Quelles pistes de vaccins pour les infections associées aux soins?

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

Service d'Infectiologie (CHU de Saint-Etienne)

Inserm CIC 1408- Axe Vaccinologie, I-Reivac

Présage (Institut de prévention en santé globale)

Liens d’Intérêt

- Membre du groupe prévention de la SPILF
- Investigateur associé/ principal essai vaccins académiques et industriels CIC 1408 Axe vaccinologie-I-REIVAC: Sanofi Pasteur; GSK, MSD, Pfizer….
- Bourse par Pfizer pour un travail sur la couverture vaccinale des patients immunodéprimés au CHU de Saint-Etienne
- Formations aux MG (Pfizer, Sanofi-Pasteur)
- Advisory Board Vaccin *S. aureus* (Pfizer)
- Collaboration étude préclinique (Sanofi -Pasteur)
- Investigateur principal d’un PHRC CIBERSTAPH: décolonisation ciblée des porteurs persistants en hémodialyse

- Conflit d’intêret: AUCUN

Plan

- Pourquoi a-t-on besoin de vaccins?
- Les infections pouvant être prévenues: état des lieux
  - *Staphylococcus aureus*
  - *Clostridium difficile*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - Les autres
- Les populations cibles

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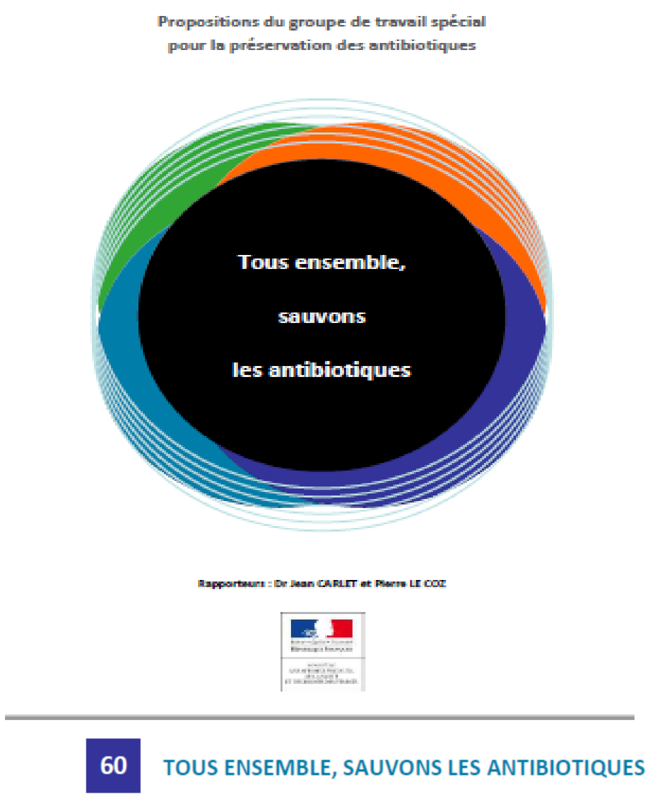
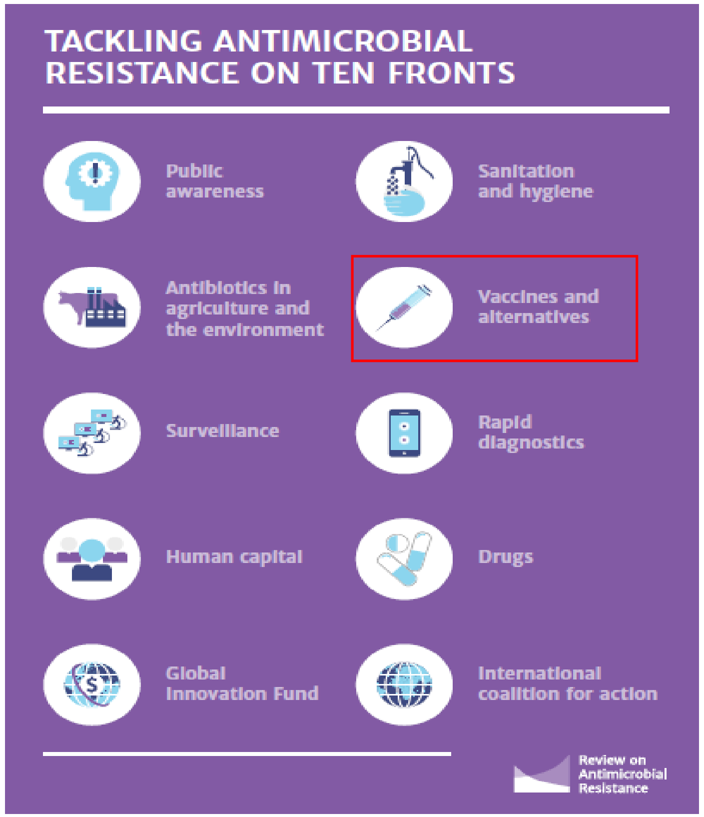
Pourquoi a-t-on besoin de vaccins?

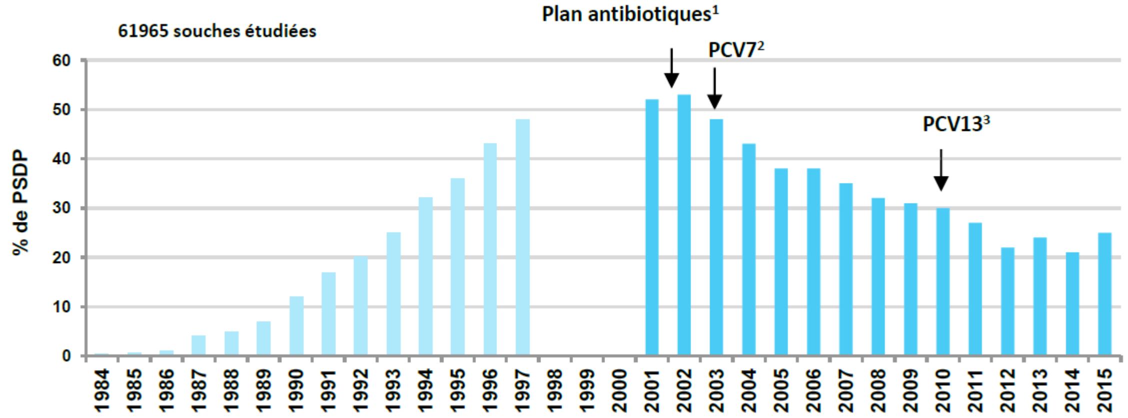
- Les Infections associées aux soins (IAS) sont un problème de Santé Publique
- Associées à des surcoûts majeurs
- Malgré les mesures de prévention, prévalence stable, 4-9%
- ENP 2017 : stabilité des IAS mais augmentation des infections du site opératoire
- *E.coli, S. aureus, P.aeruginosa, C. difficile, Klebsiella* spp…..
- De plus en plus ces agents infectieux, notamment les BGN sont multirésistants voire hautement résistants aux antibiotiques
- Impasses thérapeutiques, liées à cette antibiorésistance
- Au-delà de la transmission croisée (infection exogène), le portage est souvent en jeu dans les IAS (infection endogène)

Enquête de prévalence 2012 et 2017des infections associées aux soins. SPF
Point prevalence survey of healthcare-associated infections-ECDC
Magill SS et al., N Engl J Med 2014;370:1198.
Marchetti A *et al*., J Med Econ 2013; 16:1399
Climo MW *et al.,* N Engl J Med 2013; 368:533





Priorités		Recherche/ objectifs
1	L'amélioration d'antibiotiques déjà connus et de leur utilisation optimum au cours des traitements, la mise au point de nouveaux antibiotiques et de thérapeutiques alternatives (immunothérapie ciblée, adjuvants à l'antibiothérapie pour limiter le développement des résistances selon le concept de EcoEvodrugs, vaccination, phagothérapie, cibles originales et viables, …	• Trouver de nouvelles cibles pour des antibiotiques. • Développer de nouveaux antibiotiques. • Améliorer la pharmacocinétique et la pharmacodynamique des antibiotiques négligés. • Développer des protocoles de traitement avec des combinaisons d'antibiotiques existants et nouveaux. • Développer des alternatives aux antibiotiques (vaccins, phages…). • Incitations pour minimiser les obstacles au développement et l'introduction de nouveaux antibiotiques ou de thérapeutiques alternatives.



Available online at www.sciencedirect.com
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Vaccine 22S (2004) S1–S4
Vaccine
www.elsevier.com/locate/vaccine

Preface

Immunological approaches against nosocomial infections

EXPERT REVIEW OF VACCINES, 2018
https://doi.org/10.1080/14760584.2018.1470507
Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

Vaccines for healthcare-associated infections: present, future, and expectations

Amandine Gagneux-Brunon[a,b], Frédéric Lucht[a,b], Odile Launay[c], Philippe Berthelot[b,d] and Elisabeth Botelho-Nevers[a,b]

[a]Inserm, CIC 1408, I-REIVAC, University Hospital of Saint-Etienne, Saint-Etienne, France; [b]GIMAP EA 3064, University of Lyon, France; [c]Inserm CIC 1417, I-REIVAC, University of Paris-Descartes, University Hospital of Cochin-Broca-Hôtel-Dieu, Paris, France; [d]Infection control unit, University Hospital of Saint-Etienne, Saint-Etienne, France

ABSTRACT

Introduction: In spite of the widespread implementation of preventive strategies, the prevalence of healthcare-associated infections (HAIs) remains high. HAIs are associated with multidrug resistant organisms, and in the post-antibiotic era, alternative strategies such as vaccines are needed for their management.

Areas covered: Vaccines to prevent HAIs could be proposed to at-risk patients, or to healthcare workers (HCWs) to prevent cross-transmission. After searches in Pubmed and clinicaltrials.gov, existing vaccines and vaccines under clinical development are presented in this narrative review. Issues associated with the use of vaccines to prevent HAIs are discussed.

Expert commentary: Future vaccines against HAIs will contribute to fight antibiotic resistance and thus reduce the burden of HAIs. At this stage, the goal of obtaining effective vaccines against *S.aureus*, *C. difficile* and gram-negative bacteria has not yet been achieved. Obtaining an efficient response to vaccines in at-risk patients for HAIs is also challenging, and future strategies of vaccination need to address this difficulty. The efficacy of vaccines for HCWs in reducing the spread of nosocomial outbreaks is counterbalanced by the lack of adherence to vaccine policies among HCWs. The acceptance of future vaccines to prevent carriage and infection with organisms involved in HAIs in HCWs will probably be a challenge.

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KEYWORDS
Healthcare-associated infections; prevention; vaccines; immunization; antimicrobial resistance; cross-transmission

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IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD
HEALTHCARE EPIDEMIOLOGY: Robert A. Weinstein, Section Editor

Vaccines for Healthcare-associated Infections: Promise and Challenge

Jane M. Knisely, Baoying Liu, Ryan T. Ranallo, and Lanling Zou

Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, Maryland

As antibiotic resistance increases and the rate of antibiotic development slows, it is becoming more urgent to develop novel approaches to prevent and mitigate serious bacterial and fungal infections. Healthcare-associated infections (HAIs), including those caused by *Clostridium difficile*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, carbapenem-resistant Enterobacteriaceae, and *Candida* species, are a major cause of morbidity, mortality, and healthcare costs. HAIs are also a key driver of antibiotic use. Vaccines directed toward these pathogens could help prevent a large number of HAIs and associated antibiotic use if administered to targeted populations. Despite numerous scientific and operational challenges, there are vaccine candidates in late-stage clinical development for *C. difficile, S. aureus, and P. aeruginosa*. Basic, preclinical, and early clinical research to develop vaccines for other types of HAIs is also under way. In addition, other prophylactic immune interventions, such as monoclonal antibodies, for several of these pathogens are in advanced development. Here we describe the promise, challenges, and current pipeline of vaccines to prevent HAIs.

Keywords. vaccines; healthcare-associated infections; *Clostridium difficile*; *Staphylococcus aureus*; antibiotic resistance.

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VACCINATION

Les vaccins dans la prévention des infections associées aux soins

Vaccines against healthcare-associated infections

A. Gagneux-Brunon[a,b,c], F. Lucht[a,b,c], O. Launay[d,e], P. Berthelot[c,f], E. Botelho-Nevers[a,*,b,c]

Plan

- Pourquoi a-t-on besoin de vaccins?
- Les infections pouvant être prévenues: état des lieux
  - *Staphylococcus aureus*
  - *Clostridium difficile*
  - *Escherichia coli*
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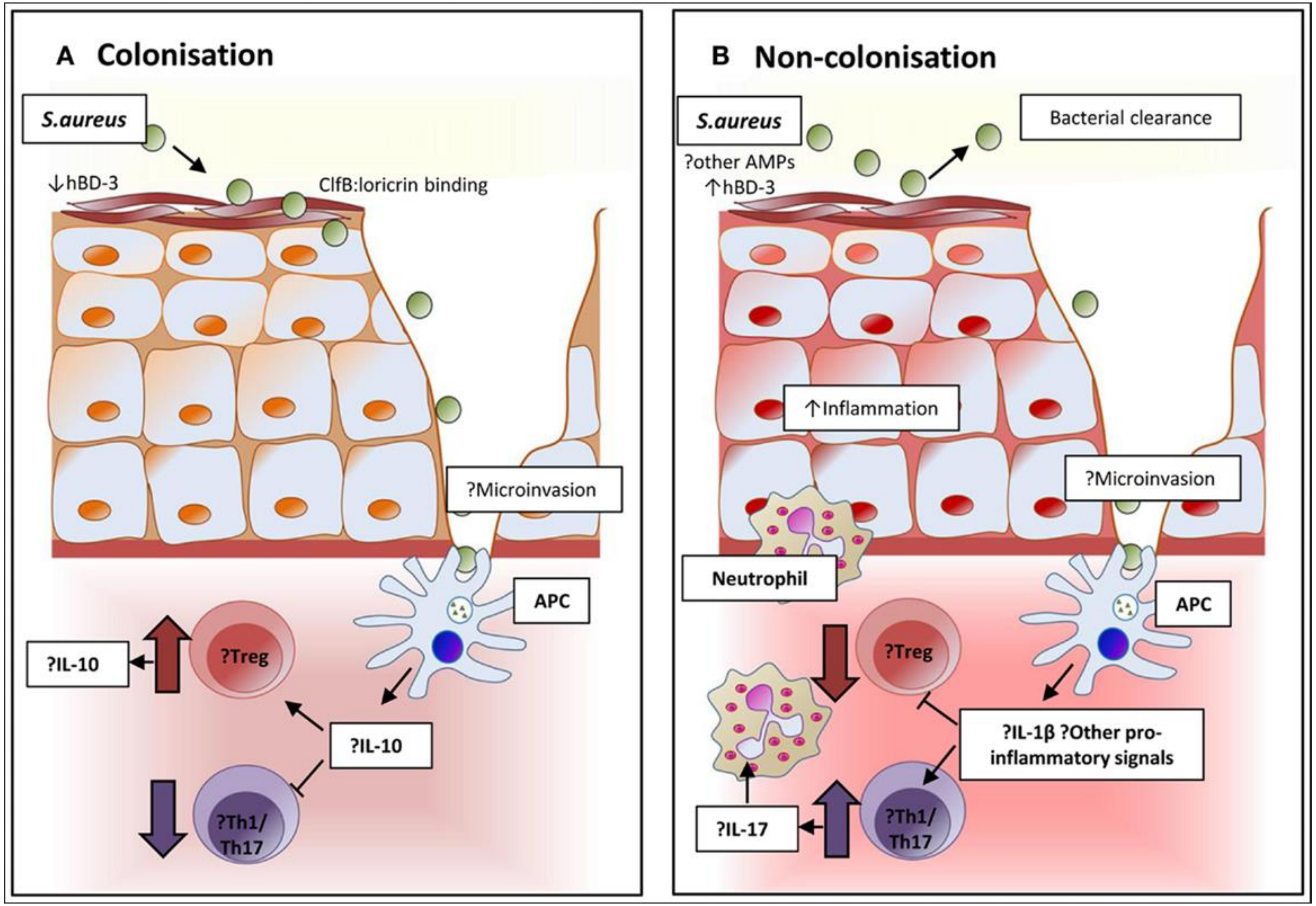
  - Les autres
- Les populations cibles

Staphylococcus aureus: agent double

- Flore commensale
- Bactérie pathogène
- ≠ flore transitoire



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% (13·2–19·8)	15·7% (12·7–19·2)

-32206 patients vus en médecine générale

-9 pays d'Europe

5

20

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 et virulent

- Agent patho… …ent, en pathol…
  - 1er agen… …t d…
  - 1er agen…
  - 2ème ag…

Malgré les stratégies existantes: mesures d'Hygiène et antibiothérapies

- Agent … …soins
  - … …ections n…
  - … d'infection en réanim…

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

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
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Munoz *et al*., J Hosp Infect 2008
Donker JMW, PLoS ONE 2012
Nouwen et al., Kidney International 2005
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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

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*
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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]

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]

STAPHYLOCOCCUS AUREUS CONJUGATE VACCINE IN PATIENTS RECEIVING HEMODIALYSIS

USE OF A *STAPHYLOCOCCUS AUREUS* CONJUGATE VACCINE IN PATIENTS RECEIVING HEMODIALYSIS

HENRY SHINEFIELD, M.D., STEVEN BLACK, M.D., ALI FATTOM, PH.D., GARY HORWITH, M.D., SCOTT RASGON, M.D., JUAN ORDONEZ, M.D., HOCK YEOH, M.D., DAVID LAW, M.D., JOHN B. ROBBINS, M.D., RACHEL SCHNEERSON, M.D., LARRY MUENZ, PH.D., AND ROBERT NASO, PH.D.

N Engl J Med. 2002 Feb 14;346(7):491-6

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……

Nabi: StaphVAX®

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.

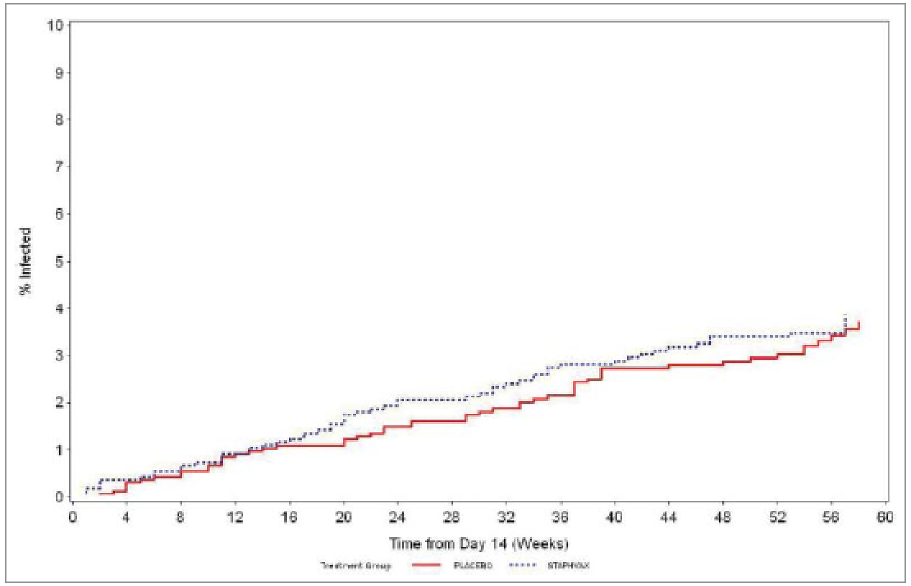


Figure 2. Kaplan-Meier estimate of time-to-*S. aureus* bacteremia in the vaccine and placebo groups (weeks 3–60, Modified–intention-to-treat-for-efficacy cohort).

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

JAMA. 2013 Apr 3;309(13):1368-78

- 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 165 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.

Human Vaccines & Immunotherapeutics 10:12, 3513–3516; December 2014;

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

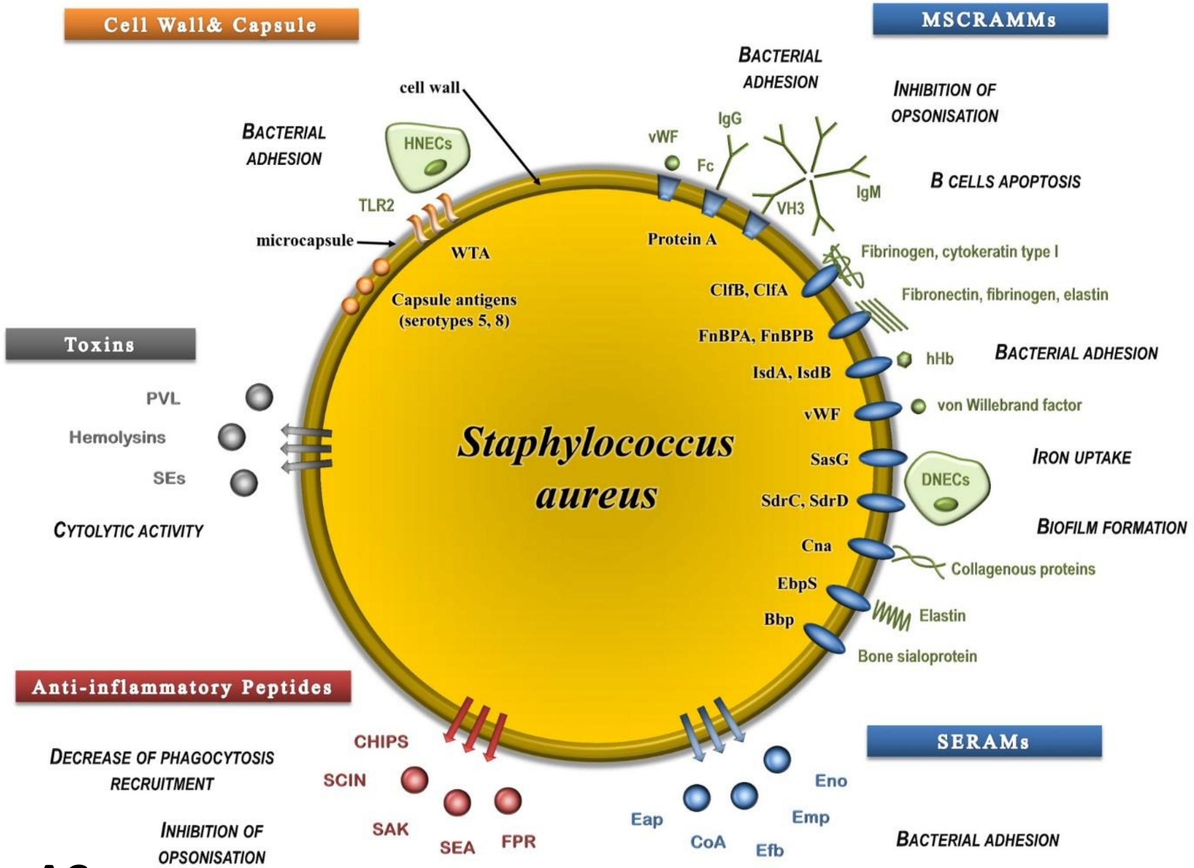
			V710 recipients 15/29 (52%) died in selected sample		Placebo recipients 4/22 (18%) died in selected sample	
			Mortality Rate n/m (%)	Relative Risk of Death (undetectable IL /detectable IL)	Mortality Rate n/m (%)	Relative Risk of Death (undetectable IL /detectable IL)
IL2 Level	Day of vaccination	undetectable	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%)	

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)

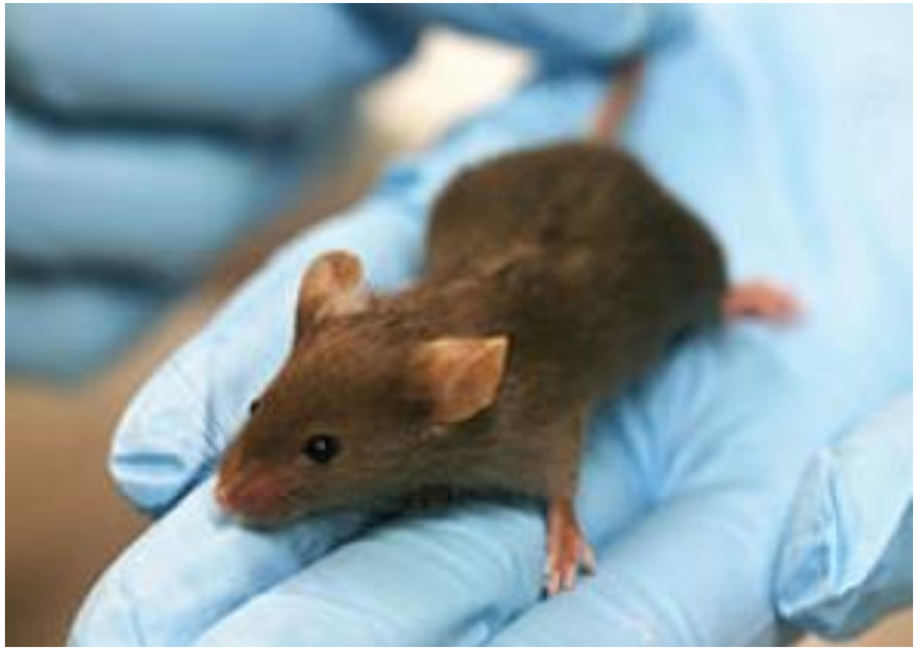
Ces 2 vaccins ne ciblaient que des AG de surface et **engendrait des AC opsonisants (inefficaces)**



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

Ecueils de la recherche vaccinale anti-staphylococcique

- ***Modèles animaux inadaptés…***
  - Tous les vaccins 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

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) Clamping factor A (ClfA) Manganese transporter C	2 polysaccharide conjugates (CP5-CRM & CP8-CRM) + 2 recombinant proteins (ClfA & MntC) Formulation: non-adjuvanted	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
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 en cours

- 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……..il en faudra 6000!
- 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
- Fin de l'étude prévue été 2019
- Efficacité?

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

Pistes pour les vaccins anti *S. aureus* 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 précliniques
- 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

Plan

- Pourquoi a-t-on besoin de vaccins?
- Les infections pouvant être prévenues: état des lieux
  - *Staphylococcus aureus*
  - *Clostridium difficile*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - Les autres
- Les populations cibles

Clostridium difficile: IAS par essence

- *C. difficile* est une bactérie à Gram positif, formant des spores résistantes dans l'environnement
- Pathogénicité en lien avec les toxines A, B ou binaire
- C'est le premier agent responsable de diarrhées associées aux antibiotiques.
- Les facteurs de risque sont l'utilisation d'antibiotiques à large spectre, l'âge supérieur à 65 ans, l'hospitalisation et les comorbidités.
- *C. difficile* est principalement d'origine endogène
- C'est la 1ère cause d'IAS aux USA, la 8ème en Europe, et représentait 3 % des IAS en 2012 dans l'ENP des IN.
- Après un 1er épisode, récidives fréquentes, de PEC difficile
- AC neutralisants anti-toxines ++++

Nissle K,et al., . BMC Geriatr 947 2016;16:185
Magill SS et al., N Engl J Med 2014;370:1198.
Point prevalence survey of healthcare-associated infections-ECDC
Enquête de prévalence 2012 des infections associées aux soins. INVS
Cammarota G,et al.,Gut. 2017 Apr;66(4):569-580.

C. difficile: immunisation active

- SANOFI Pasteur: *Cdiffense*

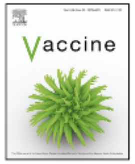
Vaccine 34 (2016) 2170–2178

Contents lists available at ScienceDirect

Vaccine

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

ELSEVIER



Defining the optimal formulation and schedule of a candidate toxoid vaccine against *Clostridium difficile* infection: A randomized Phase 2 clinical trial☆

Guy de Bruyn[a,*], Jamshid Saleh[b], David Workman[c], Richard Pollak[d], Victor Elinoff[e], Neil J. Fraser[f], Gigi Lefebvre[g], Mark Martens[h], Richard E. Mills[i], Richard Nathan[j], Miguel Trevino[k], Martin van Cleeff[l], Ginamarie Foglia[m], Ayca Ozol-Godfrey[a,1], Dhaval M. Patel[a], Patricia J. Pietrobon[a], Richard Gesser[a], On behalf of the H-030-012 Clinical Investigator Study Team

Vaccin toxoïde à base de toxine A et de toxine B inactivées, adjuvanté par l'alun. 3 injections pour obtenir le taux d'AC. Population cible 50-85 ans

Novembre 2017
Following an external analysis of study data the Independent Data Monitoring Committee (IDMC) has recommended that the *Cdiffense* study be stopped for **futility** (non-efficacy). The planned interim analysis by the IDMC of the *Cdiffense* trial concluded that the probability the study would meet its primary objective is low.

C. difficile: immunisation active

- PFIZER*: Clover*

J Pharm Sci. 2016 Jul;105(7):2032-41. doi: 10.1016/j.xphs.2016.04.017. Epub 2016 May 25.

Production and Characterization of Chemically Inactivated Genetically Engineered Clostridium difficile Toxoids.

Vidunas E[1], Mathews A[1], Weaver M[1], Cai P[1], Koh EH[1], Patel-Brown S[1], Yuan H[1], Zheng ZR[1], Carriere M[1], Johnson JE[1], Lotvin J[1], Moran J[2].

Vaccine 34 (2016) 2082–2091

Contents lists available at ScienceDirect

Vaccine

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

ELSEVIER

A phase 1, placebo-controlled, randomized study of the safety, tolerability, and immunogenicity of a *Clostridium difficile* vaccine administered with or without aluminum hydroxide in healthy adults

Eric Sheldon[a], Nicholas Kitchin[b,*], Yahong Peng[c], Joseph Eiden[c], William Gruber[c], Erik Johnson[c], Kathrin U. Jansen[c], Michael W. Pride[c], Louise Pedneault[c]

[a] *Miami Research Associates, 6141 Sunset Drive, Suite 501, South Miami, FL 33143, United States*
[b] *Pfizer Vaccine Research & Development, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS, United Kingdom*
[c] *Pfizer Vaccine Research & Development, 401 North Middletown Road, Pearl River, NY 10965, United States*

En cours:
Étude de phase III randomisée, contrôlée contre placebo, avec observateur en aveugle, visant à évaluer l'efficacité, la sécurité et la tolérance d'un vaccin contre le *Clostridium difficile* chez l'adulte âgé de 50 ans et plus.
Vaccin adjuvanté (hydroxyde d'aluminium)
3 injections
Fin prévue Sept 2020

C. difficile: immunisation active

- Valneva (ex Intercell):
  - Essais de phase 1 et 2 terminés avec un vaccin utilisant une toxine recombinante avec ou sans adjuvant de type hydroxide de l'aluminium (VLA84).
  - La sécurité d'emploi, la tolérance et l'immunogénicité ont été confirmées (sujets sains et des sujets à risque mais en bonne santé (volontaires de plus de 65 ans).
  - Pas de données publiées
- **Ces vaccins n'auront pas d'action préventive sur la colonisation**
- D'autres vaccins, en phases précliniques, devraient, grâce à des Ag toxiniques et de surface agir sur le portage également.

Ghose C, et al., Infect Dis Clin North Am. 2015 Mar;29(1):145-62

Clostridium difficile: immunisation passive

JO

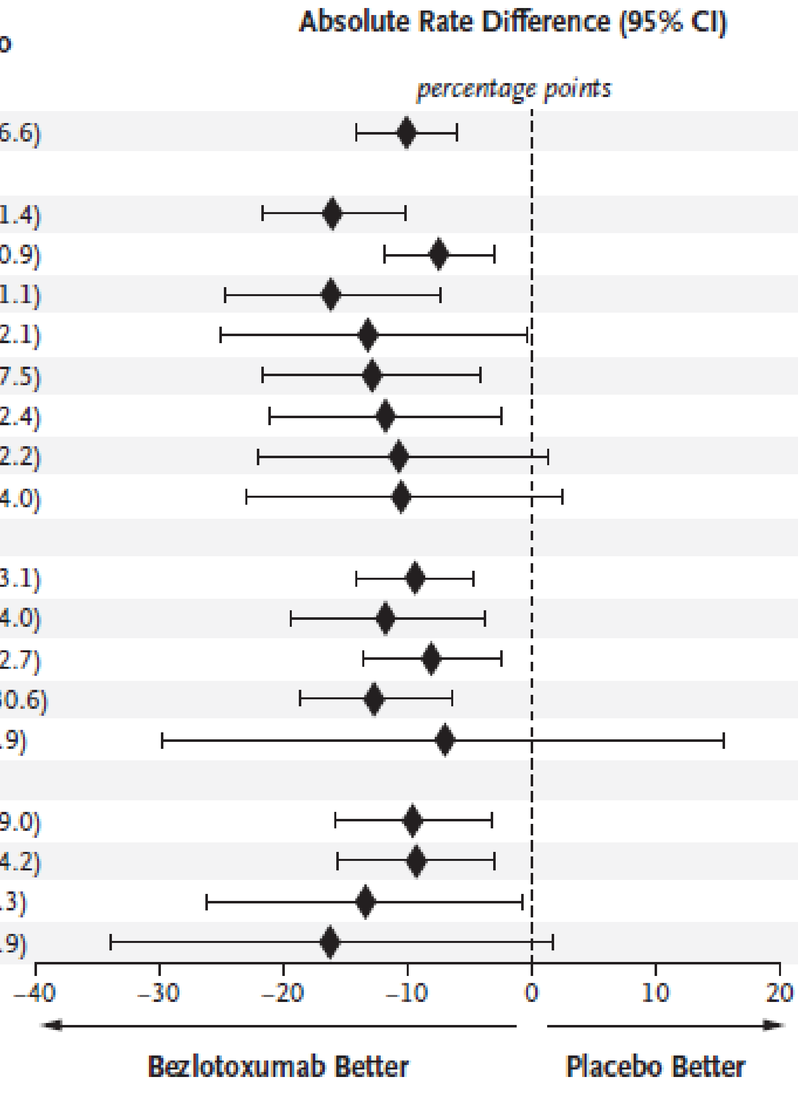
ESTABLISH

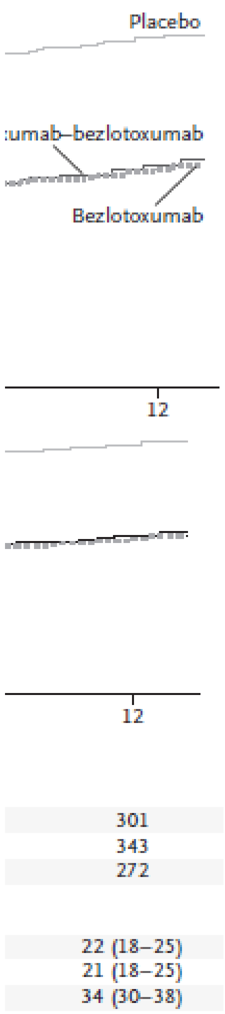
Bezlotoxun

M.H. Wilcox, D.N. C
G. Jenkin, W. Jensen

A

Subgroup	Bezlotoxumab	Placebo	Rate Difference Absolute	Rate Difference Relative
	no./total no. (%)		percentage points	
All participants	129/781 (16.5)	206/773 (26.6)	−10.0	−37.5
Risk factors for recurrence				
≥65 yr of age	60/390 (15.4)	127/405 (31.4)	−16.0	−50.9
No CDI in past 6 mo	75/556 (13.5)	114/545 (20.9)	−7.4	−35.5
≥1 CDI episodes in past 6 mo	54/216 (25.0)	90/219 (41.1)	−16.1	−39.2
≥2 previous CDI episodes ever	29/100 (29.0)	53/126 (42.1)	−13.1	−31.1
Immunocompromised	26/178 (14.6)	42/153 (27.5)	−12.8	−46.8
Severe CDI: Zar score ≥2	13/122 (10.7)	28/125 (22.4)	−11.7	−52.4
027, 078, or 244 strain	22/102 (21.6)	37/115 (32.2)	−10.6	−33.0
027 strain	21/89 (23.6)	34/100 (34.0)	−10.4	−30.6
Stratification variables				
Inpatient	73/530 (13.8)	120/520 (23.1)	−9.3	−40.3
Outpatient	56/251 (22.3)	86/253 (34.0)	−11.7	−34.4
Metronidazole	56/379 (14.8)	85/374 (22.7)	−8.0	−35.0
Vancomycin	67/372 (18.0)	114/373 (30.6)	−12.6	−41.1
Fidaxomicin	6/30 (20.0)	7/26 (26.9)	−6.9	−25.7
Geographic region				
North America	69/354 (19.5)	106/366 (29.0)	−9.5	−32.7
Europe	47/313 (15.0)	71/293 (24.2)	−9.2	−38.0
Asia–Pacific	11/79 (13.9)	21/77 (27.3)	−13.3	−48.9
Latin America	2/30 (6.7)	8/35 (22.9)	−16.2	−70.8





Clostridium difficile: immunisation passive

Clinical Infectious Diseases

MAJOR ARTICLE

Bezlotoxumab for Prevention of Recurrent *Clostridium difficile* Infection in Patients at Increased Risk for Recurrence

Dale N. Gerding,[1] Ciaran P. Kelly,[2] Galia Rahav,[3] Christine Lee,[4,5] Erik R. Dubberke,[6] Princy N. Kumar,[7] Bruce Yacyshyn,[8] Dina Kao,[9] Karen Eves,[10] Misoo C. Ellison,[11] Mary E. Hanson,[12] Dalya Guris,[10] an

[1]Department of Veterans Affairs, Edward Hines Jr Veterans Affairs H
Massachusetts; [3]Infectious Diseases, Sheba Medical Center, Tel Has
University of British Columbia, Vancouver, and [5]McMaster University
[7]Division of Infectious Diseases and Travel Medicine, Georgetown U
Medicine, Division of Gastroenterology, University of Alberta, Edmon
and Medical Publications, Infectious Diseases, Merck & Co, Inc, Ken

Background. Bezlotoxumab is a human monoclonal antibody against *Clostridium difficile* toxin B indicated to prevent *C. difficile* infection (CDI) recurrence (rCDI) in adults at high risk for rCDI. This post hoc analysis of pooled monocolonal antibodies for *C. difficile* therapy (MODIFY) I/II data assessed bezlotoxumab efficacy in participants with characteristics associated with increased risk for rCDI.

Methods. The analysis population was the modified intent-to-treat population who received bezlotoxumab or placebo (n = 1554) by risk factors for rCDI that were prespecified in the statistical analysis plan: age ≥65 years, history of CDI, compromised immunity, severe CDI, and ribotype 027/078/244. The proportion of participants with rCDI in 12 weeks, fecal microbiota transplant procedures, 30-day all cause and CDI-associated hospital readmissions, and mortality at 30 and 90 days after randomization were presented.

Results. The majority of enrolled participants (75.6%) had ≥1 risk factor; these participants were older and a higher proportion had comorbidities compared with participants with no risk factors. The proportion of placebo participants who experienced rCDI exceeded 30% for each risk factor compared with 20.9% among those without a risk factor, and the rCDI rate increased with the number of risk factors (1 risk factor: 31.3%; ≥3 risk factors: 46.1%). Bezlotoxumab reduced rCDI, fecal microbiota transplants, and CDI-associated 30-day readmissions in participants with risk factors for rCDI.

Conclusions. The risk factors prespecified in the MODIFY statistical analysis plan are appropriate to identify patients at high risk for rCDI. While participants with ≥3 risk factors had the greatest reduction of rCDI with bezlotoxumab, those with 1 or 2 risk factors may also benefit.

Clinical Trials Registration. NCT01241552 (MODIFY I) and NCT01513239 (MODIFY II).

Keywords. *C. difficile* infection; CDI; recurrence; bezlotoxumab.

Plan

- Pourquoi besoin de vaccins?
- Les infections pouvant être prévenues: état des lieux
  - *Staphylococcus aureus*
  - *Clostridium difficile*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - Les autres
- Les populations cibles

E. coli: immunisation active

- *E. coli*, est comme *S. aureus* également une bactérie commensale de l'Homme
- La stratégie de développement vaccinal est différente, profils d'*E. coli* responsables d'infections « Extraintestinal pathogenic Escherichia coli (ExPEC)»
- Plusieurs essais de phase 1 ou phase 1/2 sont actuellement en cours dans la prévention des diarrhées à *E. coli* enterotoxinogène ou des infections urinaires à répétitions dues à *E. Coli* uropathogène.
- Vaccin très attendu car *E. coli* serait associé à la moitié de la résistance aux antibactériens

Poolman, J.T. et al. *The Journal of infectious diseases* **213**, 6-13 (2016).

E. coli: immunisation active

Safety, immunogenicity, and preliminary clinical efficacy of a vaccine against extraintestinal pathogenic *Escherichia coli* in women with a history of recurrent urinary tract infection: a randomised, single-blind, placebo-controlled phase 1b trial

Angela Huttner, Christoph Hatz, Germie van den Dobbelsteen, Darren Abbanat, Alena Hornacek, Rahel Frölich, Anita M Dreyer, Patricia Martin, Todd Davies, Kellen Fae, Ingrid van den Nieuwenhof, Stefan Thoelen, Serge de Vallière, Anette Kuhn, Enos Bernasconi, Volker Viereck, Tilemachos Kavvadias, Kerstin Kling, Gloria Ryu, Tanja Hülder, Sabine Gröger, David Scheiner, Cristina Alaimo, Stephan Harbarth, Jan Poolman, Veronica Gambillara Fonck

Lancet Infect Dis 2017; 17: 528–37
Published Online February 23, 2017
http://dx.doi.org/10.1016/S1473-3099(17)30108-1
See Comment page 467

Infection Control Program, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland (A Huttner MD, S Harbarth MD); Epidemiology, Biostatistics and Prevention Institute, Zurich University, Zurich, Switzerland (Prof C Hatz MD); Swiss Tropical and Public Health Institute, Basel University, Basel, Switzerland (Prof C Hatz, K Kling MD); Bacterial Vaccines Discovery & Early Development, Janssen Vaccines and Prevention, Leiden, Netherlands (G van den Dobbelsteen PhD, K Fae PhD, I van den Nieuwenhof PhD, S Thoelen MD, J Poolman PhD); Janssen Research and Development, Raritan, NJ, USA (D Abbanat PhD, T Davies PhD); LimmaTech Biologics, Schlieren, Switzerland (A Hornacek MSc, R Frölich BSc, A M Dreyer PhD, P Martin PhD

Summary

Background *Escherichia coli* infections are increasing worldwide in community and hospital settings. The *E coli* O-antigen is a promising vaccine target. We aimed to assess the safety and immunogenicity of a bioconjugate vaccine containing the O-antigens of four *E coli* serotypes (ExPEC4V).

Methods In this multicentre phase 1b, first-in-human, single-blind, placebo-controlled trial, we randomly assigned (1:1) healthy adult women with a history of recurrent urinary tract infection (UTI) to receive a single injection of either intramuscular ExPEC4V or placebo. The primary outcome was the incidence of adverse events among vaccine and placebo recipients throughout the study. Secondary outcomes included immunogenicity and antibody functionality, and the incidence of UTIs caused by *E coli* vaccine serotypes in each group. This study is registered with ClinicalTrials.gov, number NCT02289794.

Findings Between Jan 20, 2014, and Aug 27, 2014, 93 women received target-dose ExPEC4V and 95 received placebo. The vaccine was well tolerated: no vaccine-related serious adverse events occurred. Overall, 56 (60%) target-dose vaccines and 47 (49%) placebo recipients experienced at least one adverse event that was possibly, probably, or certainly related to injection. Vaccination induced significant IgG responses for all serotypes: at day 30 compared with baseline, O1A titres were 4·6 times higher, O2 titres were 9·4 times higher, O6A titres were 4·9 times higher, and O25B titres were 5·9 times higher (overall $p<0·0001$). Immune responses persisted at 270 days but were lower than those at 30 days. Opsonophagocytic killing activity showed antibody functionality. No reduction in the incidence of UTIs with 10^3 or more colony-forming units per mL of vaccine-serotype *E coli* was noted in the vaccine compared with the placebo group (0·149 mean episodes *vs* 0·146 mean episodes; p=0·522). In post-hoc exploratory analyses of UTIs with higher bacterial counts ($\geq 10^5$ colony-forming units per mL), the number of vaccine serotype UTIs did not differ significantly between groups (0·046 mean episodes in the vaccine group *vs* 0·110 mean episodes in the placebo group; p=0·074). However, significantly fewer UTIs caused by *E coli* of any serotype were noted in the vaccine group compared with the placebo group (0·207 mean episodes *vs* 0·463 mean episodes; p=0·002).

Interpretation This tetravalent *E coli* bioconjugate vaccine candidate was well tolerated and elicited functional antibody responses against all vaccine serotypes. Phase 2 studies have been initiated to confirm these findings.

Funding GlycoVaxyn, Janssen Vaccines

- GlycoVaxyn, Janssen vaccines
- Vaccin ciblant l'antigène O de *E. coli des* sérotypes O1A,O2, O6A, et O25B les plus fréquemment associés à des IU en Suisse
- Conjugué à l'exoprotéine A de *P. aeruginosa*
- Processus de bioconjugaison
- Phase II en cours
- **Utilité dans la prévention des IAS???**

E. coli: immunisation active

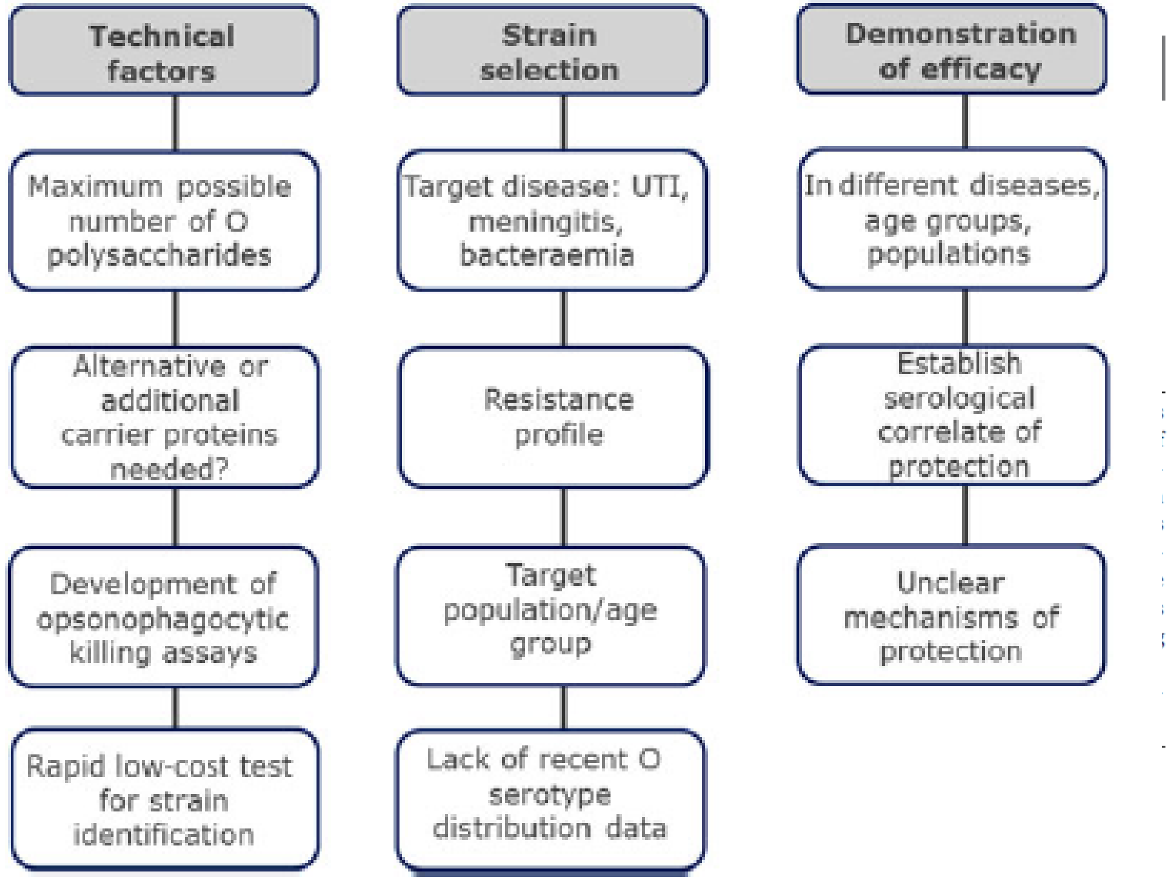


Figure 5. Challenges to extraintestinal pathogenic *Escherichia coli* vaccine development. Individual challenges to vaccine development need to be surmounted to achieve successful technical development, appropriate strain selection, and demonstration of efficacy in the target population. Abbreviation: UTI, urinary tract infection.

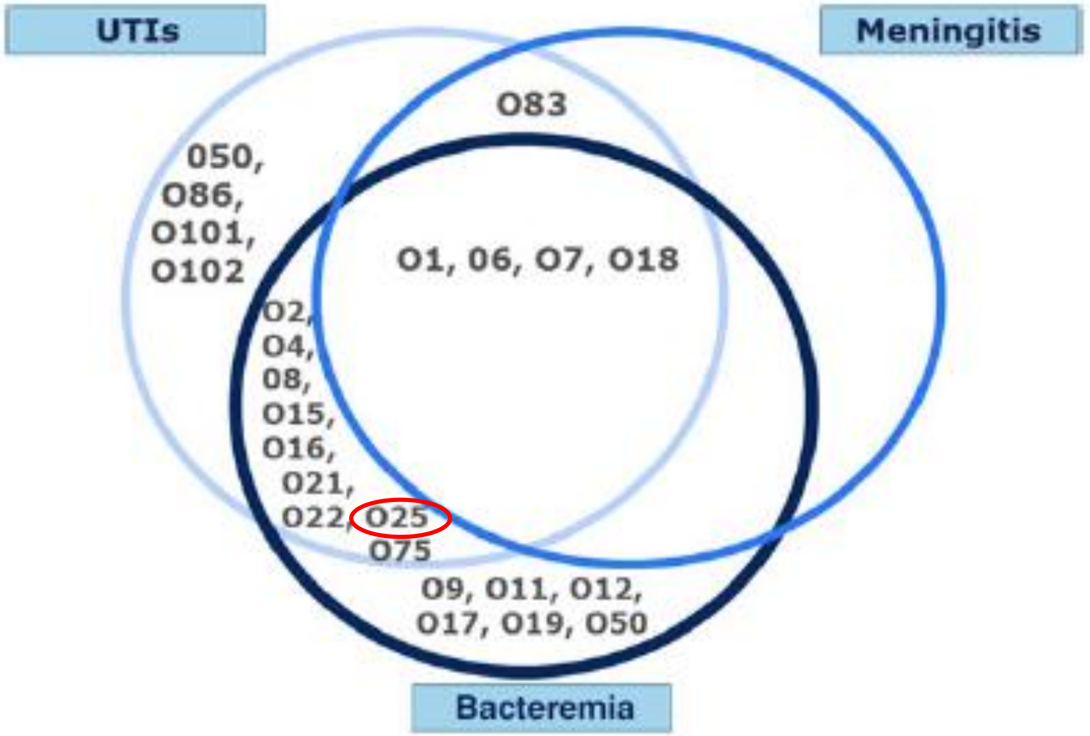


Figure 3. *Escherichia coli* O serotypes causing extraintestinal infections. Data are from the article by Orskov et al [41]. Abbreviation: UTIs, urinary tract infections.

Plan

- Pourquoi a-t-on besoin de vaccins?
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  - *Pseudomonas aeruginosa*
  - Les autres
- Les populations cibles

P. aeruginosa: immunisation active

- *P. aeruginosa*: difficulté de PEC, ATB résistance
- Nombreux essais vaccinaux, au delà d'une phase I.
- Valneva a développé un vaccin ciblant 2 protéines externes de la membrane (outer membrane proteins) OprF, et OprI, en réanimation
- Après une phase II encourageante, une phase II/III n'a pas confirmé les résultats d'efficacité. (données non publiées).
- Données orientant vers le besoin d'une réponse humorale et cellulaire
- Données précliniques encourageantes pour d'autres vaccins (voie muqueuse, killed metabolic active *P aeruginosa* vaccine…)

Priebe GP et al., Expert Rev Vaccines 2014;13:507—19.
Grimwood K, et al., Hum Vaccin Immunother. 2015;11(1):14-20
Meynet E, et al.,Vaccine. 2018 Mar 27;36(14):1893-1900

P. aeruginosa: immunisation passive

- Essais de phase I ou II en cours ou terminés mais sans résultats pour des Ac monoclonaux dans le **traitement** des infections à *P.aeruginosa* chez des patients de réanimation.
  - Panobacumab (Kenta Biotech, Zürich-Schlieren, Switzerland) AC monoclonal IgM/κ- anti LPO-*O*-polysaccharide de *P. aeruginosa* serotype IATS O11
  - KB001-A Ac monoclonal ciblant la protéine PcrV (T3SS): en réanimation et en cas de mucoviscidose
  - Ac monoclonal anti alginate de *P. aeruginosa* (Aerucin®)*:* phase 2 en cours

Vincent JL.. Future Microbiol. 2014;9(4):457-63
Clinical trial.gov

Plan

- Pourquoi a-t-on besoin de vaccins?
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  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - *Les autres*
- Les populations cibles

Les autres……

- poly-b-1,6-N-acetylglucosamine (PNAG):

Taylor & Francis
Taylor & Francis Group

Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: http://www.tandfonline.com/loi/ierv20

The exceptionally broad-based potential of active and passive vaccination targeting the conserved microbial surface polysaccharide PNAG

David Skurnik, Colette Cywes-Bentley & Gerald B. Pier

Données *in vitro* et *in vivo* y compris sur BMR

A. Organisms verified to produce PNAG by chemical, genetic and immunologic criteria
Actinobacillus pleuropneumoniae
Acinetobacter baumannii
Aggregatibacter actinomycetemcomitans
Bacillus subtilis
Escherichia coli
Staphylococcus aureus
Staphylococcus epidermidis
Vibrio parahemolyticus
Yersinia pestis
B. Organisms verified to produce PNAG by genetic and immunologic criteria
Bordetella pertussis
B. parapertussis
B. bronchiseptica
Burkholderia cepacia complex
Enterobacter cloacae
Klebsiella pneumoniae
Shigella spp.
Stenotrophomonas maltophilia
Yersinia entercolitica
Yersinia pseudotuberculosis
C. Organisms verified to produce PNAG by immunologic criteria
Bacteroides fragilis
Candida albicans
Hemophilus ducreyi
Hemophilus influenzae
Listeria monocytogenes
Mycobacterium tuberculosis
Neisseria gonorrhoeae
Neisseria meningitides
Streptococcus pyogenes
Streptococcus agalactiae
Streptococcus pneumoniae
Plasmodium spp.
Trichmonas vaginalis

SCIENTIFIC REPORTS

OPEN

Received: 25 February 2016
Accepted: 27 October 2016
Published: 16 November 2016

Employing *Escherichia coli*-derived outer membrane vesicles as an antigen delivery platform elicits protective immunity against *Acinetobacter baumannii* infection

OPEN

Experimental & Molecular Medicine (2015) 47, e183; doi:10.1038/emm.2015.59

www.nature.com/emm

ORIGINAL ARTICLE

Vaccination with *Klebsiella pneumoniae*-derived extracellular vesicles protects against bacteria-induced lethality via both humoral and cellular immunity

Won-Hee Lee[1], Hyun-Il Choi[1], Sung-Wook Hong[1], Kwang-sun Kim[2], Yong Song Gho[1] and Seong Gyu Jeon[3]

PNAS

Immunization with outer membrane vesicles displaying conserved surface polysaccharide antigen elicits broadly antimicrobial antibodies

Taylor C. Stevenson[a], Colette Cywes-Bentley[b], Tyler D. Moeller[c], Kevin B. Weyant[c], David Putnam[a,c], Yung-Fu Chang[d], Bradley D. Jones[e,f], Gerald B. Pier[b], and Matthew P. DeLisa[a,c,1]

[a]Nancy E. and Peter C. Meinig School of Biomedical Engineering, Cornell University, Ithaca, NY 14853; [b]Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115; [c]Robert Frederick Smith School of Chemical and Biomolecular Engineering, Cornell University, Ithaca, NY 14853; [d]Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853; [e]Department of Microbiology, University of Iowa, Iowa City, IA 52242; and [f]Genetics Program, University of Iowa, Iowa City, IA 52242

Dans tous les cas, besoin de données épidémiologiques réelles, récentes

Vaccine 35 (2017) 6934–6937

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ELSEVIER

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

CrossMark

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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.

		Statistical power		
SASSI rate (%)	VE (%)	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
[illegible]	[illegible]	650	1322	3987
[illegible]	[illegible]	109	199	654
[illegible]	[illegible]	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.

Projet COMBACTE actuel pour mieux définir les patients à risque en chirurgie stratifié selon portage: ASPIRE ICU

Plan

- Pourquoi a-t-on besoin de vaccins?
- Les infections pouvant être prévenues: état des lieux
  - *Staphylococcus aureus*
  - *Clostridium difficile*
  - *Escherichia coli*
  - *Pseudomonas aeruginosa*
  - Les autres
- Les populations cibles

Les populations cibles: les patients

- Patients à risque sont variables selon le pathogène+++
  - Crucial de bien définir la cible pour chaque vaccin
- Cependant les FR classiques d'IAS:
  - Sujets âgés
  - Immunodéprimés
  - Séjour hospitalier prolongé
  - Hospitalisation en réanimation
  - Présence de matériel invasif (cathéters etc…)

➡ Immunosénescence
Réponse immune altérée (immunosuppresseurs etc..)

} Challenge pour obtenir une réponse immune efficace si immunisation active

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+++

⋮

SHORT REPORT

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

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Keywords: orthopedic surgery, *Staplylococcus 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***…..

Les populations cibles: les patients

- Choisir les patients vraiment à risque: données épidémiologiques fiables
- Choisir le bon moment pour la vaccination
  - Pré-exposition: ex chirurgie, antibiothérapie prolongée, institutionalisation etc….
- Encore faudra-t-il que les patients acceptent!
  - Étude en chirurgie orthopédique:
    - acceptabilité d'un vaccin anti-*S. aureus* hypothétique*: 51%*
    - acceptabilité d'un vaccin anti-*C. difficile* hypothétique: 22,6%
    - En qualitatif, ne considèrent pas que cela leur incombe

Les populations cibles: les soignants?

- C’est déjà le cas pour beaucoup de vaccins
- Rôle d’immunité de groupe?
- Bien que IAS soient souvent endogènes, portage asymptomatique chez les soignants possible et à l’origine de transmission aux patients
- Dans l’objectif de protéger les soignants
- A condition qu’ils acceptent!

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Take home messages

- NE PAS OUBLIER LES VACCINS DÉJÀ UTILES POUR REDUIRE LES IAS: chez les patients, chez les soignants!
- Ne pas oublier les mesures existantes efficaces ayant déjà fait la preuve de leur efficacité
- Face à l'antibiorésistance , immunisation active ou passive sont des stratégies utiles+++
- Probablement encore un long chemin pour la plupart des IAS
- Encore beaucoup d'inconnues: réponse immune, véritable épidémiologie etc…
- Hésitation vaccinale?

Merci de votre attention

Merci à tous!

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