Staphyloccocus aureus :
Point sur la vaccination des patients

Pr Elisabeth Botelho-Nevers

GIMAP EA 3064 (Campus Santé Innovations, UJM comue UL) équipe associée CIRI

Service d'Infectiologie (CHU de Saint-Etienne)

Inserm CIC 1408- Axe Vaccinologie, I-Reivac

Présage (Institut de prévention)

Plan

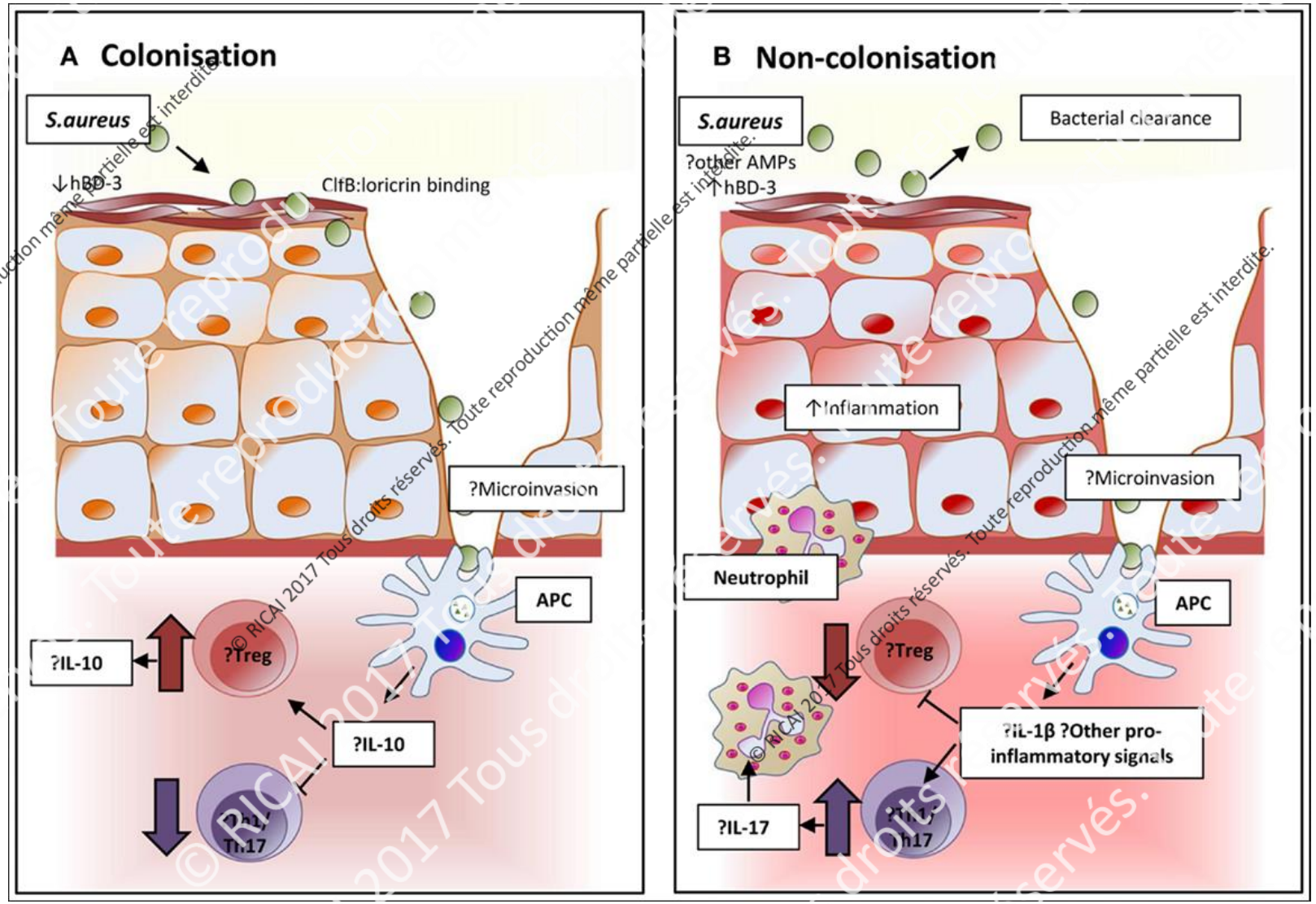
- Ce que représente *S. aureus*
- Quelles populations à risque / populations cibles?
- Que nous apprennent les essais passés?
- Les raisons des échecs
- Le présent
- Le futur?

Plan

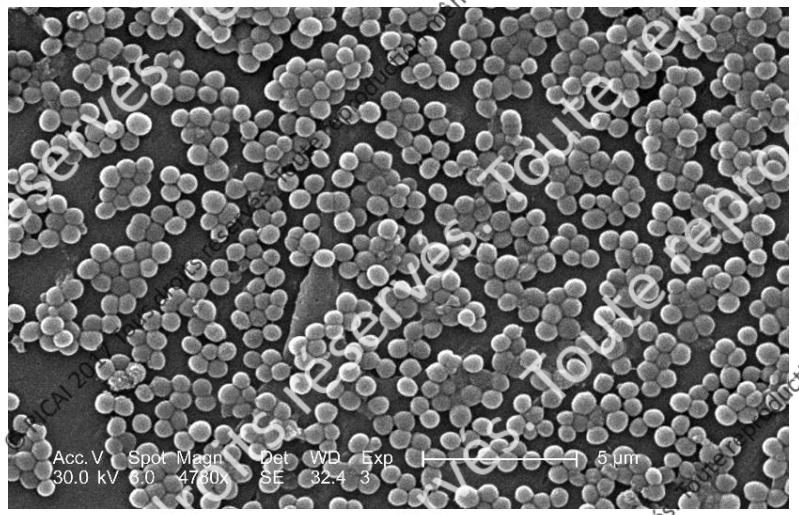
- Ce que représente *S. aureus*
- Quelles populations à risque / populations cibles?
- Que nous apprennent les essais passés?
- Les raisons des échecs
- Le présent
- Le futur?

Staphylococcus aureus: agent double

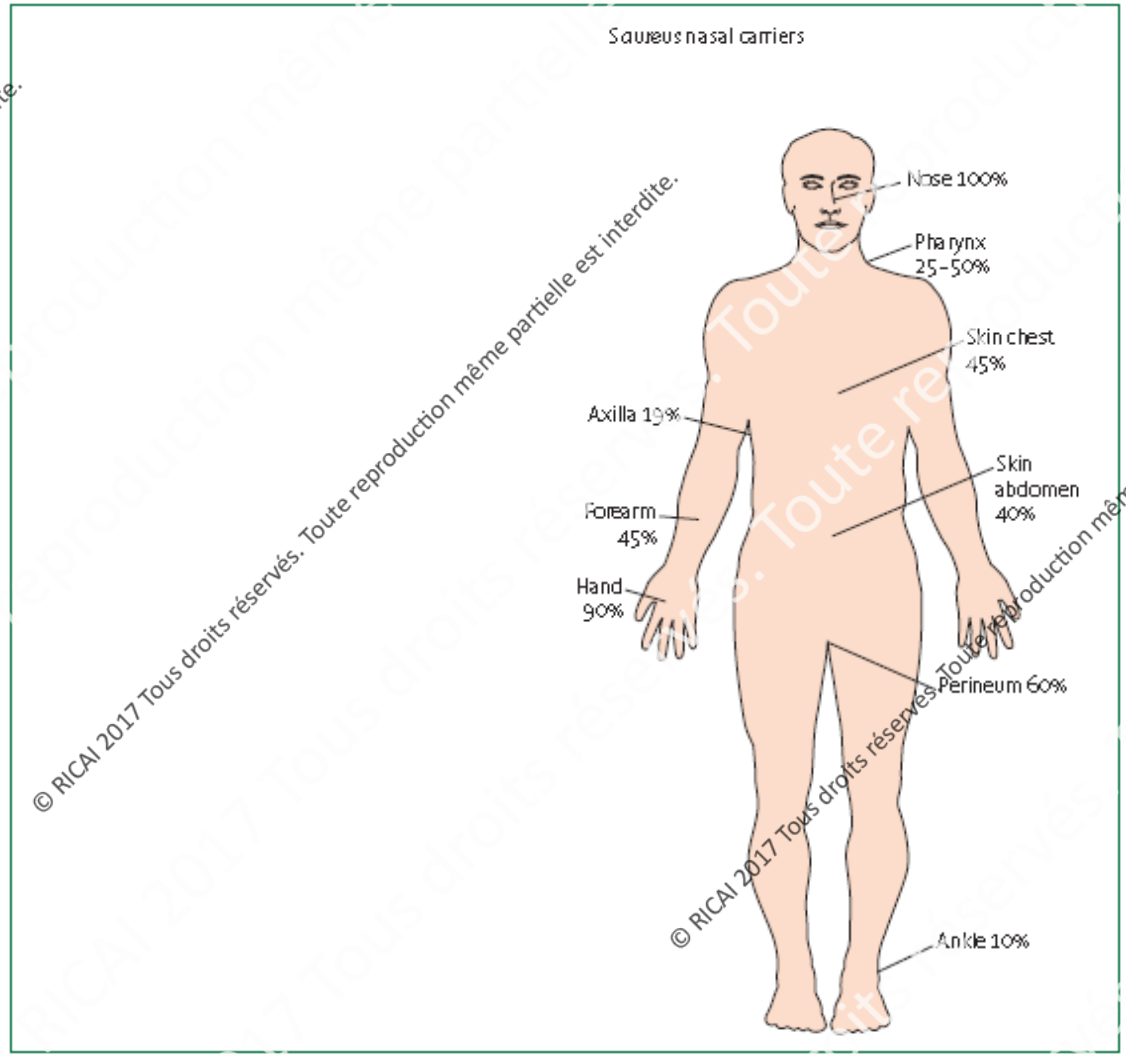
- Flore commensale
- Bactérie pathogène
- ≠ flore transitoire



S. aureus utile, non pathogène



- Flore commensale cutanée, muqueuse



Portage muqueux et cutané:

- Commensalité+++
- Co-évolution Homme / *S. aureus*
- Co-habitation, tolérance
- *S. aureus* à la surface
- Pas (peu d'inflammation)
- Equilibre

Wertheim *et al.,* Lancet Inf Dis. 2005; 5: 751-62

S. aureus: portage

	Swabs tested (n)	Prevalence of *S aureus* nasal carriage (% [95% CI])		
		Unadjusted	Adjusted* (all ages†)	Adjusted* (aged ≥18 years only‡)
Austria	3309	16·6% (15·4–17·9)	16·2% (13·3–19·8)	15·7% (12·7–19·2)

-32206 patients vus en médecine générale

-9 pays d'Europe

Virtuellement, 100% des gens seront porteurs à un moment donné
TOUS ont un contact +/- répété avec cette bactérie selon qu'ils sont porteurs persistants ou non de la bactérie

- Soignants : 26,6% [16.8-56,1] (38,9%-46% à St-Etienne)
- Diabétiques insulino dépendants : 56,4% [24.1-76,4]
- Patients dialysés :
  - Hémodialyse : 51,5% [30,1-84,4]
  - dialyse péritonéale : 43,3% [16,8-51,4]
- Infections cutanées à *S. aureus* : 65,9% [42-100]
- HIV + > 30%, FR d'infections à *S. aureus* , dans le passé en Europe, toujours le cas aux USA
- Obésité (BMI>30): 32,4% vs 25,8%

S. aureus pathogène-fréquent

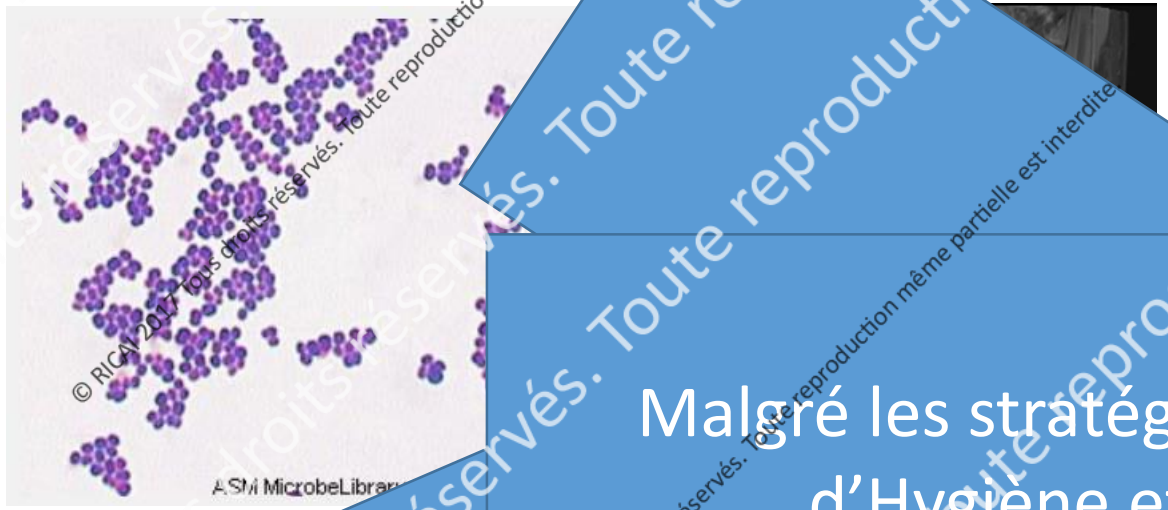
- Agent pathogène très fréquent, en pathologie communautaire:
  - 1er agent d'infections de la peau et des tissus mous
  - 1er agent responsable d'endocardite infectieuse
  - 2ème agent responsable de bactériémie

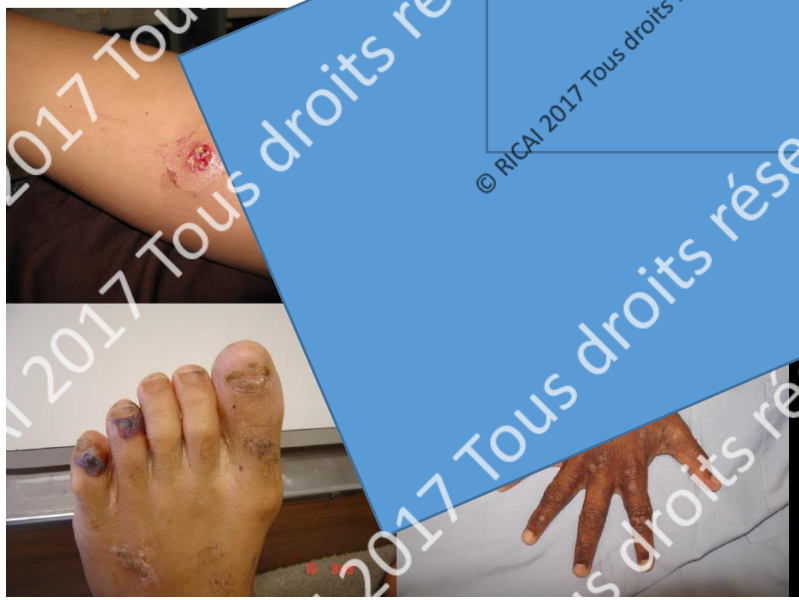
- Agent pathogène très fréquent, en pathologie associée aux soins
  - 1er agent responsable d'ISO, toute chirurgie confondue
  - 1er agent responsable d'infection en dialyse
  - 2ème agent responsable des infections nosocomiales
  - 2ème agent responsable d'infection en réanimation

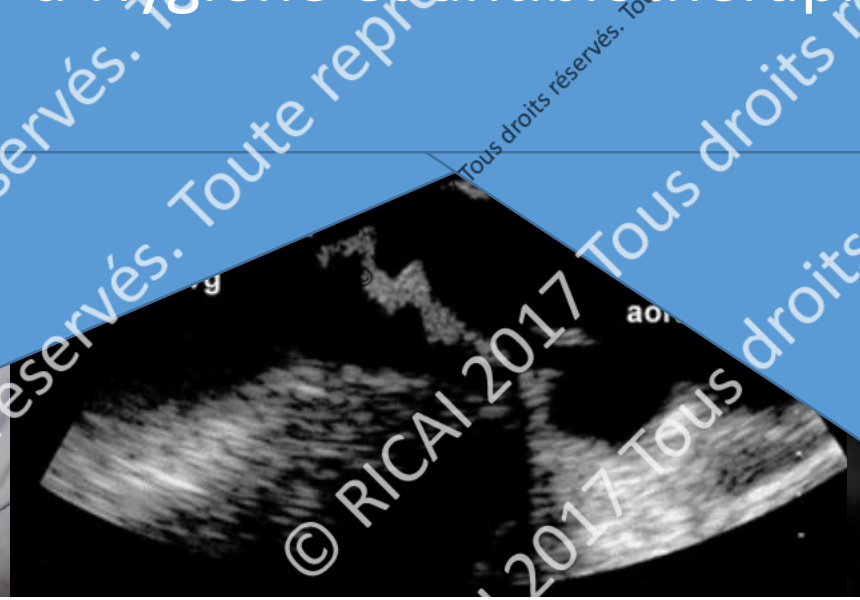
Tong et al., CMR 2015
Fowler VG et al., JAMA 2005
ISO Raisin, DIALIN, Enquête de prévalence des infections nosocomiales, Rea Raisin,

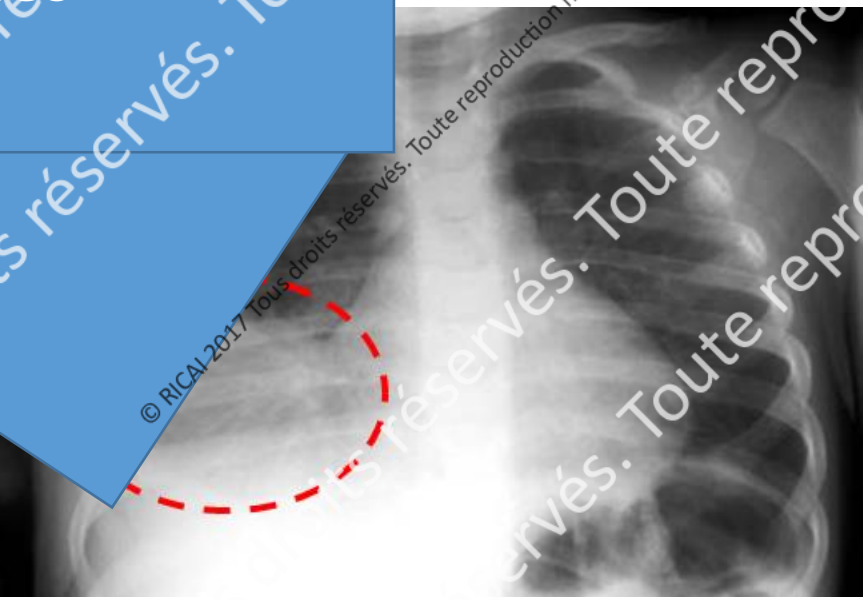
S. aureus pathogène-virulent

- Infections peau
- bactérié
- a









Malgré les stratégies existantes: mesures d'Hygiène et antibiothérapies

Plan

- Ce que représente *S. aureus*
- Quelles populations à risque / populations cibles?
- Que nous apprennent les essais passés?
- Les raisons des échecs
- Le présent
- Le futur?

Lien entre portage de S. aureus et infection à S. aureus

- Le portage est un FR de risque connu d'infection « endogène »
  - Chirurgie orthopédique: X 3 à 16
  - Chirurgie cardio-thoracique: x 3 à 9
  - Chirurgie vasculaire: X10
  - Dialyse péritonéale: X3 à 10
  - Hémodialyse: x 1,8 à 4,7
  - Patients de réanimation: X 4 à 14
  - Patients HIV+: X 3 à 5
  - Infections cutanées à répétitions
  - ……

Kalmeijer *et al.,* ICHE 2000
Berthelot *et al.,* EJCMID 2010
Kluytmans *et al.,* J Infect Dis 1995
Munoz *et al.*, J Hosp Infect 2008
Donker JMW, PLoS ONE 2012
Nouwen et al., Kidney International 2005
Verhoeven et al., Medicine 2016
Allen *et al.*,Open Forum Infect Dis. 2014
Paling et al., CMI 2016
Wertheim et al., LID 2005
Hedstrom SA *Scand J Infect Dis* 1981
Durupt F *et al.*, Br J Dermatol 2007

Population à risque d'infections à *S. aureus*?

Du fait du terrain:

- Déficits immunitaires innés: Syndrome de Job, déficit en Th17, granulomatose chronique septique…
- Déficits immunitaires acquis: VIH, corticothérapie, biothérapies…..
- Diabétique
- Obèse
- Granulomatose de Wegener
- Dermatoses chroniques: atopiques…
- Enfants, nouveaux nés…..

PORTAGE

Population à risque?

Du fait des procédures:

- Matériel prothétique: chirurgie
- Chirurgie sans matériel
- Cathéters
- Gestes invasifs
- Dialysés+++
- ……

Human Vaccines & Immunotherapeutics 10:12, 3517–3521; December 2014; Published with license by Taylor & Francis Group, LLC

SHORT REPORT

Use of surveillance data to identify target populations for *Staphylococcus aureus* vaccines and prevent surgical site infections: A pilot study

Marie-Paule Gustin[1,2,*], Marine Giard[3], Thomas Bénet[1,4], and Philippe Vanhems[1,3]

[1]Service d'Hygiène; Epidémiologie et Prévention; Hôpital Edouard Herriot; Hospices Civils de Lyon; Lyon, France; [2]Département de santé publique; Pôle biostatistique; Faculté de Pharmacie; Université de Lyon; Université Lyon 1; Lyon, France; [3]Centre de Coordination de la Lutte contre les Infections Nosocomiales Sud-Est; Saint-Genis-Laval; France; [4]Equipe d'Epidémiologie et de Santé Publique; Université de Lyon; Université Lyon; Lyon, France

Keywords: orthopedic surgery, *Staphylococcus aureus*, surgical site infection, surveillance, target population, vaccination

Abbreviations: SSI, surgical site infection; SA, *Staphylococcus aureus*; ASA, American Society of Anesthesiologists; OR, Odds ratio; CI, confidence interval

The development of anti-staphylococcal vaccines is nowadays a priority to prevent surgical site infections (SSI). The objective of the present study was to identify a potential target population by assessing surveillance data on surgery patients for possible anti-staphylococcal vaccine administration. Individuals at high risk of SSI by *Staphylococcus aureus* (SA) were targeted by the French SSI Surveillance Network in south-eastern France between 2008 and 2011. Among 238,470 patients, those undergoing primary total hip replacement appeared to be an interesting and healthy enough population for anti-staphylococcal vaccine testing. These male patients, subjected to multiple procedures and with American Society of Anesthesiologists score ≥ 2, had a probability of SA SSI about 21 times higher than females with no severe systemic disease and no multiple procedures. Our study indicates that surveillance data on SSI might be an interesting epidemiological source for planning vaccine trials to prevent nosocomial infections.

Toutes ces populations pourraient être des cibles pour un ***vaccin préventif***….ou pour de ***l'immunité passive***…..

Vaccine 28 (2010) 2465–2471

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Staphylococcus aureus vaccine for orthopedic patients: An economic model and analysis

Bruce Y. Lee[a,b,c,*], Ann E. Wiringa[a,b,c], Rachel R. Bailey[a,b,c], G. Jonathan Lewis[a,b,c], Jared Feura[a,b,c], Robert R. Muder[d]

[a] Section of Decision Sciences and Clinical Systems Modeling, University of Pittsburgh, Pittsburgh, PA, United States
[b] Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA, United States
[c] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States
[d] Division of Infectious Diseases, VA Pittsburgh Health System, University of Pittsburgh, Pittsburgh, PA, United States

ARTICLE INFO

Article history:
Received 18 October 2009
Received in revised form
19 December 2009
Accepted 25 December 2009
Available online 9 January 2010

ABSTRACT

To evaluate the potential economic value of a *Staphylococcus aureus* vaccine for pre-operative orthopedic surgery patients, we developed an economic computer simulation model. At MRSA colonization rates as low as 1%, a $50 vaccine was cost-effective [≤$50,000 per quality-adjusted life year (QALY) saved] at vaccine efficacy ≥30%, and a $100 vaccine at vaccine efficacy ≥70%. High MRSA prevalence (≥25%) could justify a vaccine price as high as $1000. Our results suggest that a *S. aureus* vaccine for the pre-operative orthopedic population would be very cost-effective over a wide range of MRSA prevalence and vaccine efficacies and costs.

Vaccine 30 (2012) 3675–3682

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The potential economic value of a *Staphylococcus aureus* vaccine among hemodialysis patients

Yeohan Song[a,b,c], Julie H.Y. Tai[a,b,c], Sarah M. Bartsch[a,b,c], Richard K. Zimmerman[d], Robert R. Muder[e], Bruce Y. Lee[a,b,c,*]

Vaccine 28 (2010) 4653–4660

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The potential economic value of a *Staphylococcus aureus* vaccine for neonates

Bruce Y. Lee[a,b,c,*], Paul J. Ufberg[a,b,c,d], Rachel R. Bailey[a,b,c], Ann E. Wiringa[a,b,c], Kenneth J. Smith[a], Andrew J. Nowalk[e], Conor Higgins[a,b,c], Angela R. Wateska[a,b,c], Robert R. Muder[f]

Vaccine 35 (2017) 6934–6937

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Use of surveillance data to calculate the sample size and the statistical power of randomized clinical trials testing *Staphylococcus aureus* vaccine efficacy in orthopedic surgery

Marie-Paule Gustin [a,b,c,*], Robin Ohannessian [a], Marine Giard [a,e], Emmanuelle Caillat-Vallet [e], Anne Savey [a,e], Philippe Vanhems [a,c,d], CCLIN Sud-Est study group

[a] Laboratory of Emerging Pathogens, International Center for Infectiology Research (CIRI), University of Lyon 1, Lyon, France
[b] Institute of Pharmacy, Department of Public Health, University of Lyon 1, Lyon, France
[c] Infection Control and Epidemiology Unit, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France
[d] Innovative Clinical Research Network in VACcinology (iREIVAC), Lyon, France
[e] Coordination Center for Healthcare-associated Infection Prevention and Control in South-Eastern France (CCLIN Sud-Est), Hospices Civils de Lyon, Saint-Genis-Laval, France

Données de vie réelle+++
Véritable taux d'infection relativement bas
Pas de données du portage!

Predicted sample size per arm according to *S aureus* surgical site infection (SASSI) rate, theoretical vaccine efficacy (VE) and required power.

SASSI rate (%)	VE (%)	Statistical power		
		20%	40%	80%
1	20	6004	11,867	36,956
1	40	1180	2591	8022
1	80	214	391	1316
2	20	2989	5930	18,588
2	40	650	1322	3987
2	80	109	199	654
4	20	1492	2968	9147
4	40	310	672	1992
4	80	46	100	343

For a 1% SASSI rate, to be able to evidence positive significant VE of 80% at 2.5% alpha risk for one-tailed testing with probability of at least 80%, the sample size required would be at least 1316 per arm.

Plan

- Ce que représente *S. aureus*
- Quelles populations à risque / populations cibles?
- Que nous apprennent les essais passés?
- Les raisons des échecs
- Le présent
- Le futur?

Essais de phase III passés= ECHECS

Nabi: StaphVAX®

- Vaccin polysaccharidique capsulaire (5 et 8) conjugué à exotoxine A de *P. aeruginosa*
- Modèles animaux encourageants
- Essai chez l'homme en hémodialyse (1800 patients, de 1998 à 2000) avec bactériémie en objectif principal
- Pic d'AC à 80 µg/ml, disparaissant en 6 semaines
- Non différent entre patients bactériémiques et non bactériémiques
- Pas de réduction des bactériémies entre la 3 et la 54 ème semaine (p=0,23)
- Mais....efficacité sur la réduction de bactériémie jusqu'à 40 semaines (p=0,02), jugée encourageante![1]
- Amélioration de l'immunogénicité avec un second boost testé chez 3600 hémodialysés, sur 200 sites, suivis jusqu'à S35, puis boost et suivi 6 mois de plus[2]……

1. Shinefield H et al. NEJM 2002
2. Fattom A et al. Vaccine 2004

RESEARCH PAPER

Human Vaccines & Immunotherapeutics 11:3, 632–641; March 2015; Published with license by Taylor & Francis Group, LLC

Efficacy profile of a bivalent *Staphylococcus aureus* glycoconjugated vaccine in adults on hemodialysis: Phase III randomized study

Ali Fattom[1,2], Albert Matalon[3], John Buerkert[4], Kimberly Taylor[1,5], Silvia Damaso[6], and Dominique Boutriau[6,*]

[1]Nabi Biopharmaceuticals; Rockville, MD USA; [2]Current affiliation: NanoBio Corp. and University of Michigan; Ann Arbor, MI USA; [3]New York University School of Medicine; Department of Medicine; New York, NY USA; [4]Columbia Nephrology Associates; Columbia, SC USA; [5]Current affiliation: National Institute of Allergy and Infectious Diseases (NIAID); Bethesda, MD USA; [6]GlaxoSmithKline Vaccines; Vaccine Discovery and Development; Rixensart, Belgium

Keywords: end stage renal disease, hemodialysis, immunogenicity, *Staphylococcus aureus*, vaccine, vaccine safety

Abbreviations: T5/T8, *Staphylococcus aureus* type 5 and 8 capsular polysaccharides; CI, confidence interval; ClfA, *S. aureus* clumping factor A; ELISA, enzyme-linked immunosorbent assay; ESRD, end-stage renal disease; GMC, geometric mean concentration; OPK, opsonophagocytic killing; SAE, Serious adverse event; VE, vaccine efficacy.

In a previous study in end-stage renal disease (ESRD) hemodialysis patients, a single dose of *Staphylococcus aureus* type 5 and 8 capsular polysaccharides (T5/T8) conjugated to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A investigational vaccine showed no efficacy against *S. aureus* bacteremia 1 year post-vaccination, but a trend for efficacy was observed over the first 40 weeks post-vaccination. Vaccine efficacy (VE) of 2 vaccine doses was therefore evaluated. In a double-blind trial 3359 ESRD patients were randomized (1:1) to receive vaccine or placebo at week 0 and 35. VE in preventing *S. aureus* bacteremia was assessed between 3–35 weeks and 3–60 weeks post-dose-1. Anti-T5 and anti-T8 antibodies were measured. Serious adverse events (SAEs) were recorded for 42 days post-vaccination and deaths until study end. No significant difference in the incidence of *S. aureus* bacteremia was observed between vaccine and placebo groups between weeks 3–35 weeks post-dose 1 (VE -23%, 95%CI: -98;23, p = 0.39) or at 3–60 weeks post-dose-1 (VE -8%, 95%CI: -57;26, p = 0.70). Day 42 geometric mean antibody concentrations were 272.4 µg/ml and 242.0 µg/ml (T5 and T8, respectively) in vaccinees. SAEs were reported by 24%/25.3% of vaccinees/placebo recipients. These data do not show a protective effect of either 1 or 2 vaccine doses against *S. aureus* bacteremia in ESRD patients. The vaccine induced a robust immune response and had an acceptable safety profile. Further investigation suggested possible suboptimal vaccine quality (manufacturing) and a need to expand the antigen composition of the vaccine. This study is registered at www.clinicaltrials.gov NCT00071214.

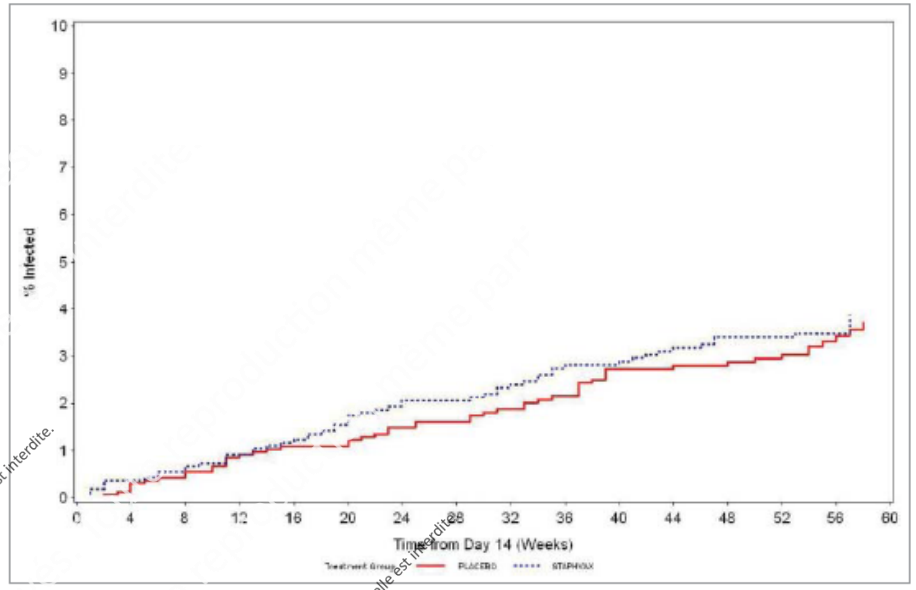


Figure 2. Kaplan-Meier estimate of time-to-*S. aureus* bacteremia in the vaccine and placebo groups (weeks 3–60, Modified–intention-to-treat-for-efficacy cohort).

Etude ancillaire sur 88 patients:
Aucun impact sur le portage nasal de *S. aureus*

Buddy Creech II C. et al. Vaccine 2010

Les échecs humains: essais de phase III

Etude de Merck Intercell: V710

Effect of an Investigational Vaccine for Preventing *Staphylococcus aureus* Infections After Cardiothoracic Surgery

A Randomized Trial

- IsdB
- > 8000 patients inclus
- Réponse AC robuste
- Arrêt prématuré de l'étude
- 5 fois plus de décès par infection à *S. aureus*

dans le groupe vaccin vs groupe placébo

Importance Infections due to *Staphylococcus aureus* are serious complications of cardiothoracic surgery. A novel vaccine candidate (V710) containing the highly conserved *S aureus* iron surface determinant B is immunogenic and generally well tolerated in volunteers.

Objective To evaluate the efficacy and safety of preoperative vaccination in preventing serious postoperative *S aureus* infection in patients undergoing cardiothoracic surgery.

Design, Setting, and Participants Double-blind, randomized, event-driven trial conducted between December 2007 and August 2011 among 8031 patients aged 18 years or older who were scheduled for full median sternotomy within 14 to 60 days of vaccination at 185 sites in 26 countries.

Intervention Participants were randomly assigned to receive a single 0.5-mL intramuscular injection of either V710 vaccine, 60 μg (n=4015), or placebo (n=4016).

Main Outcome Measures The primary efficacy end point was prevention of *S aureus* bacteremia and/or deep sternal wound infection (including mediastinitis) through postoperative day 90. Secondary end points included all *S aureus* surgical site and invasive infections through postoperative day 90. Three interim analyses with futility assessments were planned.

Results The independent data monitoring committee recommended termination of the study after the second interim analysis because of safety concerns and low efficacy. At the end of the study, the V710 vaccine was not significantly more efficacious than placebo in preventing either the primary end points (22/3528 V710 vaccine recipients [2.6 per 100 person-years] vs 27/3517 placebo recipients [3.2 per 100 person-years]; relative risk, 0.81; 95% CI, 0.44-1.48; *P*=.58) or secondary end points, despite eliciting robust antibody responses. Compared with placebo, the V710 vaccine was associated with more adverse experiences during the first 14 days after vaccination (1219/3958 vaccine recipients [30.8%; 95% CI, 29.4%-32.3%] and 866/3967 placebo recipients [21.8%; 95% CI, 20.6%-23.1%], including 797 [20.1%; 95% CI, 18.9%-21.4%] and 378 [9.5%; 95% CI, 8.6%-10.5%] with injection site reactions and 66 [1.7%; 95% CI, 1.3%-2.1%] and 51 [1.3%; 95% CI, 1.0%-1.7%] with serious adverse events, respectively) and a significantly higher rate of multiorgan failure during the entire study (31 vs 17 events; 0.9 [95% CI, 0.6-1.2] vs 0.5 [95% CI, 0.3-0.8] events per 100 person-years; *P*=.04). Although the overall incidence of vaccine-related serious adverse events (1 in each group) and the all-cause mortality rate (201/3958 vs 177/3967; 5.7 [95% CI, 4.9-6.5] vs 5.0 [95% CI, 4.3-5.7] deaths per 100 person-years; *P*=.20) were not statistically different between groups, the mortality rate in patients with staphylococcal infections was significantly higher among V710 vaccine than placebo recipients (15/73 vs 4/96; 23.0 [95% CI, 12.9-37.9] vs 4.2 [95% CI, 1.2-10.8] per 100 person-years; difference, 18.8 [95% CI, 8.0-34.1] per 100 person-years).

Conclusions and Relevance Among patients undergoing cardiothoracic surgery with median sternotomy, the use of a vaccine against *S aureus* compared with placebo did not reduce the rate of serious postoperative *S aureus* infections and was associated with increased mortality among patients who developed *S aureus* infections. These findings do not support the use of the V710 vaccine for patients undergoing surgical interventions.

- ***V710*** et portage

Table 1. Selected Baseline Characteristics of Randomized Patients by Group[a]

Characteristics	V710 Vaccine Group (n = 4005)	Placebo Group (n = 4005)	Total (n = 8010)
Vaccinated	3931 (99)	3982 (99)	7963 (99)
Nasal colonization			
Colonized with any *Staphylococcus aureus*	738 (18)	714 (18)	1452 (18)
Colonized with MRSA	72 (2)	65 (2)	137 (2)

- *Infections à Staphylococcus aureus:*
  - groupe V710, 3,3% (95% CI,2,1%-4,9%) chez les porteurs vs 1,6% (95% CI, 1,2%-2,2%) chez les non porteurs
  - groupe placebo 5,5% (95% CI, 3,9%-7,6%) chez les porteurs vs 1,8% (95% CI, 1,4%-2,4%) chez les non porteurs (*P*=0,09).

Human Vaccines & Immunotherapeutics 10:12, 3513–3516; December 2014; © 2014 Taylor & Francis Group, LLC

Mortality among recipients of the Merck V710 *Staphylococcus aureus* vaccine after postoperative *S. aureus* infections: An analysis of possible contributing host factors

Tessie B McNeely[1,†], Najaf A Shah[1], Arthur Fridman[1], Amita Joshi[1], Jonathan S Hartzel[1], Ravi S Keshari[2], Florea Lupu[2], and Mark J DiNubile[3,*]

Table 1. Relative mortality rates in patients with postoperative *S. aureus* infections by vaccination group and preoperative IL2 and IL17a levels

			V710 recipients 15/29 (52%) died in selected sample		Placebo recipients 4/22 (18%) died in selected sample	
			Mortality Rate n/m (%)	Relative Risk of Death (undetectable IL /detectable IL)	Mortality Rate n/m (%)	Relative Risk of Death (undetectable IL /detectable IL)
IL2 Level	Day of vaccination	undetectable	12/12 (100%)	5.6	1/13 (8%)	0.2
		detectable	3/17 (18%)		3/9 (33%)	
	Day of admission	undetectable	11/11 (100%)	5.6	1/10 (10%)	0.4
		detectable	3/17 (18%)		3/12 (25%)	
IL17a Level	Day of vaccination	undetectable	9/10 (90%)	2.8	0/10 (0%)	0
		detectable	6/19 (32%)		4/12 (33%)	
	Day of admission	undetectable	10/10 (100%)	4.5	0/10 (0%)	0
		detectable	4/18 (22%)		4/12 (33%)	

Plan

- Ce que représente *S. aureus*
- Quelles populations à risque / populations cibles?
- Que nous apprennent les essais passés?
- Les raisons des échecs… au moins une partie!
- Le présent
- Le futur?

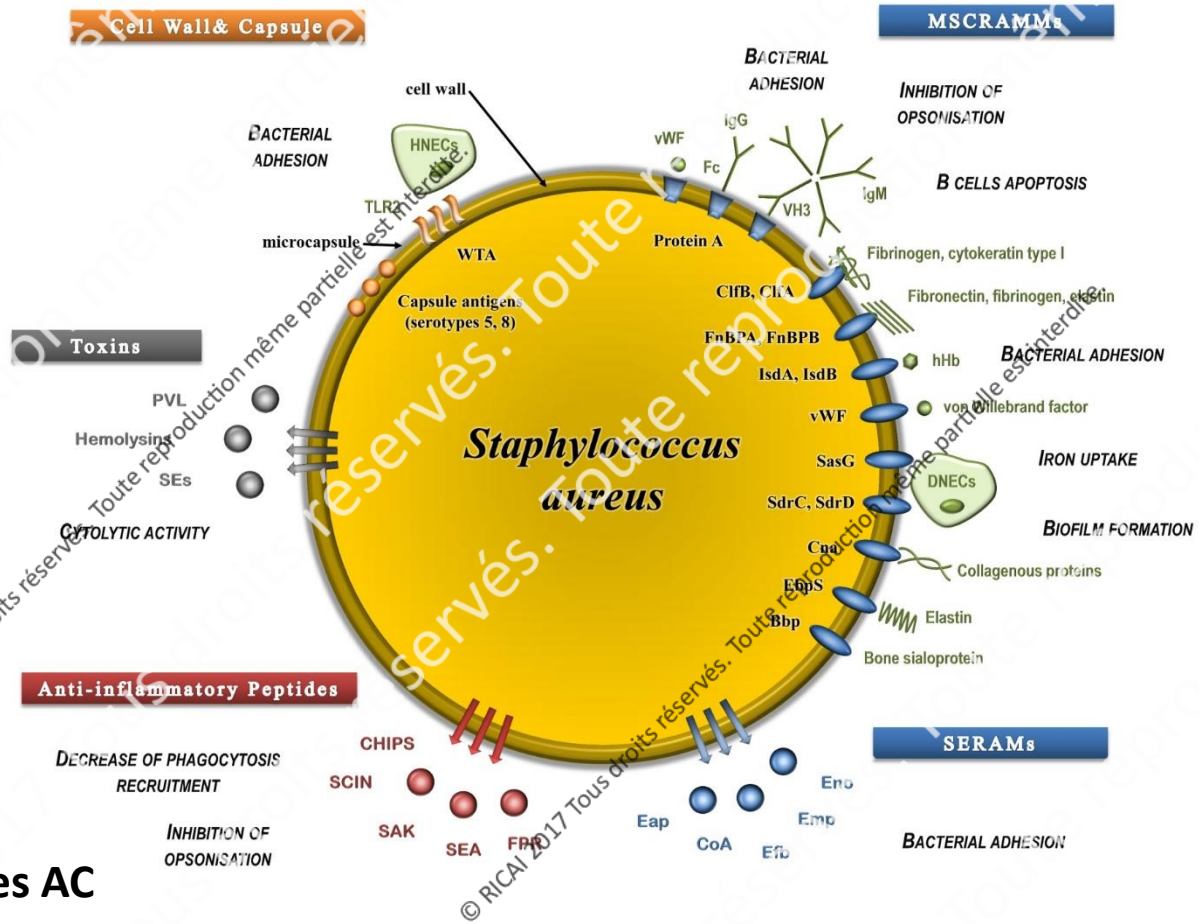
Ecueils de la recherche vaccinale anti-staphylococcique

- ***Cibler un seul Ag vaccinal….***
  - Multiplicité des Ag, expression modulable
  - Complexité de la réponse anti- *S. aureus,* subversion immunité

•*NABI Biopharmaceuticals & StaphVax*:
Vaccin polysaccharidique capsulaire (5 et 8)

•*Merck & intercell et essai V710* :
Vaccin ciblant IsdB, un récepteur de surface captant le fer (Hb)

Ces 2 vaccins ne ciblaient que des AG de surface et **engendrait des AC opsonisants (inefficaces)**



Botelho-Nevers E. *et al.*, 2013. *Expert review of vaccines*.

Ecueils de la recherche vaccinale anti-staphylococcique

- ***Modèles animaux inadaptés…***
  - Tous les essais vaccin anti- *S. aureus* ayant échoué chez l'homme avaient pourtant montré une protection chez la souris ou le lapin
  - Pas de portage de *S. aureus* chez la souris
  - Biomarqueur d'efficacité était notamment les AC induisant opsono-phagocytose

Ecueils de la recherche vaccinale anti-staphylococcique

- ***Immunité cellulaire non ou peu stimulée…***
  - Les patients ayant des déficits immunitaires de type cellulaire sont à risque d'infection à *S. aureus*
  - *Idem si déficit en neutrophiles*

    → *rôle Th17 et IL17*

  - *V710: stimulation de la voie TH17…….*
- ***Essais ne se sont pas intéressés au portage….***
- ***Pas de biomarqueurs immunitaires gagent de protection (surtout pas les Ac!): PAS de corrélats de protection***

Proctor2015
Fowler , Proctor 2014

Plan

- Ce que représente *S. aureus*
- Les populations à risque / populations cibles
- Les essais vaccinaux passés et infructueux
- Les raisons des échecs
- Le présent
- Le futur?

En cours: immunisation active

Sponsor	Product type & name	Target antigen(s)	Product composition	Expected mechanism of action	Clinical phase, target population & key endpoints (see www.clinicaltrials.gov)
Pfizer	Vaccine SA4Ag (*S. aureus* 4-Antigen vaccine)	All surface antigens: Capsular Polysaccharides type 5 & 8 (CP5 & CP8)	2 polysaccharide conjugates (CP5-CRM & CP8-CRM) + 2 recombinant proteins (ClfA & MntC)	Induction of antibodies able to induce opsonophagocytosis and inhibit adhesive properties of the bacterium	Phase IIb in elective spinal fusion surgery patients for the prevention of *S. aureus* blood stream infections and/or deep incisional or organ/space surgical site infections
		Clamping factor A (ClfA)			
		Manganese transporter C	Formulation: non-adjuvanted		
Novadigm	Vaccine NDV 3A	Surface antigen from *Candida albicans*: agglutinin-like sequence 3 (Als3)	1 recombinant protein Formulation: non-adjuvanted	Induction of protective T-cell response	Phase IIa in patients with STAT3-mutated hyper-IgE syndrome to evaluate immunogenicity of NDV-3A vaccine

Terminé…pas de résultats
Pas de phase III débutée

STRIVE (SA4Ag): essai Pfizer

- ClfA (clumping factor A)+ CP5 and CP8 (polysaccharides capsulaires types 5 and 8) +MntC = transporteur du manganèse
- Etude multicentrique, randomisée versus placebo, double aveugle. Phase IIb
- USA et Europe (Allemagne, Angleterre, Espagne, France)
- 2600 patients (42 infections); 18-86 ans
- Randomization 1:1 SA4Ag vs placebo 10 à 60 jours avant une **chirurgie vertébrale** postérieure instrumentalisée de type fusion avec vertèbre lombaire
- Evaluations: efficacité, sécurité, tolérance, immunogénicité, colonisation à SA
- Objectifs= Prévention des infections post-opératoires à SA (90 jours)= bactériémie; ISO profonde; ISO espace organe

Vaccine xxx (2016) xxx–xxx

Vaccine 35 (2017) 385–394

ELSEVIER

journal h

Safety, tolerability, and imm
3-antigen *Staphylococcus aur*
of a randomised trial

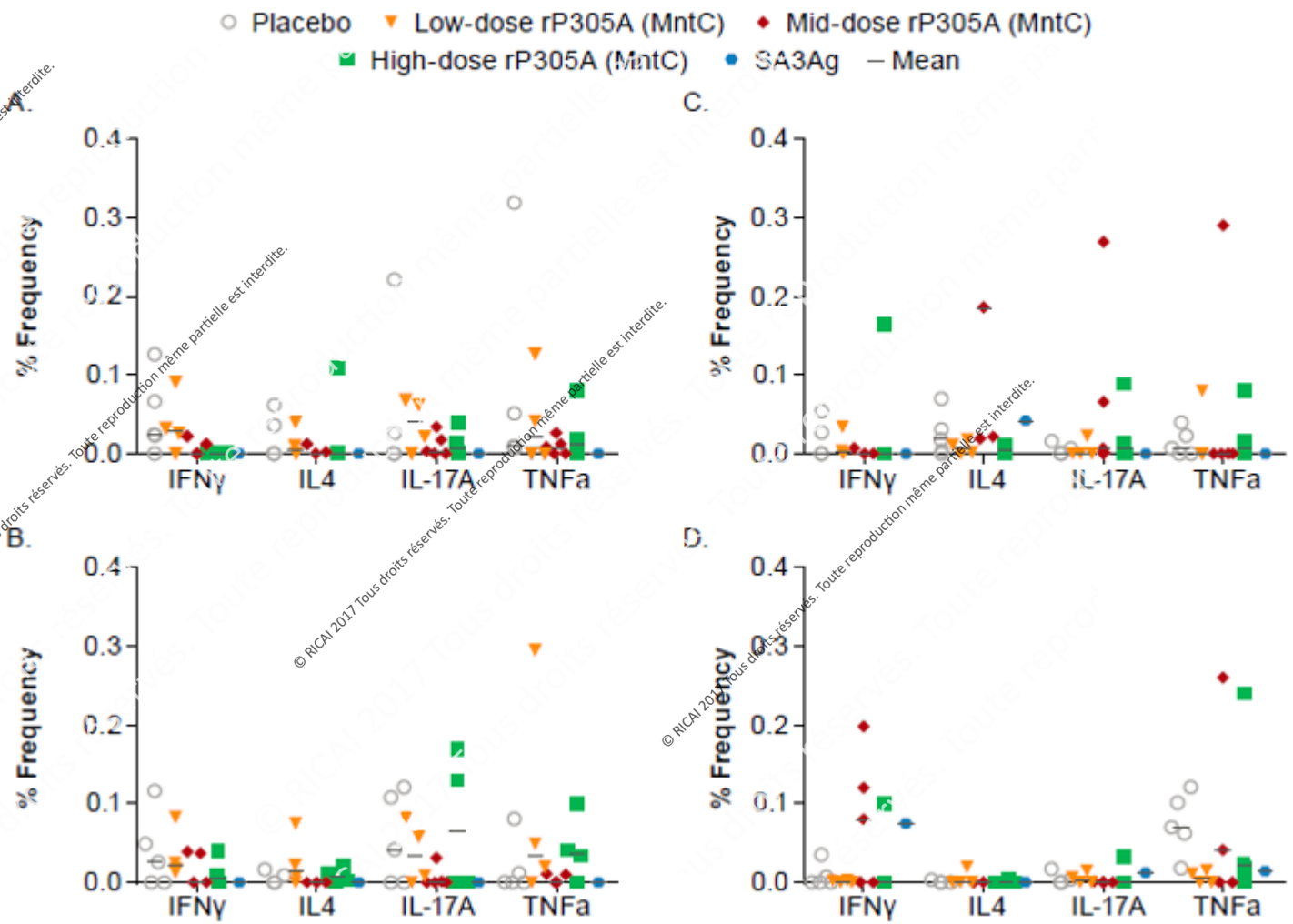
C. Buddy Creech [a,*], Robert W. Frenc
Edward T. Zito [f,2,4], Douglas Girgenti
Lisa K. McNeil [g,4], David Cooper [g], Ka
Annaliesa S. Anderson [g], James Babel

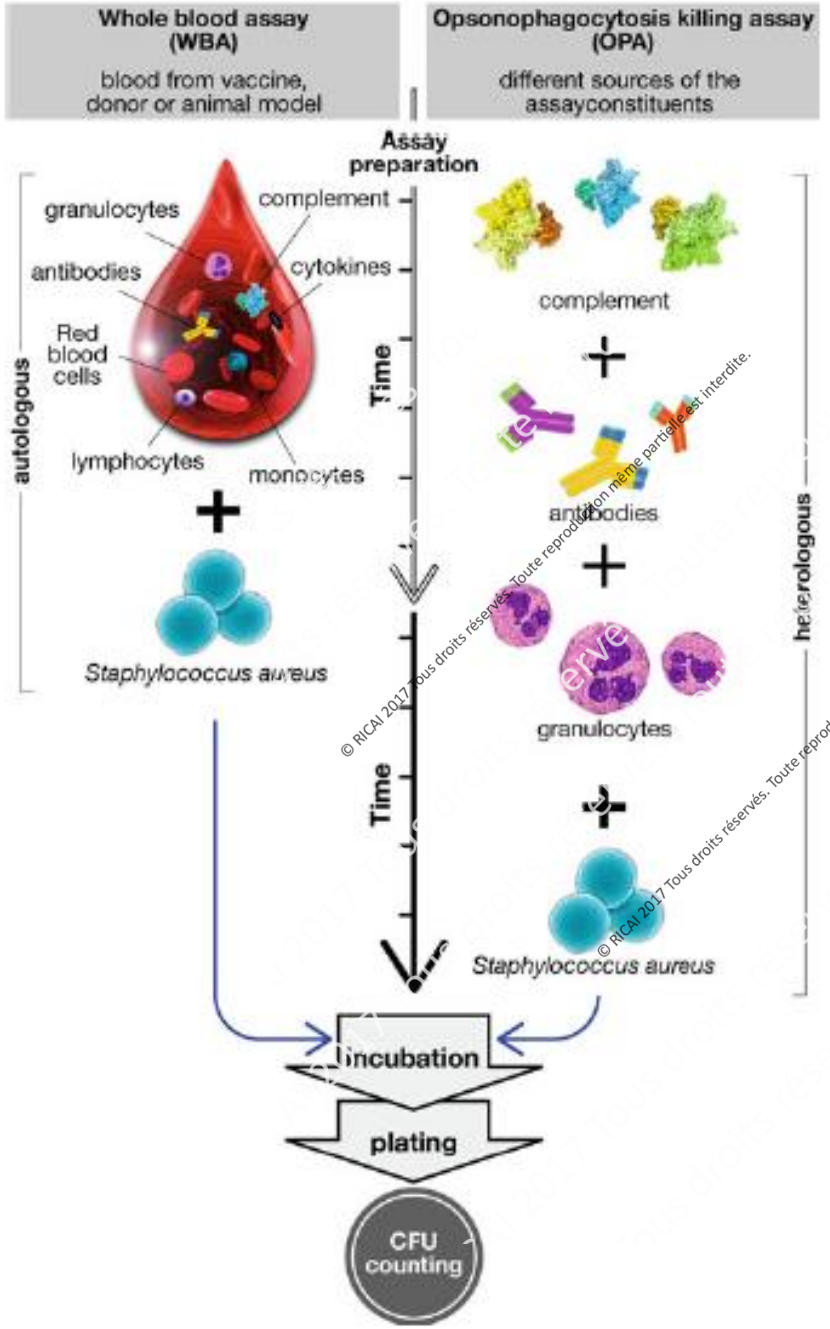
[a] *Vanderbilt Vaccine Research Program. Vanderbilt University*
[b] *Cincinnati Children's Hospital Medical Center, 3333 Burnet*
[c] *Miami Research Associates, 6141 Sunset Dr., South Miami, F*
[d] *Broward Research Group, 7261 Sheridan Street, Suite 210, H*
[e] *Vince and Associates Clinical Research, 10103 Metcalf Ave, C*
[f] *Pfizer Inc, 500 Arcola Road, Collegeville, PA 19426, United St*
[g] *Pfizer Inc, 401 N Middletown Road, Pearl River, NY 10965, U*
[h] *Pfizer Australia Pty Ltd, Sydney, 38-42 Wharf Rd, West Ryde*

ous adverse events were reported.
Conclusions: Single-dose vaccinatic
and robust functional immune resp
opment of this vaccine. Trial registration number: NCT01364571

réponse cellulaire

Supplemental Figure S1. Frequency of cytokine-positive cells at Day 29 visit Per Vaccination Group
(A) CD4+ T cells stimulated with 5 ug rP305A (MntC) **(B)** CD4+ T cells stimulated with 5 ugClfA
(C) CD8+ T cells stimulated with 1 ug rP305A (MntC), and **(D)** CD8+ T cells stimulated with 1 ugClfA.
All values are background subtracted using the no antigen control value for each subject.





cine 35 (2017) 1132–1139

ists available at ScienceDirect

Vaccine

www.elsevier.com/locate/vaccine

ureus vaccine, rapidly induces high

chael Patton [c], Edward Zito [d], Joseph Severs [a], David Cooper [e],
. Jansen [e], Annaliesa S. Anderson [e], Alejandra Gurtman [a]

Activité opsonophagocytique ne semble pas être un gage de protection…..

Pozzi C,. Curr Top Microbiol Immunol. 2017

En cours: immunisation passive

Xbiotech	Human mAb 514G3	Surface protein Staphylococcal protein A (SpA)	1 human mAb against SpA	Induction of antibodies able to block SpA-mediated immune evasion and induce opsonophagocytosis Curatif	Phase I-II in hospitalized patients with bacteremia due to *S. aureus* to evaluate efficacy (sterile blood culture) from date of randomization of 514G3 antibody in addition to standard of care antibiotic treatment
MedImmune	Human mAb MEDI4893	Toxin α-hemolysin (Hla)	1 human mAb against Hla	Neutralization of toxicity associated with Hla Préventif	Phase II in mechanically ventilated patients to evaluate efficacy of MEDI4893 as measured by clinical symptoms of pneumonia and other *S. aureus* serious infection
Arsanis	Human mAb combination of ASN-1 and ASN-2 ASN100	Toxins α-hemolysin (Hla)	2 human mAbs: 1) ASN-1 against Hla and with cross-reactivity to four of the five leukocidins, HlgAB, HlgCB, LukED, and LukSF 2) ASN-2 neutralizes the fifth leukocidin LukAB	Neutralization of toxicity associated with Hla and leukocidins Préventif	Phase II in in Heavily Colonized, Mechanically Ventilated Subjects to evaluate efficacy of ASN100 as measured by clinical symptoms of pneumonia and other *S. aureus* serious infection
Aridis	Human mAb AR-301	Toxin α-hemolysin (Hla)	1 human mAb against Hla	Neutralization of toxicity associated with Hla Curatif	Phase I-II in patients who have severe pneumonia caused by *S. aureus* to evaluate efficacy (survival, bacterial load from respiratory samples) of AR-301 in addition to standard of care antibiotic treatment

Plan

- Ce que représente *S. aureus*
- Les populations à risque / populations cibles
- Les essais vaccinaux passés et infructueux
- Les raisons des échecs
- Le présent
- Le futur: tenir compte des leçons apprises et….. innover

Immunité préalable chez les porteurs

- Mortalité en cas de bactériémie endogène ***moindre*** chez le porteurs

Infect Control Hosp Epidemiol. 2012 Aug;33(8):796-802. doi: 10.1086/666628. Epub 2012 Jun 11.

Staphylococcus aureus colonization before infection is not associated with mortality among S. aureus-infected patients: a meta-analysis.

Schweizer ML[1], Bossen A, McDanel JS, Dennis LK.

Author information

Abstract

BACKGROUND AND OBJECTIVE: The literature is conflicted as to whether people colonized with Staphylococcus aureus are at an increased risk of mortality. The aim of this meta-analysis was to review and analyze the current literature to determine whether prior history of S. aureus colonization is associated with mortality among S. aureus-infected patients.

METHODS: The PUBMED databases were searched with keywords related to S. aureus colonization and mortality. After reviewing 380 article abstracts and 59 articles in detail, only 7 studies had data on the association between S. aureus colonization and mortality among S. aureus-infected patients. Crude estimates of study odds ratios (ORs) were calculated on the basis of data from subset analyses. We pooled crude ORs from the 7 studies using a random-effects model. Woolf's test for heterogeneity was assessed.

	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 HF et al., Lancet. 2004

Immunité préalable chez les porteurs

- Taux d'Ac dirigés contre *S. aureus* différent entre porteurs et non porteurs

Anti-Staphylococcal Humoral Immune Response in Persistent Nasal Carriers and Noncarriers of *Staphylococcus aureus*

Nelianne J. Verkaik,[1] Corné P. de Vogel,[1] Hélène A. Boelens,[1] Dorothee Grumann,[4] Theo Hoogenboezem,[3] Cornelis Vink,[3] Herbert Hooijkaas,[2] Timothy J. Foster,[5] Henri A. Verbrugh,[1] Alex van Belkum,[1] and Willem J. B. van Wamel[1]

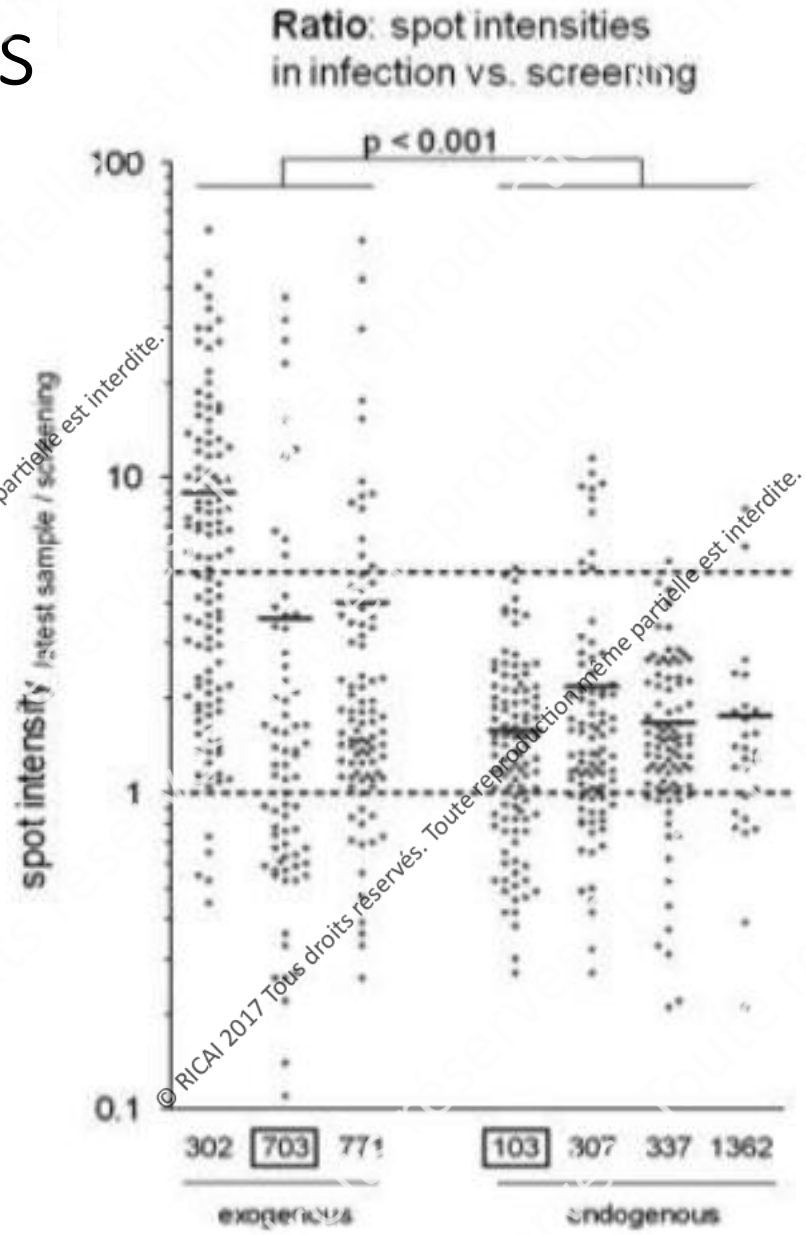
Departments of [1]Medical Microbiology and Infectious Diseases and [2]Immunology, and [3]Laboratory of Pediatrics, Erasmus Medical Center, Rotterdam, the Netherlands; [4]Department of Immunology, University of Greifswald, Greifswald, Germany; [5]Department of Microbiology, Moyne Institute of Preventive Medicine, Trinity College, Dublin, Ireland

Background. Persistent carriers have a higher risk of *Staphylococcus aureus* infections than noncarriers but a lower risk of bacteremia-related death. Here, the role played by anti-staphylococcal antibodies was studied.

Methods. Serum samples from 15 persistent carriers and 19 noncarriers were analyzed for immunoglobulin (Ig) G, IgA, and IgM binding to 19 *S. aureus* antigens, by means of Luminex technology. Nasal secretions and serum samples obtained after 6 months were also analyzed.

Results. Median serum IgG levels were significantly higher in persistent carriers than in noncarriers for toxic shock syndrome toxin (TSST)–1 (median fluorescence intensity [MFI] value, 11,554 vs. 4291; $P < .001$) and staphylococcal enterotoxin (SE) A (742 vs. 218; $P < .05$); median IgA levels were higher for TSST-1 ($P < .01$), SEA, and clumping factor (Clf) A and B ($P < .05$). The in vitro neutralizing capacity of anti–TSST-1 antibodies was correlated with the MFI value ($R^2 = 0.93$) and was higher in persistent carriers (90.6% vs. 70.6%; $P < .05$). Antibody levels were stable over time and correlated with levels in nasal secretions (for IgG, $R^2 = 0.87$; for IgA, $R^2 = 0.77$).

Conclusions. Antibodies to TSST-1 have a neutralizing capacity, and median levels of antibodies to TSST-1, SEA, ClfA, and ClfB are higher in persistent carriers than in noncarriers. These antibodies might be associated with the differences in the risk and outcome of *S. aureus* infections between nasal carriers and noncarriers.



Kolata J. et al., Proteomics 2011

L’immunité anti-staphylococcique est très complexe et mal connue

International Journal of Medical Mic

Contents lists availab

International Journal of

journal homepage: www.e

Mini Review

Immune control of *Staphylococcus aureus* counter-regulation of the adaptive immur

Barbara M. Bröker[a,*], Silva Holtfreter[a], Isabelle Beker

[a] Department of Immunology, University Medicine Greifswald, Germany
[b] Institute of Medical Microbiology, Immunology and Parasitology, University of Bonn, Germ

ARTICLE INFO

Keywords:
Staphylococcus aureus
T cells
B cells
antibodies
immune memory

ABSTRACT

Successful vaccination relies
This review summarizes the
cus aureus as well as the bac
pathogens and peaceful coha
development. This begs the
against *S. aureus* infection. In
probed for potential mechani
research.

Published in final edited form as:

Nat Rev Microbiol. 2015 September ; 13(9): 529–543. doi:10.1038/nrmicro3521.

Staphylococcal manipulation of host immune responses

Vilasack Thammavongsa[*], **Hwan Keun Kim**, **Dominique Missiakas**, and **Olaf Schneewind**

Department of Microbiology, University of Chicago, 920 East 58th Street, Chicago, Illinois 60637, USA

Abstract

Staphylococcus aureus, a bacterial commensal of the human nares and skin, is a frequent cause of soft tissue and bloodstream infections. A hallmark of staphylococcal infections is their frequent recurrence, even when treated with antibiotics and surgical intervention, which demonstrates the bacterium’s ability to manipulate innate and adaptive immune responses. In this Review, we highlight how *S. aureus* virulence factors inhibit complement activation, block and destroy phagocytic cells and modify host B and T cell responses, and we discuss how these insights might be useful for the development of novel therapies against infections with antibiotic resistant strains such as methicillin-resistant *S. aureus*.

Ce qu'on sait à présent

Clearance of *Staphylococcus aureus* Nasal Carriage Is T Cell Dependent and Mediated through Interleukin-17A Expression and Neutrophil Influx

Nathan K. Archer,[a,b] Janette M. Harro,[a] Mark E. Shirtliff[a,c]

Med Microbiol Immunol (2017) 206:225–234
DOI 10.1007/s00430-017-0499-9

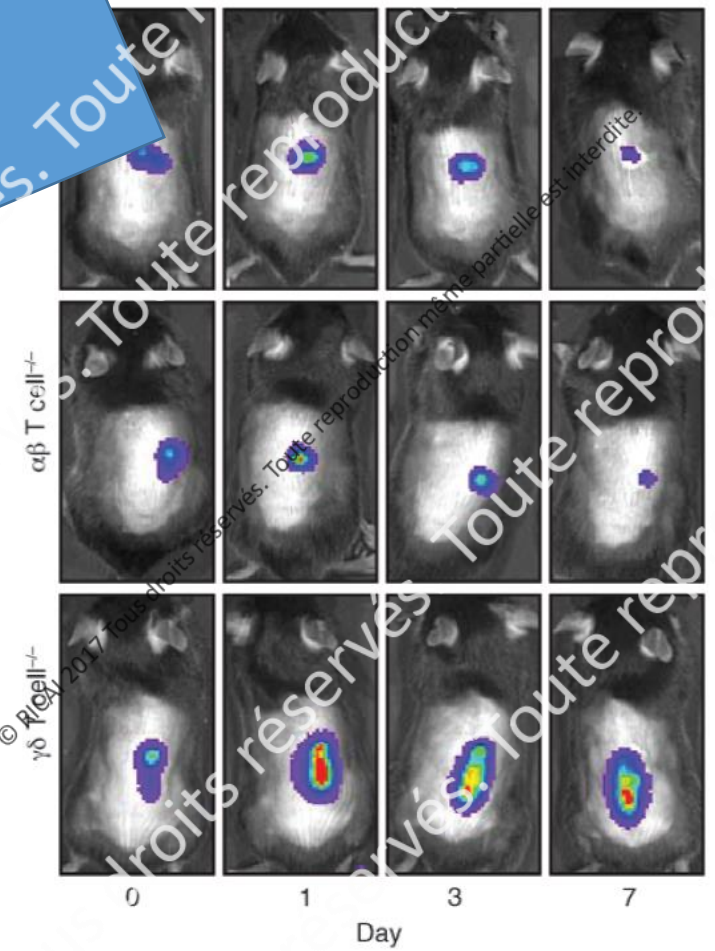
ORIGINAL INVESTIGATION

IL-17A plays an importa… by vaccination with fibro… binding protein A against …

Kouji Narita[1,2] · Krisana Asano[1] · Akio Nakai…

IL-17 … essential for host defense … eous *Staphylococcus aureus* … fection in mice

…iry C. Garcia,[1] Romela Irene Ramos,[1] David M. Farzam,[1] …,[1] Andrew Blauvelt,[3] Jay K. Kolls,[4] Ambrose L. Cheung,[5] Robert L. Modlin,[1,2] and Lloyd S. Miller[1]



IL-17 induction required IL-1, TLR2, and IL-23
γδ T cell–deficient mice inoculated with *S. aureus* and treated with a single dose of recombinant IL-17 had lesion sizes and bacterial counts resembling those of WT mice

Réponse cellulaire

Attention toutefois…. Réponse Th17 forte est associée à des maladies auto-immunes
…..durée de la réponse est à priori courte

Ce qu'on sait à présent

- Ac anti-toxines

natural infection does not provoke durable immunity [ ]larly, anti-Hla antibodies protect rabbit and Jurkat T cells from lysis a[ ](the mammalian receptor for Hla) inhibitor, R66 [50]. While [ ]short-lived, anti-Hla antibody levels did correlat[ ]*ureus* infections in children [49]. Of n[ ]levels of antibody to Hla and PV[ ]xin ED binds CCR5 re[ ]raviroc (CCR5 inhibitor), [ ][51]. Finally, other potential [ ]he observations that low anti-exotoxin [ ]psis when patients are infected with enterotoxin-[ ], and higher anti-PVL antibody levels correlate with less [ ]. That enterotoxiods might need to be given as vaccines is suggested [ ]*S. aureus* bacteremia in intravenous drug users failed to produce antibodies [ ]enterotoxin superantigens [www.clinicaltrials.gov, NCT00548002], whereas non-eneterotoxin superantigens were common and increased following *S. aureus* bacteremia [54]. Thus, there is both human and animal data suggesting that anti-staphylococcal toxin antibodies may have efficacy in reducing disease severity.

Ac anti-toxines NEUTRALISANTS

Fowler et Proctor 2014

Ce qu'on sait à présent

Future MICROBIOLOGY

EDITORIAL

For reprint orders, please contact: reprints@futuremedicine.com

Deciphering the significance of the T-cell response to *Staphylococcus aureus*

Isabelle Bekeredjian-Ding

"Vaccine developers will, thus, need to take into account that targeting different types of infection requires qualitatively different T-cell responses."

Erwin Swennen[a], Roberto Petracca[a], Cecilia Bretton[a], Sabri Juliane Bubeck Wardenburg[b], Olaf Schneewind[c], Derek T. C Sylvie Bertholet[a], Ennio De Gregorio[a], Rino Rappuoli[a,1], and

[a]Novartis Vaccines Research Center, 53100 Siena, Italy; [b]Departments of Pedi and [c]Department of Microbiology, University of Chicago, Chicago, IL 60637

Contributed by Rino Rappuoli, January 25, 2015 (sent for review September

PLOS | PATHOGENS

RESEARCH ARTICLE

Antigen delivery to dendritic cells shapes human CD4$^+$ and CD8$^+$ T cell memory responses to *Staphylococcus aureus*

Julia Uebele[1,2], Christoph Stein[1,2], Minh-Thu Nguyen[3], Anja Schneider[1], Franziska Kleinert[2], Olga Tichá[1], Gabriele Bierbaum[2], Friedrich Götz[3], Isabelle Bekeredjian-Ding[1,2]*

1 Division of Microbiology, Paul-Ehrlich Institute, Langen, Germany, **2** Institute for Medical Microbiology, Immunology and Parasitology (IMMIP), University Hospital Bonn, Bonn, Germany, **3** Interfaculty Institute of Microbiology and Infection Medicine (IMIT), University Tuebingen, Auf der Morgenstelle 28/E8, Tuebingen, Germany

* isabelle.bekeredjian-ding@pei.de

Abstract

Intracellular persistence of *Staphylococcus aureus* favors bacterial spread and chronic infections. Here, we provide evidence for the existence of human CD4$^+$ and CD8$^+$ T cell memory against staphylococcal antigens. Notably, the latter could provide a missing link in our understanding of immune control of intracellular *S. aureus*. The analyses showed that pulsing of monocyte-derived dendritic cells (MoDC) with native staphylococcal protein antigens induced release of Th2-associated cytokines and mediators linked to T regulatory cell development (G-CSF, IL-2 and IL-10) from both CD4$^+$ and CD8$^+$ T cells, thus revealing a state of tolerance predominantly arising from preformed memory T cells. Furthermore, G-CSF was identified as a suppressor of CD8$^+$ T cell-derived IFNγ secretion, thus confirming a tolerogenic role of this cytokine in the regulation of T cell responses to *S. aureus*. Nevertheless, delivery of *in vitro* transcribed mRNA-encoded staphylococcal antigens triggered Th1-biased responses, e.g. IFNγ and TNF release from both naïve and memory T cells. Collectively, our data highlight the potential of mRNA-adjuvanted antigen presentation to enable inflammatory responses, thus overriding the existing Th2/Treg-biased memory T cell response to native *S. aureus* antigens.

Check for updates

OPEN ACCESS

Citation: Uebele J, Stein C, Nguyen M-T, Schneider A, Kleinert F, Tichá O, et al. (2017) Antigen delivery to dendritic cells shapes human CD4$^+$ and CD8$^+$ T cell memory responses to *Staphylococcus aureus*. PLoS Pathog 13(5): e1006387. https://doi.org/10.1371/journal.ppat.1006387

Editor: Lloyd S. Miller, Johns Hopkins School of Medicine, UNITED STATES

Received: December 21, 2016

Accepted: April 27, 2017

Published: May 25, 2017

The Journal of Infectious Diseases

MAJOR ARTICLE

Lethal CD4 T Cell Responses Induced by Vaccination Against *Staphylococcus aureus* Bacteremia

Hatice Karauzum,[1] Christian C. Haudenschild,[1] Ian N. Moore,[3] Mahta Mahmoudieh,[1] Daniel L. Barber,[2] and Sandip K. Datta[1]

[1]Bacterial Pathogenesis Unit and [2]T-Lymphocyte Biology Unit, Laboratory of Parasitic Diseases, and [3]Infectious Disease Pathogenesis Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland

Multiple candidate vaccines against *Staphylococcus aureus* infections have failed in clinical trials. Analysis of a recent prematurely halted vaccine trial revealed increased mortality rates among vaccine recipients in whom postsurgical *S. aureus* infection developed, emphasizing the potential for induction of detrimental immune responses and the need to better understand the requirements for protective immunity against *S. aureus*. These failures of single-antigen vaccines have prompted ongoing development of multicomponent vaccines to target the multitude of *S. aureus* virulence factors. In the current study, we used lethally irradiated *S. aureus* as a model multicomponent vaccine and showed that vaccination of mice decreased survival in a bacteremia challenge model. These deleterious effects were due to a CD4 T-cell–dependent interferon γ response and could be prevented by inhibiting development of this response during vaccination. Our results identify the potential for vaccination to induce pathological immune responses, and they have implications for recent vaccine failures and the design of future staphylococcal vaccines.

Keywords. *Staphylococcus aureus*; vaccination; systemic infection; Th1 cells; IFN-γ; immunopathology.

Les réponses immunes dans des populations cibles supposées mauvaises répondeuses restent encourageantes….

Scully et al. Diabetol Metab Syndr (2017) 9:76
DOI 10.1186/s13098-017-0276-3

Diabetology & Metabolic Syndrome

RESEARCH Open Access

Neutrophil killing of *Staphylococcus aureus* in diabetes, obesity and metabolic syndrome: a prospective cellular surveillance study

Ingrid Lea Scully[1], Lisa Kristin McNeil[1], Sudam Pathirana[1], Christine Lee Singer[1], Yongdong Liu[1], Stanley Mullen[1], Douglas Girgenti[1], Alejandra Gurtman[1], Michael W. Pride[1], Kathrin Ute Jansen[1], Paul L. Huang[1] and Annaliesa S. Anderson[1*]

Abstract

Background: Obesity, metabolic syndrome (MetS), and diabetes are frequent in surgical populations and can enhance susceptibility to postoperative surgical site infections. Reduced neutrophil function has been linked with diabetes and risk of *Staphylococcus aureus* infection. Therefore, neutrophil function in diabetic and obese subjects (± MetS) was assessed in this prospective serological and cellular surveillance study to determine whether vaccines administered to protect against infections after surgery could be effective in these populations.

Methods: Neutrophil function (chemotaxis, phagocytosis, and opsonophagocytic killing of *S. aureus*) was assessed in subjects classified according to diabetes status, body mass index, and presence/absence of MetS. Neutrophils were characterized within functional subsets by flow cytometry. A serologic assay was used to measure baseline antibody presence to each antigen in SA4Ag: capsular polysaccharide (CP) type 5, CP8, recombinant mutant Clumping factor A (rmClfA), and recombinant Manganese transport protein C (rMntC).

Results: Neutrophil function was similar for comorbid and healthy cohorts, with no significant between-group differences in cell counts, migration, phagocytosis ability, neutrophil subset proportions, and *S. aureus* killing ability when neutrophils were isolated 3–6 months apart (Visit 1 [n = 90] and Visit 2 [n = 70]) and assessed. Median pre-existing antibody titers to CP5, CP8, and rmClfA were comparable for all cohorts (insufficient subjects with rMntC titers for determination).

Conclusions: MetS, diabetes, and obesity do not impact in vitro neutrophil function with regard to *S. aureus* killing, suggesting that if an effective *S. aureus* vaccine is developed it may be effective in individuals with these comorbidities.

Keywords: Diabetes, Immune function, Metabolic syndrome, Neutrophils, Obesity, *Staphylococcus aureus*, Vaccine

CVI Journals.ASM.org

Phase IIa Study of the Immunogenicity and Safety of the Novel *Staphylococcus aureus* Vaccine V710 in Adults with End-Stage Renal Disease Receiving Hemodialysis

Moustafa Moustafa,[a] George R. Aronoff,[b] Chandra Chandran,[c] Jonathan S. Hartzel,[d] Steven S. Smugar,[d] Claude M. Galphin,[e] Lionel U. Mailloux,[f] Elizabeth Brown,[d] Mark J. DiNubile,[d] Nicholas A. Kartsonis,[d] and Dalya Goris[d]

South Carolina Nephrology & Hypertension Center, Orangeburg, South Carolina, USA[a]; University of Louisville School of Medicine, Louisville, Kentucky, USA[b]; St. Joseph's Regional Medical Center, Paterson, New Jersey, USA[c]; Merck Sharp & Dohme Corp., Whitehouse Station, New Jersey, USA[d]; Southeastern Renal Research Institute, Chattanooga, Tennessee, USA[e]; and Hofstra North Shore-LIJ School of Medicine, Port Washington, New York, USA[f]

Bacteremia is the second leading cause of death in patients with end-stage renal disease who are on hemodialysis. A vaccine eliciting long-term immune responses against *Staphylococcus aureus* in patients on chronic hemodialysis may reduce the incidence of bacteremia and its complications in these patients. V710 is a vaccine containing iron surface determinant B (IsdB), a highly conserved *S. aureus* surface protein, which has been shown to be immunogenic in healthy subjects. In this blinded phase II immunogenicity study, 206 chronic hemodialysis patients between the ages of 18 and 80 years old were randomized to receive 60 μg V710 (with or without adjuvant), 90 μg V710 (with adjuvant), or a placebo in various combinations on days 1, 28, and 180. All 201 vaccinated patients were to be followed through day 360. The primary hypothesis was that at least 1 of the 3 groups receiving 2 V710 doses on days 1 and 28 would have a ≥2.5 geometric mean fold rise (GMFR) in anti-IsdB IgG titers over the baseline 28 days after the second vaccination (day 56). At day 56, all three groups receiving 2 doses of V710 achieved a ≥2.5 GMFR in anti-IsdB antibodies compared to the baseline (*P* values of <0.001 for all 3 groups), satisfying the primary immunogenicity hypothesis. None of the 33 reported serious adverse experiences were considered vaccine related by the investigators. V710 induced sustained antibody responses for at least 1 year postvaccination in patients on chronic hemodialysis.

Pistes pour les vaccins à venir….

- Importance de connaitre encore mieux la réponse immune anti-SA…. notamment celle dans les populations cibles
- Sélection d'Ag par la « reverse vaccinology »?
- Utilité de la « convergent immunity »?
- Impact de la vaccination sur le portage?
- Utilisation de nouvelles stratégies de vectorisation?
- Voie d'administration muqueuse?
- Nouveaux adjuvants
- Plus de tests préciniques
- Nouveaux modèles
- ….

Rappuoli R, et al., Nat Rev Immunol 2011, 11:865-872
Yeaman MR, et al., Front Immunol. 2014 Sep 26;5:463
Botelho-Nevers E et al., ,. Expert Rev Vaccines. 2013 Nov;12(11):1249-59
Roca A, et al.,. Clin Infect Dis. 2012 Sep;55(6):816-24
Veloso Tr et al., . Vaccine. 2015 Jul 9;33(30):3512-7
Sun H,et al.. Int J Nanomedicine. 2015 Dec 3;10:7275-90
Li X, et al., MBio. 2016:e02232-15. doi: 10.1128/mBio.02232-15
Parker D.. Front Immunol. 2017 May 4;8:512

Au total

- A la question « un vaccin anti *S. aureus* est-il possible? » la réponse est OUI mais quand? comment? pour qui?
- Immunisation passive: aide
- Bactérie commensale: comme *Escherichia coli,* rôle du portage primordial
- Besoin d'encore mieux connaitre la réponse immune
- Besoin d'obtenir des bons corrélats de protection
- Pas un mais plusieurs vaccins probablement

- Encore beaucoup de chose à définir!

- Vrai besoin++++++ mais ne pas négliger ce qui marche déjà (hygiène, décolonisation….)

Merci de votre attention

Merci à tous!

Pr Stéphane PAUL

Dr Paul VERHOEVEN

Pr Philippe BERTHELOT

Pr Thomas BOURLET
Directeur du GIMAP

Pr. Bruno POZZETTO

Dr Florence GRATTARD
Pr Frédéric LUCHT
Dr Amandine GAGNEUX-BRUNON
Et toute l'équipe du service d'Infectiologie et du CIC 1408

Université de Lyon
Université Jean Monnet Saint-Étienne
GIMAP Groupe sur l'Immunité des Muqueuses et Agents Pathogènes EA • 3064 • SAINT-ETIENNE
Centre Hospitalier Universitaire Saint-Etienne
i-reivac Innovative clinical research network in vaccinology
F-CRIN Network
Fcrin French Clinical Research Infrastructure Network
CIC 1408
Inserm