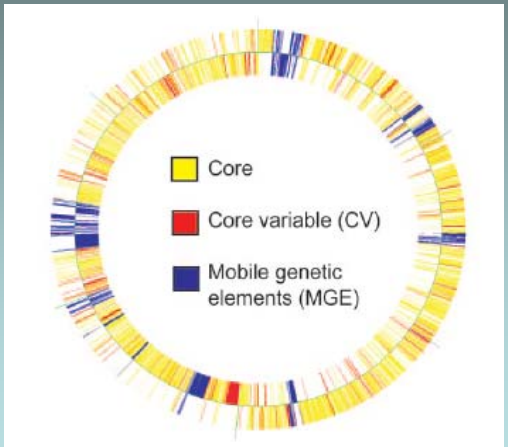
PIG ASSOCIATED MRSA AT THE RETAIL LEVEL: IT IS NOT IN HOST SPECIFIC NASAL CARRIAGE ALONE!!



FROM ANOTHER ANGLE



STAPHYLOCOCCAL GENOME COMPOSITION



Lindsay et al, 2006
Journal of Bacteriology

In conclusion, we find no evidence that certain genes or lineages are associated with invasive isolates in the community setting. However, it is possible that some genes or lineages are associated with particular types of invasive disease, e.g., bacteremia, osteomyelitis, and pneumonia, and specific isolate collections will be needed to address this question. It is also possible that this strain collection is not typical of strains carried in other parts of the United Kingdom or the world, or that *S. aureus* populations change over time, and further studies will be needed to confirm this. While we generated an enormous amount of data and identified substantial differences between isolates, it could be that virulence is due to the expression of one or more important genes under appropriate in vivo conditions. Testing for this will be complicated by identifying appropriate conditions for *S. aureus* growth.

Despite the enormous variation seen between *S. aureus* isolates and the considerable amount of genetic exchange between isolates, we have no evidence that this variation influences pathogenesis. Future studies may show that variation is important for nasal carriage. The key to understanding *S. aureus* pathogenesis may lie in the identification of host factors that contribute to colonization, and subsequent susceptibility to community-acquired infection.

ESSENTIALLY ALL
***STAPHYLOCOCCUS AUREUS* STRAINS**
HAVE THE CAPACITY
TO BECOME INVASIVE AND
ACCESORY GENES
(WHICH CAN BE IDENTIFIED AS
POLYMORPHIC MARKERS UPON TYPING)
SEEM TO BE
THE MOST RELEVANT FACTORS
IN STAPHYLOCOCCAL VIRULENCE

THE CONTRIBUTION OF HOST GENETICS

MAJOR ARTICLE

Host Polymorphisms in Interleukin 4, Complement Factor H, and C-Reactive Protein Associated with Nasal Carriage of *Staphylococcus aureus* and Occurrence of Boils

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(See the article by Gorwitz et al., on pages 1226–34; the article by David et al., on pages 1235–43; and the editorial commentary by Flynn and Cohen, on pages 1217–9.)

OUR STUDY POPULATION

Characteristic	*S. aureus* carriage status			Presence of boils		
	None	Persistent	*P*	No	Yes	*P*
Demographic						
Age, median (range), years	72 (61–101)	71 (61–95)	.11[a]	72 (61–101)	70 (61–95)	<.001
Male sex	1121/2804 (40)	333/678 (49)	<.001	868/2545 (34)	744/1270 (59)	<.001
Smoking history						
Nonsmoker	945/2804 (34)	230/678 (34)	.046	979/2545 (39)	309/1270 (24)	<.001
Past smoker	1326/2804 (47)	348/678 (51)	.007	1147/2545 (45)	712/1270 (56)	.66
Current smoker	515/2804 (18)	96/678 (14)	.99	418/2545 (16)	249/1270 (20)	.99
Clinical						
Eczema	231/2804 (8)	100/678 (15)	<.001	233/2545 (9)	130/1270 (10)	.29
Fasting glucose level, median (range), mmol/L	5.6 (1.6–18.9)	5.6 (4.0–19.8)	.001	5.6 (1.6–19.8)	5.6 (3.0–20.5)	.31
Serum CRP level, mg/L (95% CI)	1.53 (1.47–1.58)	1.64 (1.51–1.78)	.09	1.54 (1.48–1.60)	1.60 (1.51–1.69)	.47
Gene (SNP), allele[b]						
IL4 (−524)[c]						
C	1478 (85)	366 (91)	.006	1360 (87)	674 (85)	.28
T	252 (15)	38 (9)		204 (13)	116 (15)	
TNFA (−863)[c]						
C	1450 (83)	336 (83)	.78	1296 (83)	672 (84)	.26
A	290 (17)	70 (17)		274 (17)	124 (16)	
CRH (402)						
T	3272 (64)	784 (63)	.46	2913 (63)	1524 (65)	.22
C	1812 (36)	456 (37)		1675 (37)	820 (35)	
CRP (1184)						
C	3406 (69)	823 (68)	.66	3067 (69)	1551 (68)	.34
T	1550 (31)	379 (32)		1387 (31)	735 (32)	
CRP (2042)						
C	3414 (68)	798 (66)	.10	3055 (67)	1565 (68)	.66
T	1610 (32)	420 (34)		1489 (33)	745 (32)	
CRP (2911)						
C	4696 (94)	1129 (93)	.30	4225 (94)	2168 (95)	.11
G	294 (6)	81 (7)		265 (6)	122 (5)	

NOTE. Data are no. (%) of participants, unless otherwise indicated. CI, confidence interval; CRP, C-reactive protein; SNP, single-nucleotide polymorphism. Data on intermittent carriers were omitted from *S. aureus* carriage analysis, and data were missing for 36 individuals for the analyses regarding boils.

[a] In multivariate analysis, after correction for sex, smoking history, eczema, serum glucose level, and serum CRP level, the median age was significantly different ($P = .02$).

[b] Denominators are the total of the 2 alleles for each group.

[c] *IL4* and *TNFA* polymorphisms were determined in a subset of ~34% of the total population for whom *S. aureus* carriage information was available (1186 and 1192 participants, respectively; individuals with intermittent nasal carriage were included [$n = 119$]).

INTERELATEDNESS BETWEEN HUMAN SUSCEPTIBILITY TO CARRIAGE AND BACTERIAL TYPES

AFLP MAR-KER	CARRIAGE GROUP INTER-MITTENT	PERSIS-TENT	OR (p)
A	77/101 (76)	204/313 (65)	0.3-1.0 (0.04)
B	20/103 (19)	101/325 (31)	1.1-3.2 (0.02)
C	21/103 (20)	104/325 (32)	1.1-3.1 (0.03)
D	5/103 (5)	2/325 (1)	0.0-0.6 (0.01)
E	6/103 (6)	4/325 (1)	0.1-0.7 (0.02)

Certain bacterial markers seem to be more prevalent among strains from persistently rather than intermittently colonised individuals and vice versa.

HOST GENETIC INFLUENCES

***IL4*-524 C/C: more carriage**
***CRP* 1184C;2042C;2911C: more non-carriage**
***CFH*Tyr402 and *CRP*2911 C/C: more boils**

Persistent carriage of *S. aureus* is influenced subtly by genetic variation in host inflammatory response genes. In addition, host genotype was associated with carriage of certain bacterial types as well.

WHAT CAN BE CONCLUDED?

Carriage is defined by intricate interactions between host, pathogen and the (a-)biotic environment.

Spread may result from carriage

Epidemicity is incompletely understood.