SERVIZO GALEGO de SAÚDE | Complexo Hospitalario Universitario A Coruña A Coruña

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

inibic instituto de investigación biomédica de a coruña

Otra forma de luchar contra la resistencia bacteriana

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Hospital Universitario La Coruña

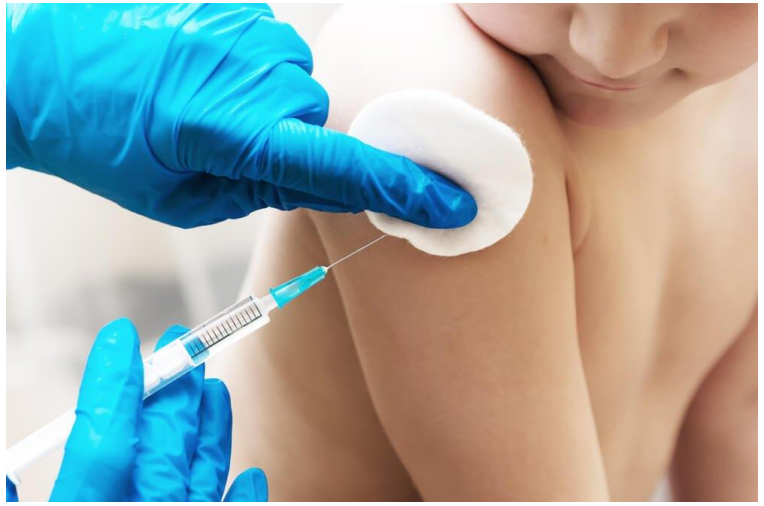
Profesor Asociado Microbiología
USC

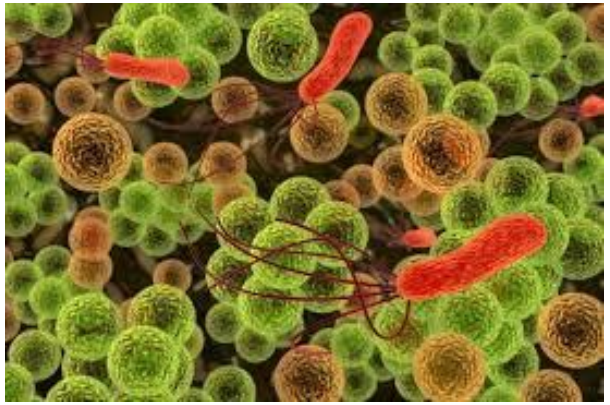
XIV JORNADAS DE VACUNAS AEP

OURENSE, 14 Y 15 DE ABRIL DE 2023

Vacunas bacterianas

i. Conceptos básicos: vacunación vs antibioterapia
ii. Vacunas frente grupo ESKAPEE
iii. Población diana o de riesgo





i. Conceptos básicos: vacunación vs antibioterapia

Available online at www.sciencedirect.com
SciVerse ScienceDirect
Current Opinion in Microbiology

Vaccines and antibiotic resistance

Ravi PN Mishra, Ernesto Oviedo-Orta, Prachi Prachi, Rino Rappuoli and Fabio Bagnoli

Current Opinion in Microbiology 2012, **15**:596–602

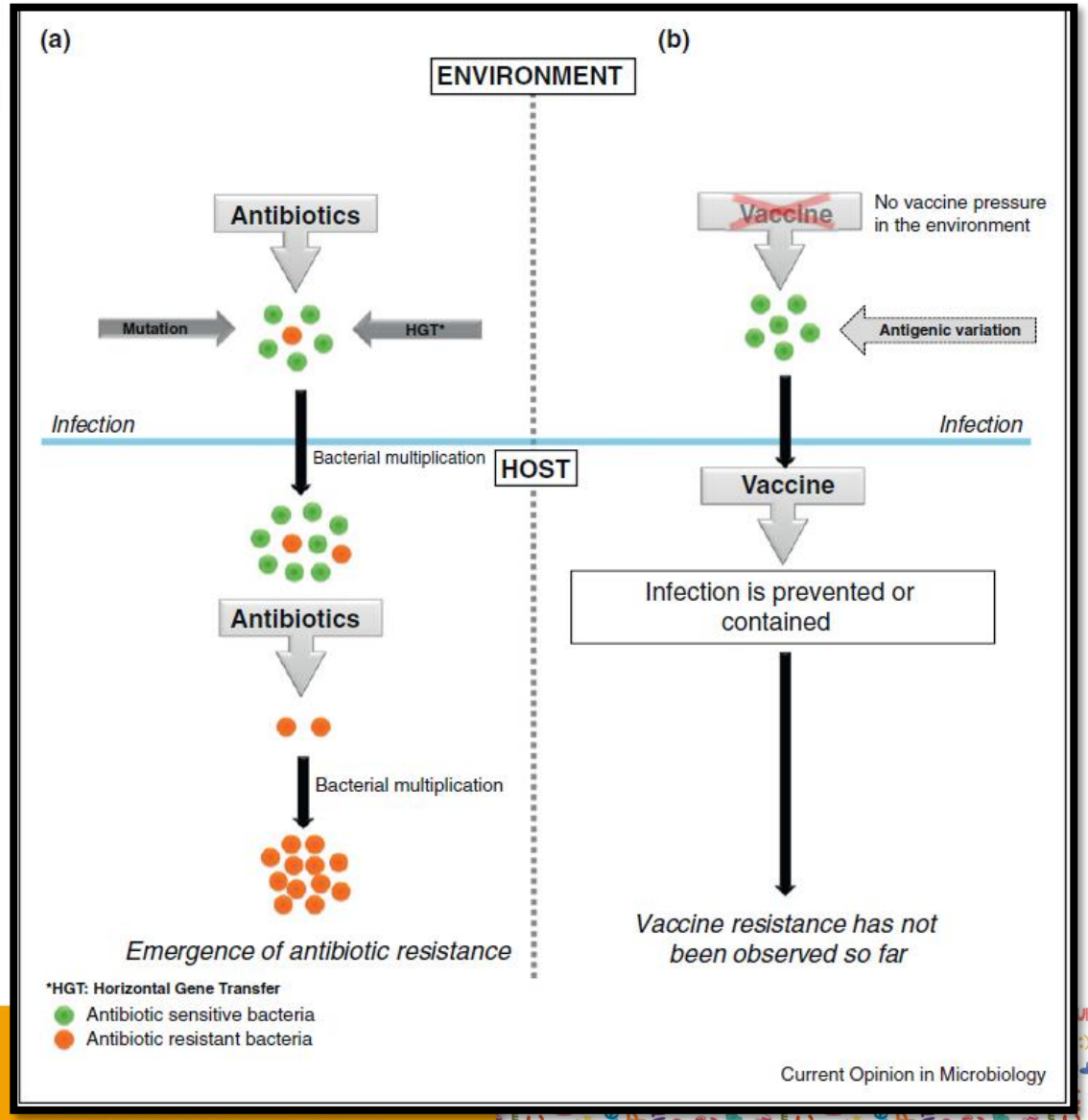


Table 1

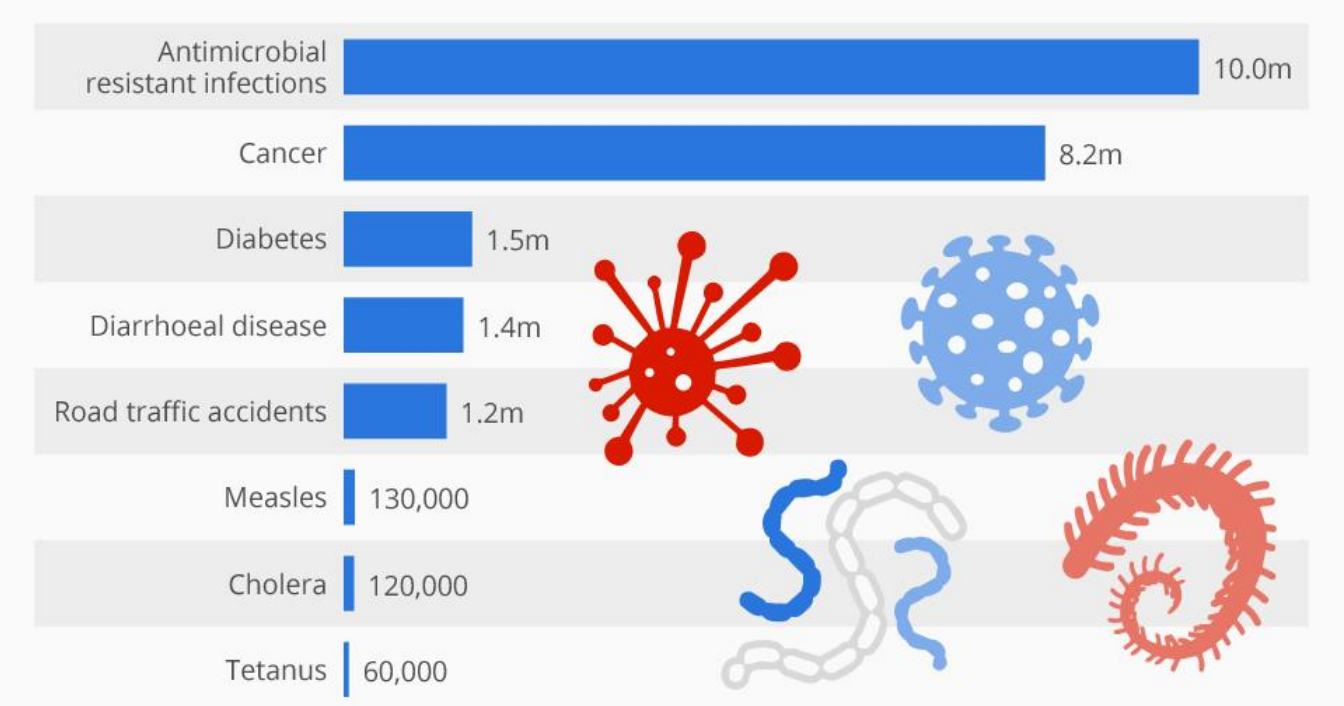
Major features of antibiotics and vaccines

Relevant features	Antibiotics	Vaccines	Reference
Therapeutic/prophylactic	Mostly therapeutic	Mostly prophylactic	See text
Coverage and specificity (different bacterial species)	Broad, indiscriminate	Narrow, very specific	See text
Resistance emergence	Common	Not observed	See text
Selective pressure	High	Low	Figure 1
Time to develop resistant strains	Short (emergence of resistance during therapy)	Not observed	Table 2
Durability	Restricted to the time of treatment	Duration of protection persists from several months to life-long	[15,16]
Treatment/prevention of viral infections	No	Yes	See text
Herd or community effect	No	Yes	See text
Prevention of perinatal infections	Yes	Yes (maternal immunity)	[17]
Prevention of cancer	No	Yes (prevention of HBV and HPV associated cancers)	[18]
Prevention of infections in cancer patients	Yes (e.g. lymphomas)	No	See text
Prevention of infections in immune compromised patients	Yes (e.g. neutropenia)	Yes (by herd immunity)	See text
Prevention of surgical-associated infections	Yes	No	See text
Cost	From few $ to thousands $ (for one therapy, depends on the length of the therapy)	From few $ to <200 $ (1 or few immunizations can be sufficient for lifelong protection)	[http://www.cdc.gov/vaccines/programs/vfc/cdc-vac-price-list.htm]

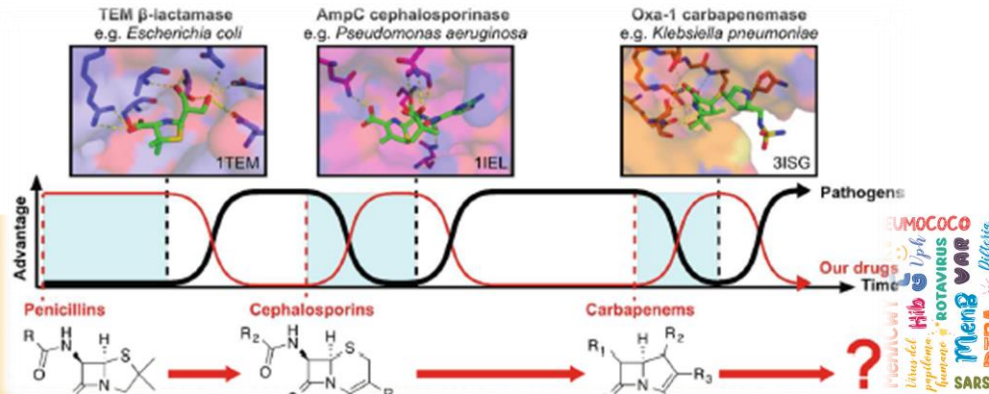
Mishra et al 2012

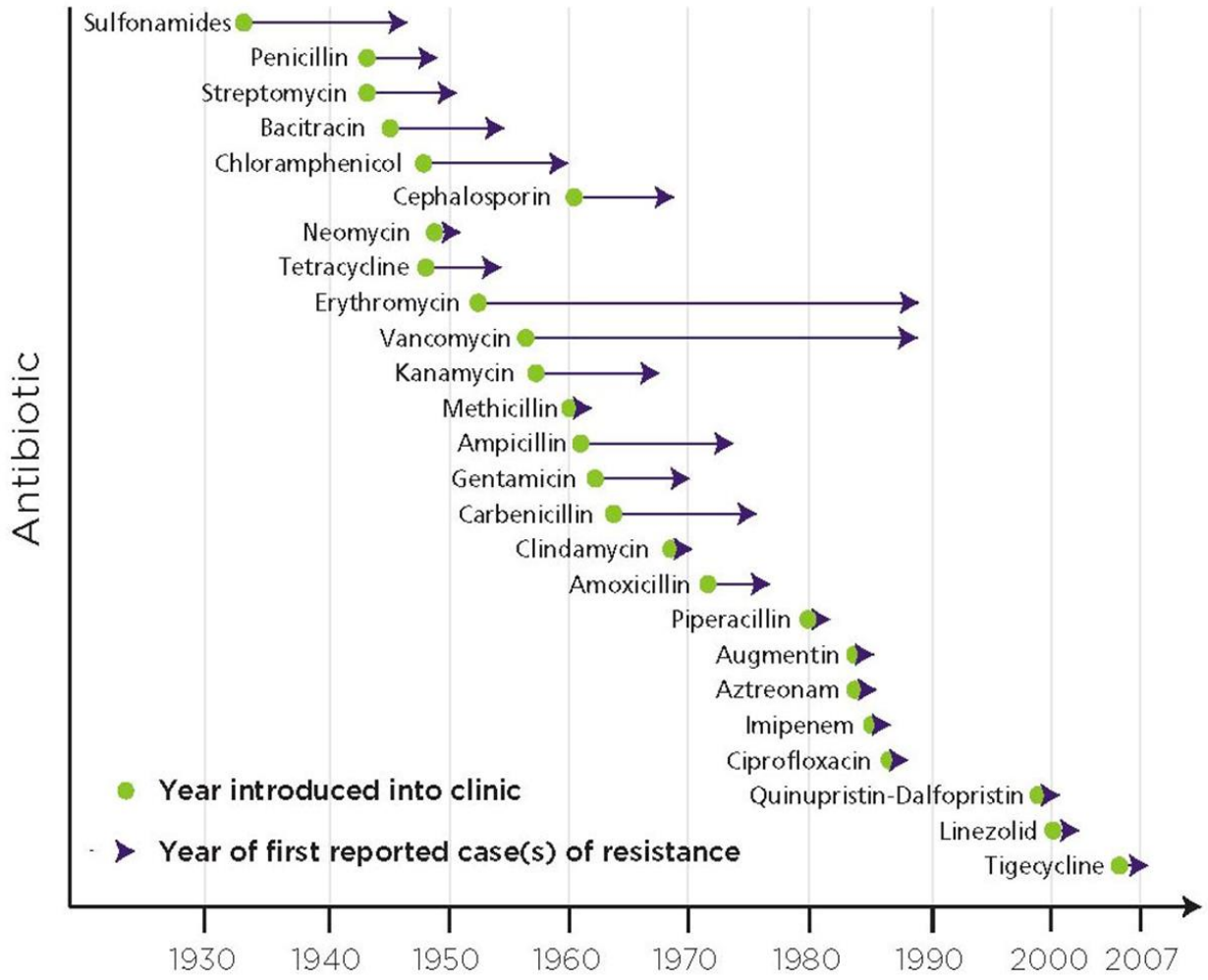
The antibiotic resistance crisis

1.9 million deaths annually due to antibiotic resistant infections



Antimicrobial resistance collaborators. Lancet, 2022.
http://amr-review.org/





Pray, L Antibiotic R&D.

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

VACCINES AND ALTERNATIVE APPROACHES: REDUCING OUR DEPENDENCE ON ANTIMICROBIALS

THE REVIEW ON ANTIMICROBIAL RESISTANCE

CHAIRED BY JIM O'NEILL

FEBRUARY 2016

VACCINES CAN REDUCE ANTIBIOTIC USE IN HUMANS

Reduce the number of bacterial infections that need antibiotics

Reduce the number of drug-resistant infections

Reduce the number a of viral infections for which antibiotics are unnecessarily given

Vaccines can reduce Antibiotic use in Humans

XIV JORNADAS DE VACUNAS AEP

OURENSE, 14 Y 15 DE ABRIL DE 2023

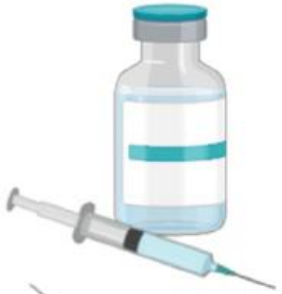
The antibiotic resistance crisis

Promote the development of new antibiotic classes.

+

Develop non-antibiotic approaches for resistant infections.

↓



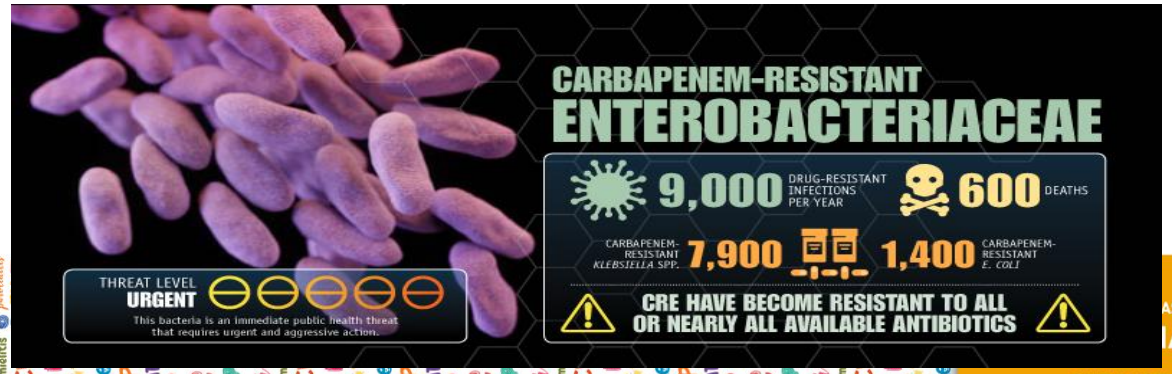
VACCINES

HAZARD LEVEL
URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

http://www.cdc.gov/



	Phase 1	Phase 2	Phase 3	In use
Neisseria gonorrhoeae	X	X	X	X
Clostridium difficile	X	2	1	X
*E. coli**	2	X	X	X
*Klebsiella**	X	X	X	X

The vaccine pipeline for MDR bacteria

There are no vaccines for preventing infections caused by MDR Gram-negative species.

Updated from Timothy Cooke, BIO Convention

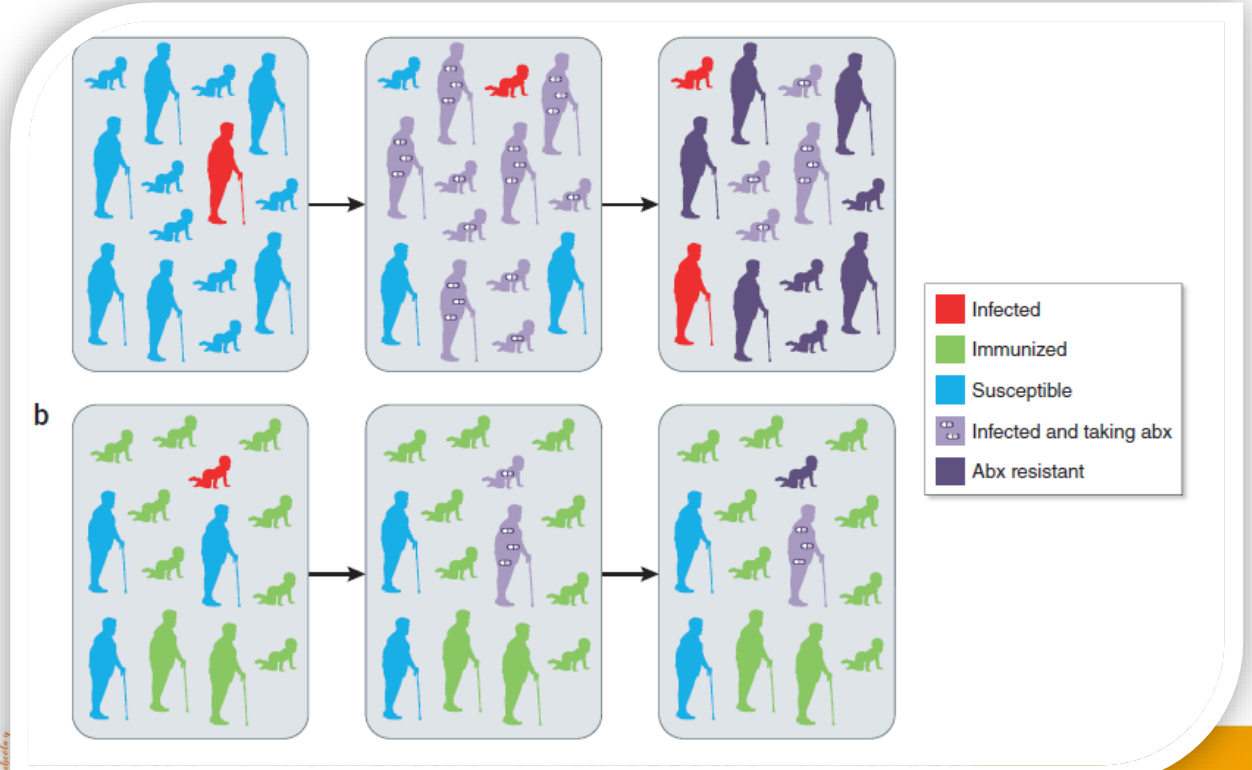
Vaccines against resistant bacteria. Industry pipeline						
TARGET	CLINICAL STAGE PIPELINE				Registered	Expected New*
	Phase 1	Phase 2	Phase 3	Total		
Candida	0	1	0	1	0	0.3
Clostridium difficile	0	1	1	2	0	0.9
Escherichia coli	1	1	0	2	0	0.5
Gorup B Streptoccocus	1	1	0	2	0	0.5
Shigella	0	1	0	1	0	0.6
Stapylococcus aureus	1	1	1	3	0	1.1
Streptococcus pneumoniae	1	3	0	4	3	1.1
Mycobacterium tuberculosis	0	2	0	2	1	0.6
Acinetobacter baumannii	**0**	**0**	**0**	**0**	**0**	**0**
Pseudomonas aeruginosa	**0**	**0**	**0**	**0**	**0**	**0**
Klebsiella pneumoniae	1	**0**	**0**	**0**	**0**	**0**
Total	4	11	2	17	4	5.6

The role of vaccines in preventing bacterial antimicrobial resistance

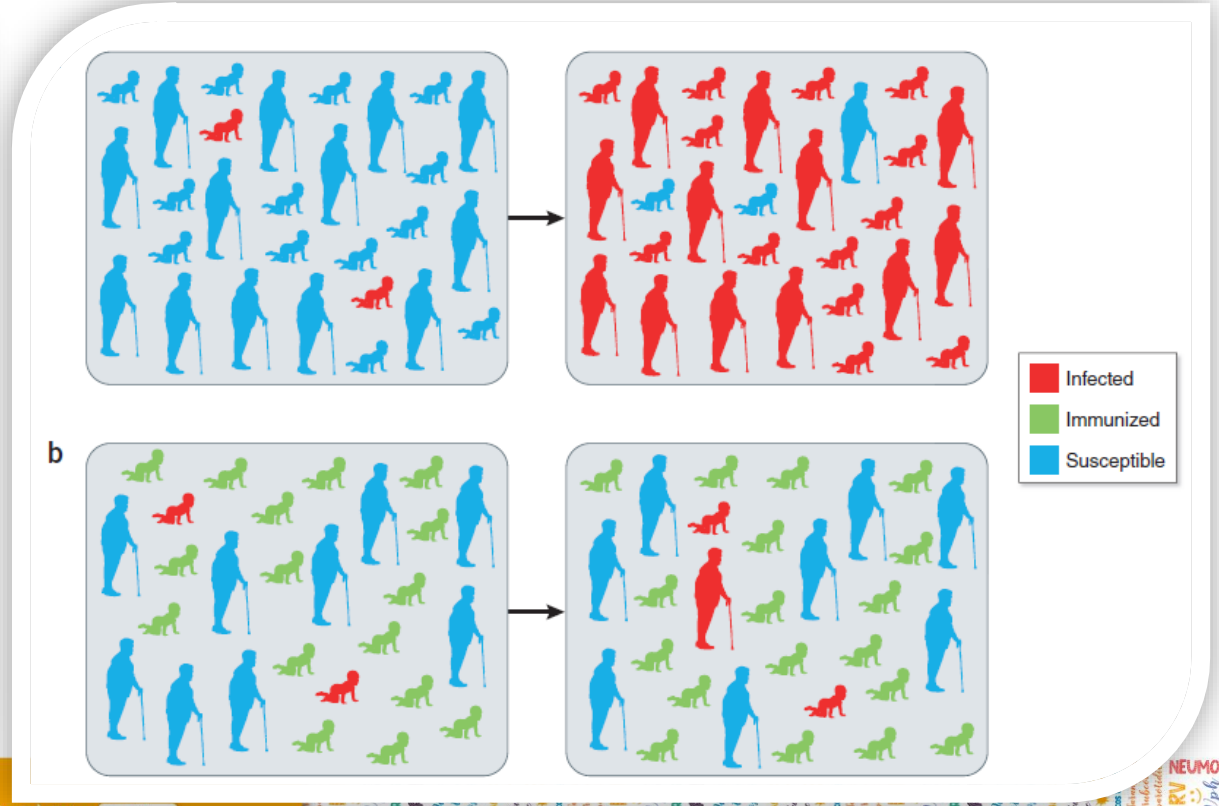
Kathrin U Jansen, Charles Knirsch & Annaliesa S Anderson

nature medicine

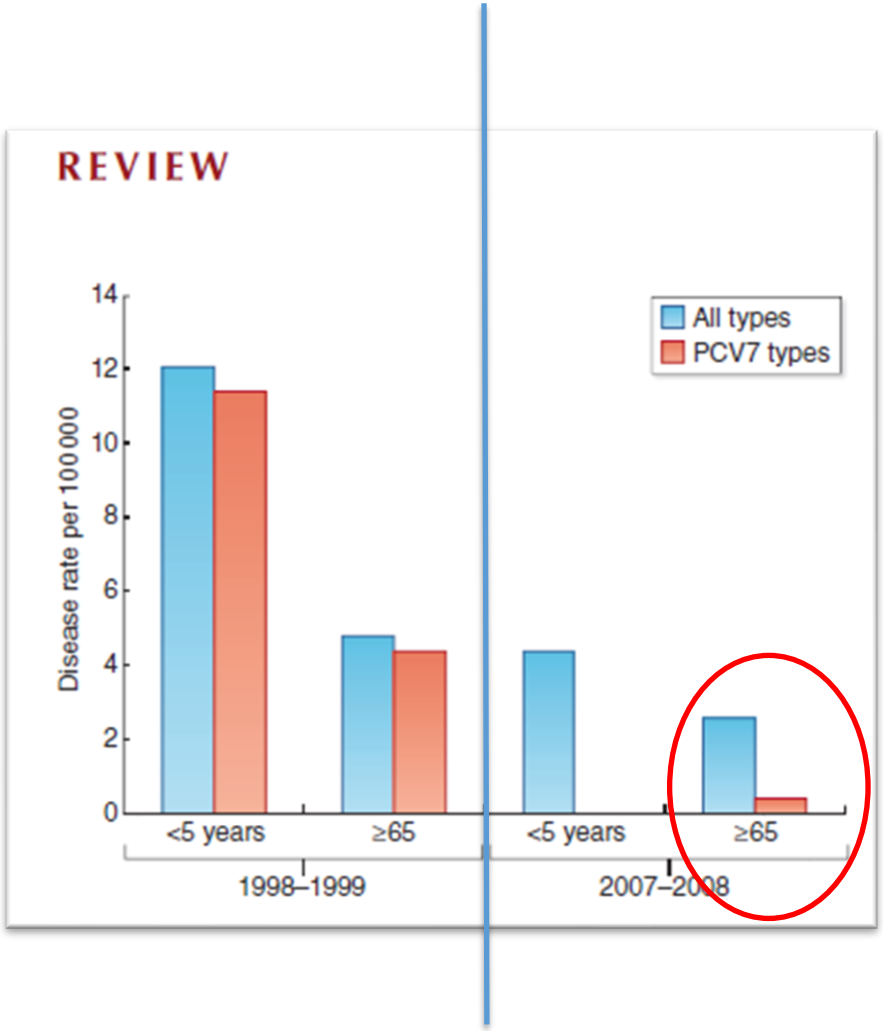
VOLUME 24 | NUMBER 1 | JANUARY 2018 NATURE MEDICINE



Inmunidad



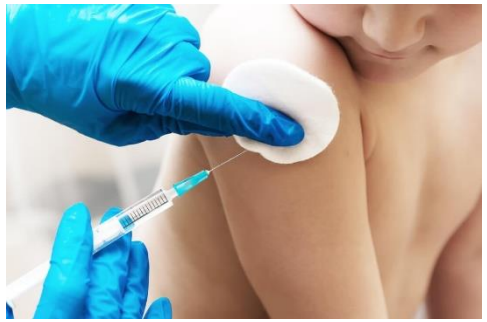
Inmunidad de grupo o rebaño



Jansen et al. 2018

Reduction of AMR after broad rollout of pneumococcal conjugate vaccine

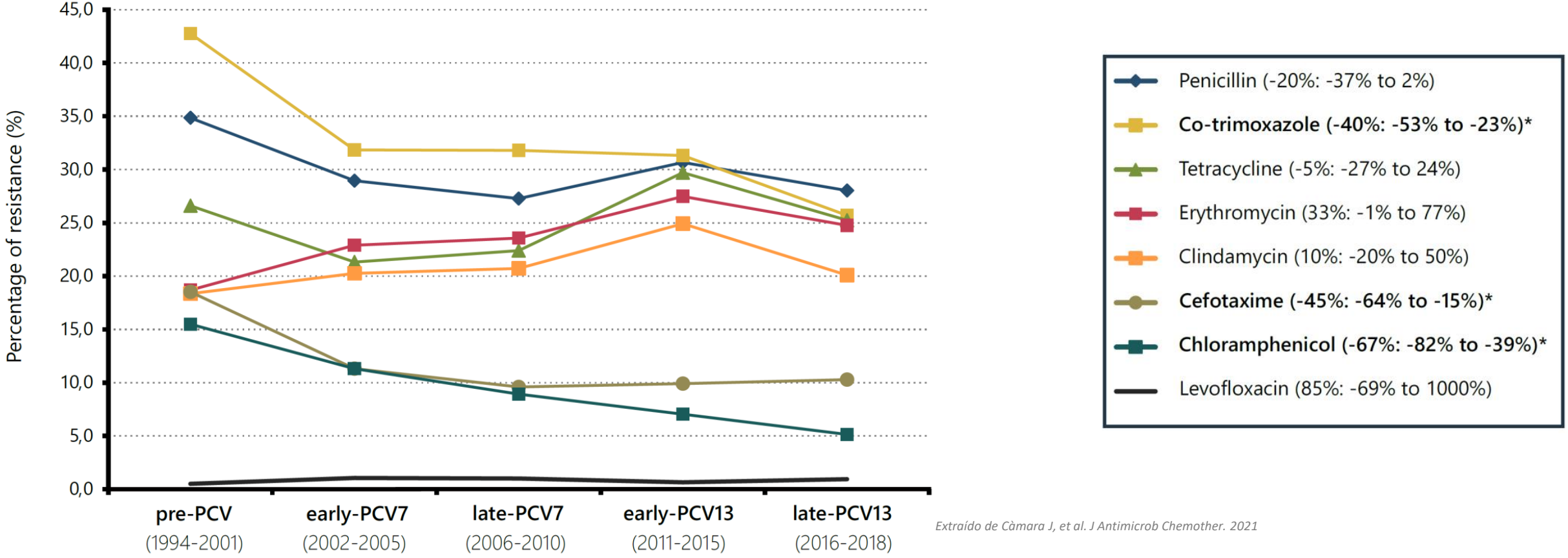
The impact of PCV7 on disease rates of *S. pneumoniae* strains not susceptible to penicillin in children under 5 years of age and the indirect effect (herd effect) on the elderly (>65 years old) is shown, comparing incidence in the time frame before PCV7 implementation (1998-1999) to that in the frame after vaccine implementation (2007-2008)



Conceptos básicos: vacunación vs antibioterapia

El caso del neumococo en España

Evolución de la resistencia antibiótica en cepas de neumococo que causan enfermedad invasiva en adultos durante 25 años



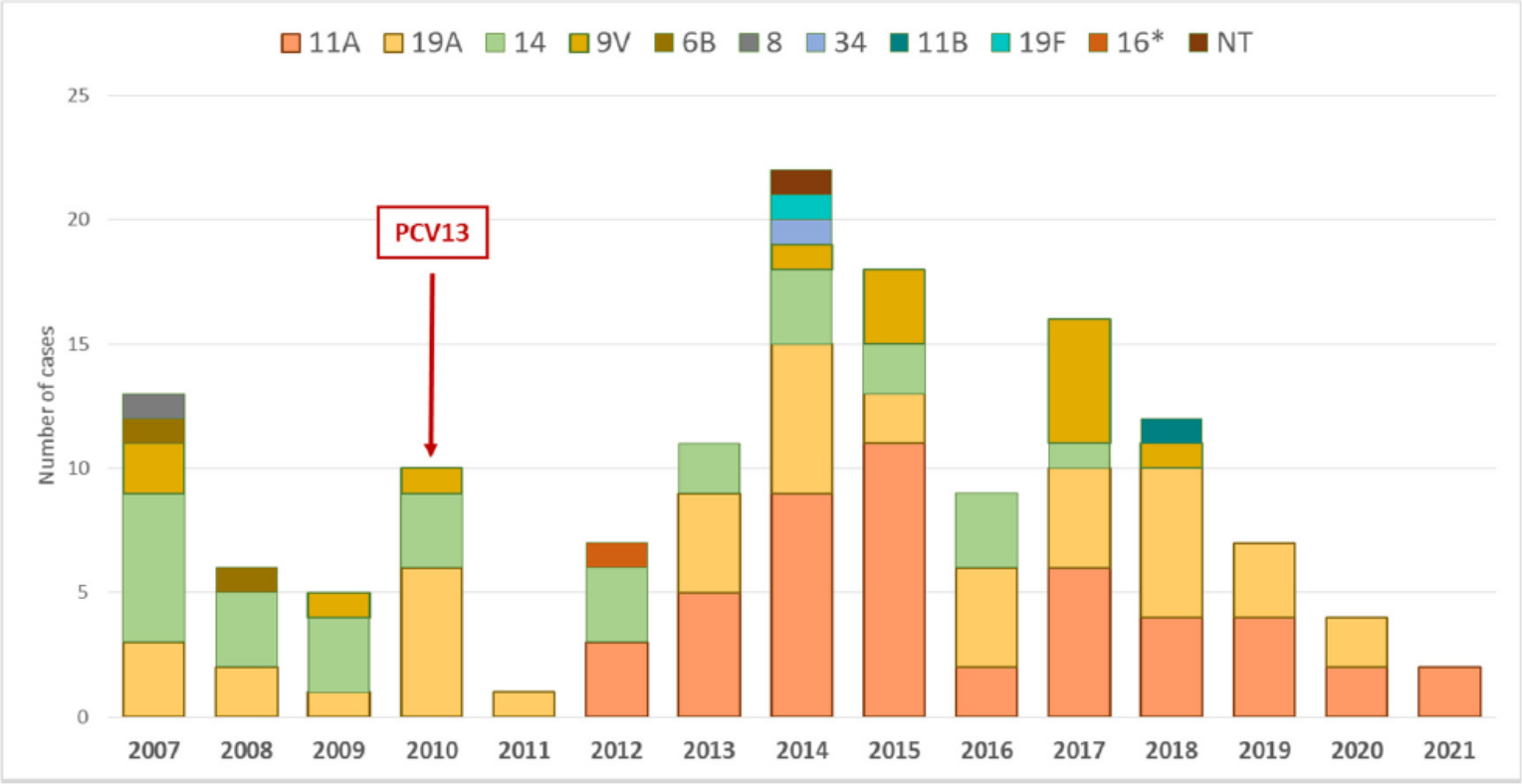
Extraído de Càmara J, et al. J Antimicrob Chemother. 2021

Figure 2. Evolution of antimicrobial susceptibility (a) and MIC_{50}/MIC_{90} values (b) over the study period. The percentage of change and the 95% CI are shown in parentheses (differences between the pre-PCV and the late-PCV13 periods). Statistically significant differences ($P<0.01$) are highlighted in bold. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Càmara J, Grau I, González-Díaz A, et al. A historical perspective of MDR invasive pneumococcal disease in Spanish adults. J Antimicrob Chemother. 2021;76(2):507-515. doi:10.1093/jac/dkaa455

El serotipo 11A fue el serotipo resistente a la penicilina más frecuentemente aislado

Evolución de la resistencia antimicrobiana de los aislamientos de ENI en Madrid; 2007-2021, n=7133



Extraído de de Miguel, Antibiotics. 2023

de Miguel S, Pérez-Abeledo M, Ramos B, García L, Arce A, Martínez-Arce R, et al. Evolution of Antimicrobial Susceptibility to Penicillin in Invasive Strains of Streptococcus pneumoniae during 2007–2021 in Madrid, Spain. Antibiotics 2023;12:289. https://doi.org/10.3390/antibiotics12020289.

El 94,4% de los aislados resistentes a penicilina pertenecen a serotipos incluidos en PCV20

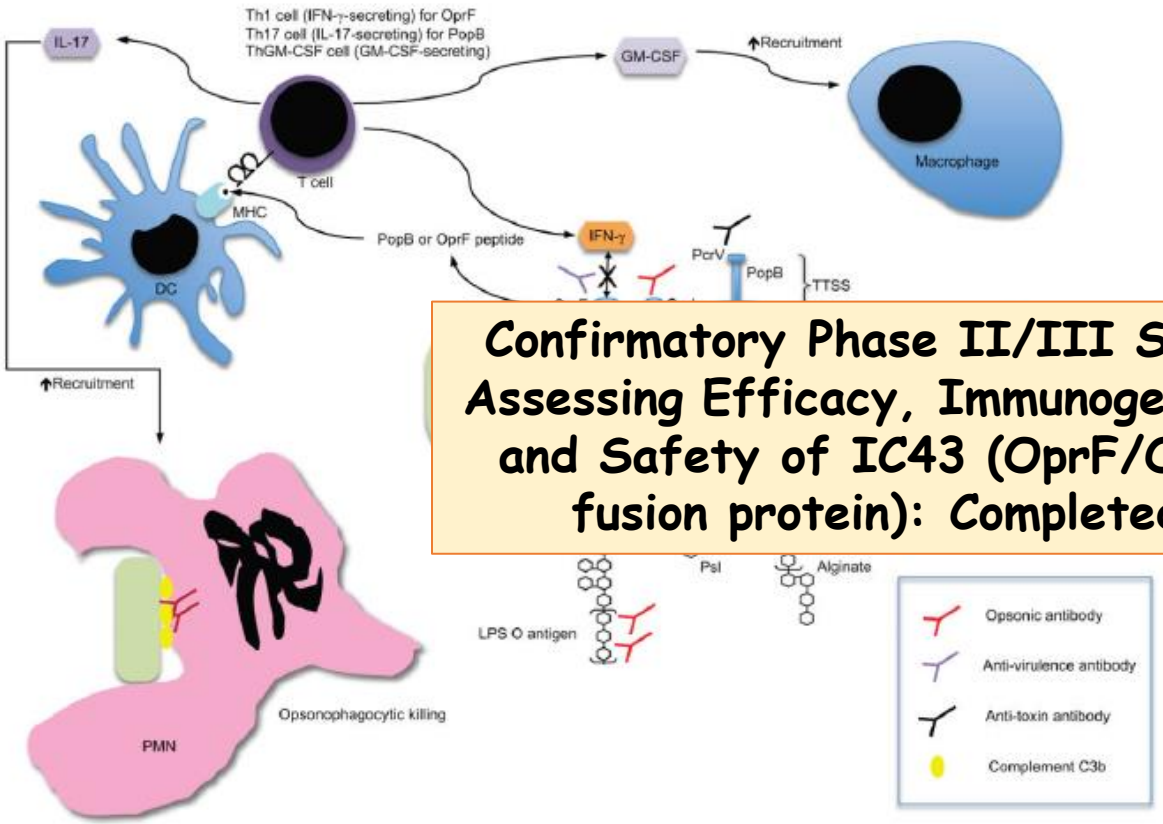
ENI: enfermedad neumocócica invasiva; **PCV20:** *vacuna antineumocócica conjugada 20-valente* (Pfizer). .

ii.Vacunas frente grupo ESKAPEE

ii. Vacunas frente grupo ESKAPEE

Enterococcus faecium
Staphylococcus aureus
Klebsiella pneumoniae
Acinetobacter baumannii
Pseudomonas aeruginosa
Enterobacter spp.
Escherichia coli

Pseudomonas aeruginosa



Confirmatory Phase II/III Study Assessing Efficacy, Immunogenicity and Safety of IC43 (OprF/OprI fusion protein): Completed

- LPS-based vaccines (30-valent)
- Vaccines for CF patients:
  Alginate
  Bivalent flagella vaccine
- Live attenuated vaccine (*aroA*)
- Outer membrane proteins:
  - OprL, FpvA, PopB (type III secretion system)
  - OMPs, like OprF and OprI
- PcrV (needle-tip component of the type III secretion system
- IgY antibodies, inhibit attachment to epitelial cells
- Anti-O11 mAb
- PsI, biofilm associated extracellular polysaccharide

Priebe GP. Expert Rev Vaccines. 2014. 13: 507-19

Acinetobacter baumannii

Contents lists available at ScienceDirect

Vaccine

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

Commentary

Considerations for the development of a prophylactic vaccine for *Acinetobacter baumannii*

Jerónimo Pachón, Michael J. McConnell *

Biomedical Institute of Sevilla (IBiS), University Hospital Virgen del Rocío/CSIC/University of Sevilla, 41013 Sevilla, Spain

Vaccine 32 (2014) 2534–2536

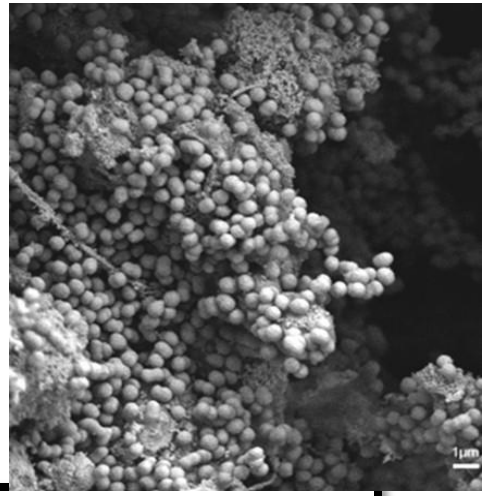
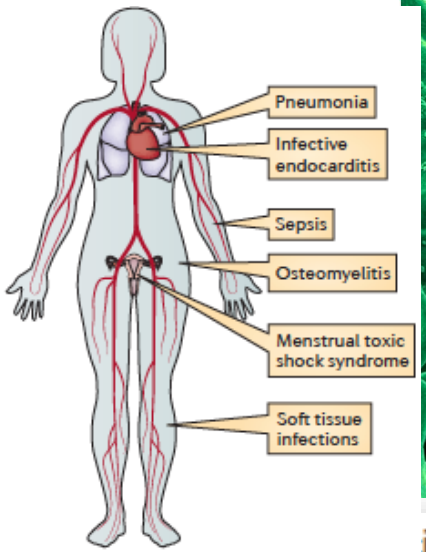


Table 1
Antigens used in experimental *Acinetobacter baumannii* vaccines.

Antigen	Results
Formalin-inactivated whole cells	Intramuscular/intranasal vaccination with or without an aluminum-based adjuvant, reduction in post-infection tissue bacterial loads, protection in a mouse model of sepsis, passive protection using antisera
Outer membrane complexes	Intramuscular vaccination with an aluminum-based adjuvant, reduction in post-infection tissue bacterial loads, protection in mouse model of sepsis, passive protection using antisera, treatment of infected mice with antisera
Outer membrane vesicles	Intramuscular vaccination with an aluminum-based adjuvant, reduction in post-infection tissue bacterial loads, protection in a mouse model of sepsis
Biofilm-associated protein (Bap)	Freund's adjuvant, reduction in post-infection tissue bacterial loads, protection in a mouse model of sepsis
Poly-*N*-acetyl-β-(1–6)-glucosamine (PNAG)	Passive intranasal/intravenous immunization, opsonophagocytosis of *A. baumannii* with antisera, reduction in tissue bacterial loads after passive immunization in a mouse model of pneumonia
Trimeric autotransporter protein (Ata)	Passive intravenous immunization, opsonophagocytosis of *A. baumannii* with antisera, complement-dependant bactericidal activity of antisera, reduction in tissue bacterial loads after passive immunization in a mouse model of pneumonia
Outer membrane protein A (OmpA)	Subcutaneous vaccination with an aluminum hydroxide adjuvant, protection in a diabetic mouse model of sepsis, opsonophagocytosis of *A. baumannii* with antisera, protection after passive immunization
K1 capsular polysaccharide	Subcutaneous passive immunization in a mouse soft tissue infection model, decrease in tissue bacterial loads

Staphylococcus aureus



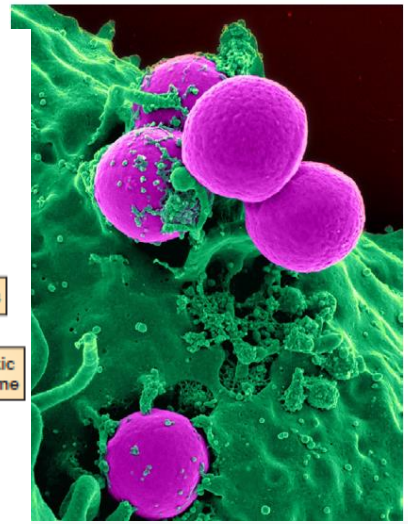


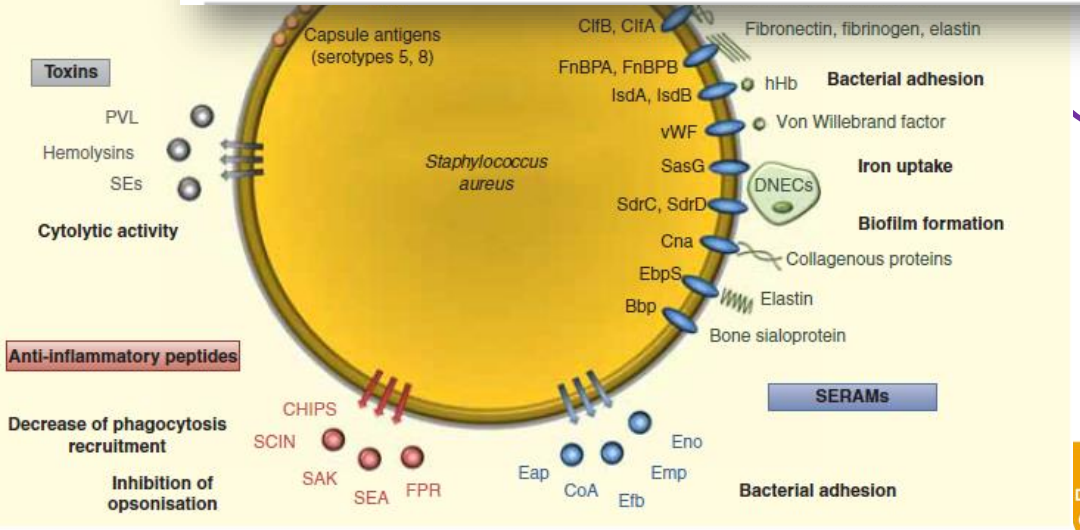
Table 1. Summary of past or ongoing *Staphylococcus aureus* vaccine clinical trials (active immunization).

Company	Antigen	Clinical indications Target population	Outcome	ClinicalTrials.gov identifier; Ref.
Nabi (StaphVAX)	Types 5 and 8 CPS conjugated to pseudomonal exoprotein A	Hemodialysis	Failed in Phase III	[28,102,103]
		Cardiovascular surgery patients	Phase III Completed 2006 No study results	NCT00211913 [101]
		Immunogenicity Orthopedic joint surgery Orthopedic implant patients	Phase III Completed 2006 No study results	NCT00211965 NCT00211926 [101]
GlaxoSmith	Nabi vaccine +	Safety immunogenicity	Phase I	NCT01160172 [101]
				NCT01018641 [101]
				NCT01364571 [101]
Merck	IsdB (V710)	Prevention of bacteremia and wound infection Cardiothoracic surgery	Failed in Phase II/III	[35] NCT00518687 [101]
		Immunogenicity Hemodialysis	Phase II Completed 2010	NCT00572910 [101]
Novadigm	rAls3p-N (*C. albicans* surface protein that cross reacts *with S. aureus*)	Safety immunogenicity Volunteers	Phase I Completed No study results	NCT01447407 [101]
VRI	Eap, GST-Can, His-Clf	Safety immunogenicity Volunteers	Phase I Completed Safe Immune response	[104]
Uniformed services University of the Health Sciences/ Nabi	Staphylococcal aureus toxoids (rAT and rLuks-PV)	Safety immunogenicity Volunteers	Phase I/II Completed 2011 No study results	NCT01011335 [101]

ATP: Adenosine triphosphate; *C. albicans Candida albicans*; ClfA: Fibrinogen adhesin; CPS: Capsular polysaccharide; Eap: Extracellular adherence protein; GST-Can: Collagen-binding protein; His-Clf: Clumping factor; Hla: A-toxin (a-hemolysin); IsdB: Iron surface determinant B; LTA: Lipoteichoic acid; SA4Ag: 4-antigen *Staphylococcus aureus* vaccine.

ine candidates in clinical development with the potential to prevent diseases caused by pathogens highlighted in this review

S. aureus		
SA4Ag (Pfizer)[88]	CP5/CP8-CRM$_{197}$, P-Y variant ClfA, MntC ClinicalTrials.gov identifier NCT02388165	Phase 2b
4C-Staph (GSK)[89]	Csa1A (Sur2), FhuD2, EsxA/EsxB, HIAH35L ClinicalTrials.gov identifier NCT01160172	Phase 1



Bothelho-Nevers et al. 2013. Expert Rev Vaccines

Possible reasons for this failure in effective vaccine development

➢**Reasons due to *S. aureus***

-Choice of inappropriate antigens: surface antigens

-High antigenic variability: regional differences in strain prevalence and variability of antigens that limit cross-protectivity remain major obstacles

-Immune evasion Spa-mediated

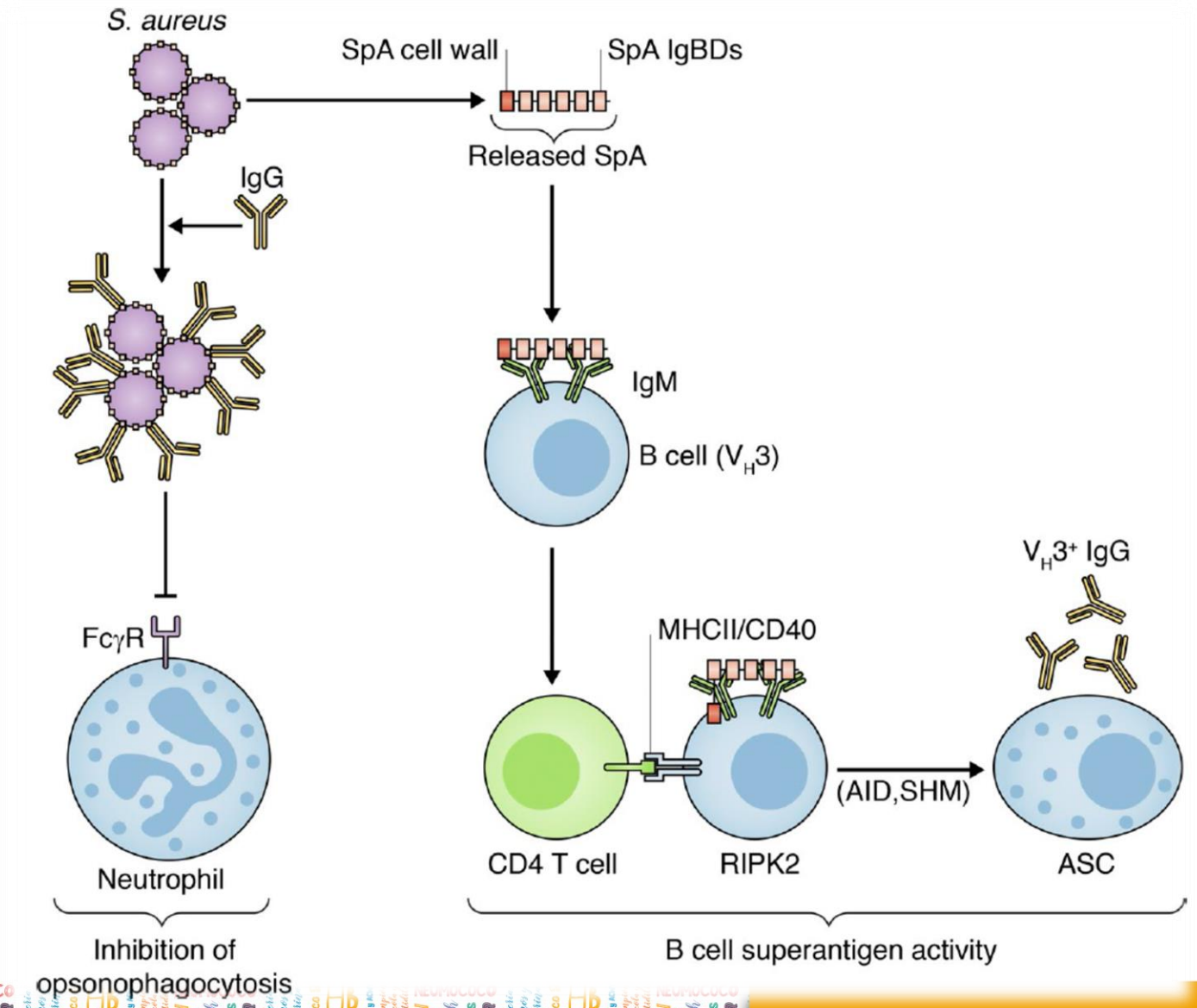
➢**Strengths and weaknesses of animal models**

➢**Immune response complexity**

-Efficient immunity against *S. aureus* does not involve antibody response

- Absence of cellular immunity response induced

➢**No impact on carriage are probably the reasons of the failures**



Spa induces the secretion of Vh3 IgG antibodies that are not reactive to staphylococci antigens

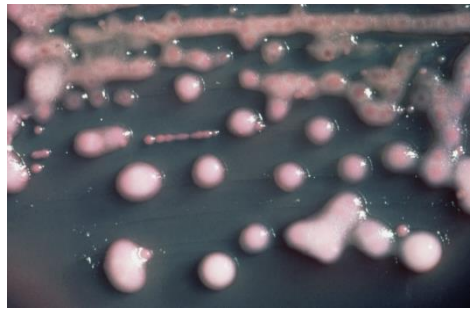
Missiakas et al. JEM. 2016

Klebsiella pneumoniae

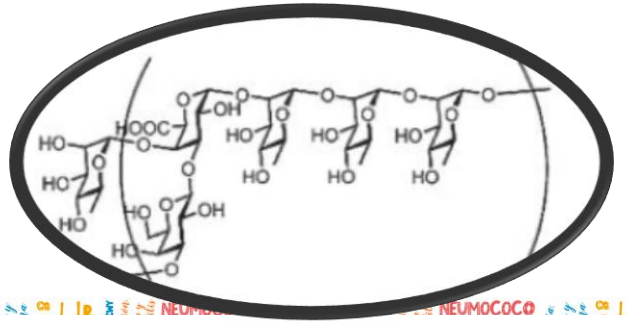
Deaths Attributable to Carbapenem-Resistant *Enterobacteriaceae* Infections

Matthew E. Falagas,[1] Giannoula S. Tansarli,[1] Drosos E. Karageorgopoulos,[1] and Konstantinos Z. Vardakas[1]

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 7, July 2014



A Semi-Synthetic Glycoconjugate Vaccine Candidate for Carbapenem-Resistant *Klebsiella pneumoniae*



Linked to the diphtheria toxin-based carrier CRM197

The CRM197-based vaccine was immunogenic in both mice and rabbits and produced antibodies that were cross-reactive with *K. pneumoniae* CPS. The semisynthetic glycoconjugate vaccine induced a high level of IgG1 antibodies and the antibodies were opsonophagocytic in differentiated HL-60 cells The ability of the vaccine to protect against *K. pneumoniae* challenge was not assessed due in large part to the absence of a good experimental model

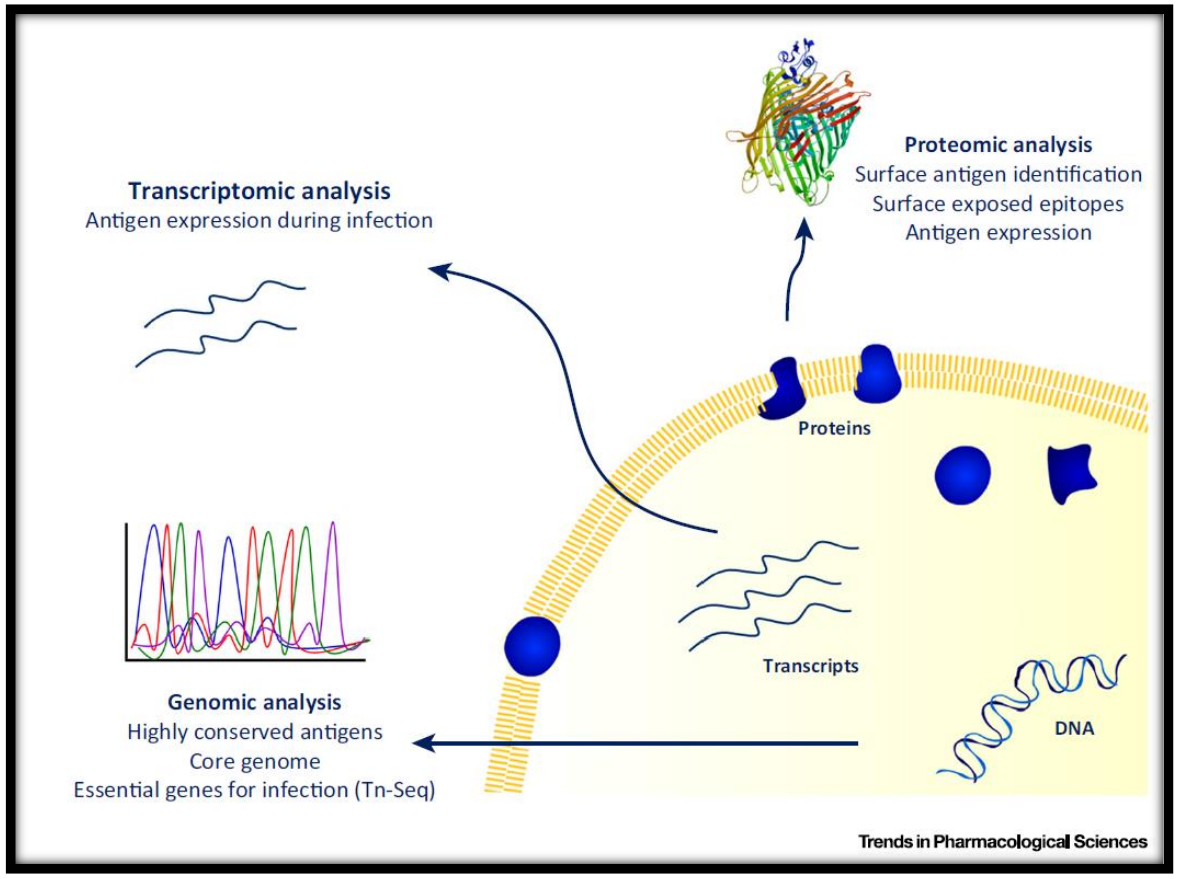
Angew Chem Int Ed Engl. 2017 November 06; 56(45): 13973–13978.

Review

Vaccines for Antibiotic-Resistant Bacteria: Possibility or Pipe Dream?

Meritxell García-Quintanilla,[1,2] Marina R. Pulido,[1,2]
Marta Carretero-Ledesma,[1] and Michael J. McConnell[1,*]

http://dx.doi.org/10.1016/j.tips.2015.10.003



nature COMMUNICATIONS

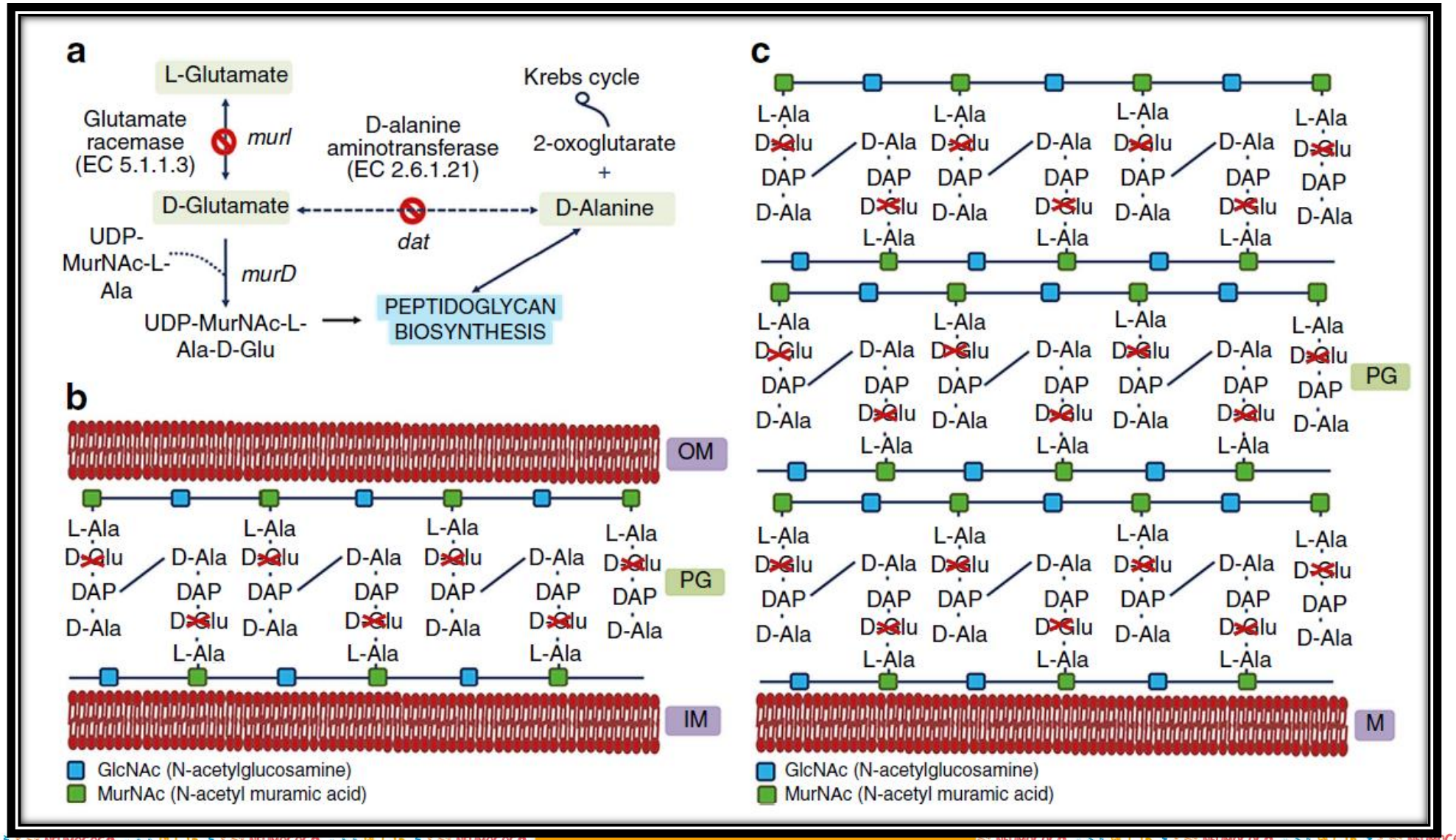
ARTICLE

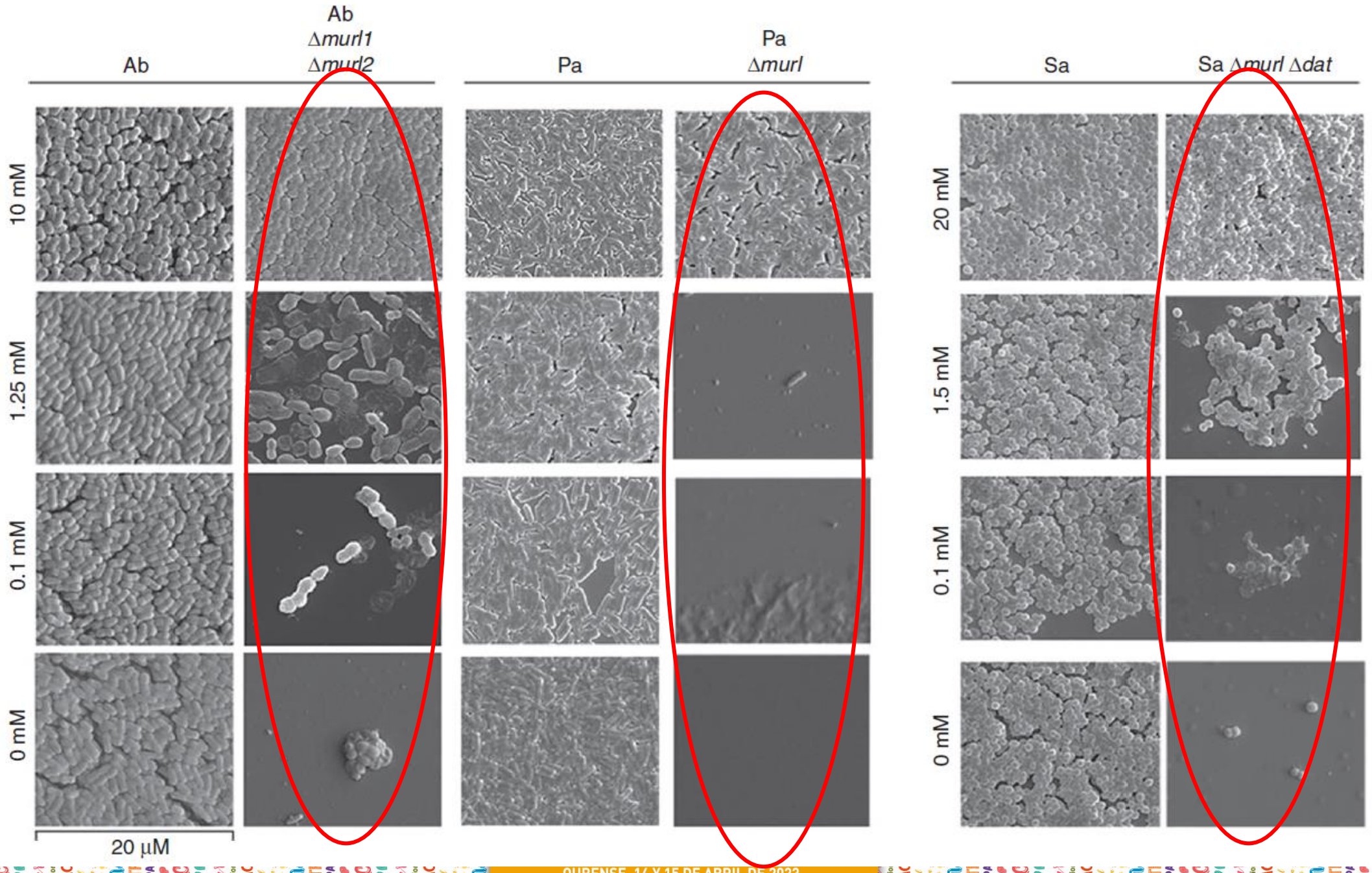
Received 4 Aug 2016 | Accepted 31 Mar 2017 | Published 26 May 2017

DOI: 10.1038/ncomms15480 OPEN

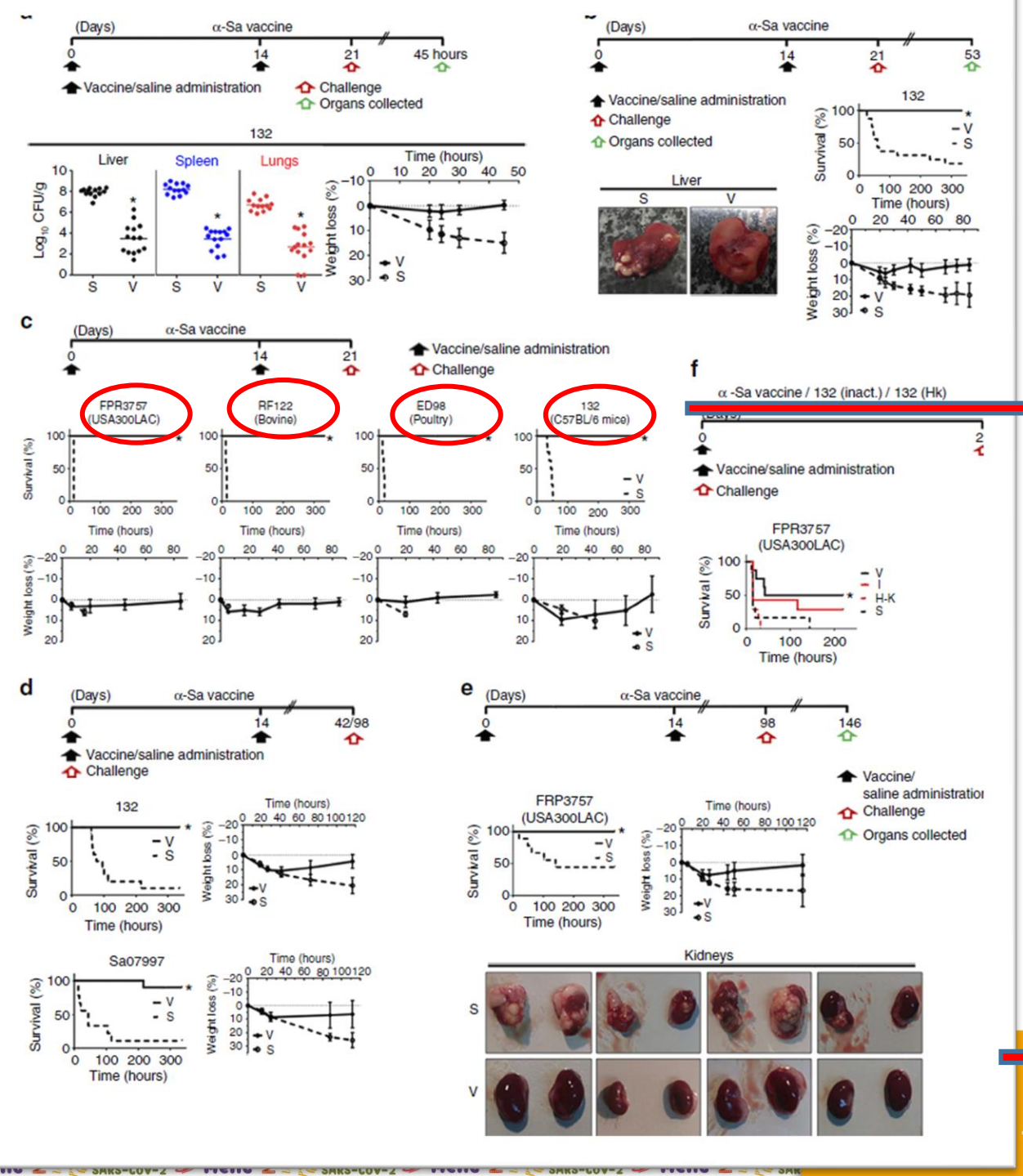
Design of live attenuated bacterial vaccines based on D-glutamate auxotrophy

Maria P. Cabral[1,*], Patricia García[1,*], Alejandro Beceiro[1], Carlos Rumbo[1], Astrid Pérez[1], Miriam Moscoso[1] & Germán Bou[1]


a
L-Glutamate
Glutamate racemase (EC 5.1.1.3)
murI
D-Glutamate
D-alanine aminotransferase (EC 2.6.1.21)
dat
Krebs cycle
2-oxoglutarate +
D-Alanine
UDP-MurNAc-L-Ala
murD
UDP-MurNAc-L-Ala-D-Glu
PEPTIDOGLYCAN BIOSYNTHESIS
b
OM
L-Ala
D-Glu
DAP
D-Ala
PG
IM
GlcNAc (N-acetylglucosamine)
MurNAc (N-acetyl muramic acid)
c
PG
M
GlcNAc (N-acetylglucosamine)
MurNAc (N-acetyl muramic acid)

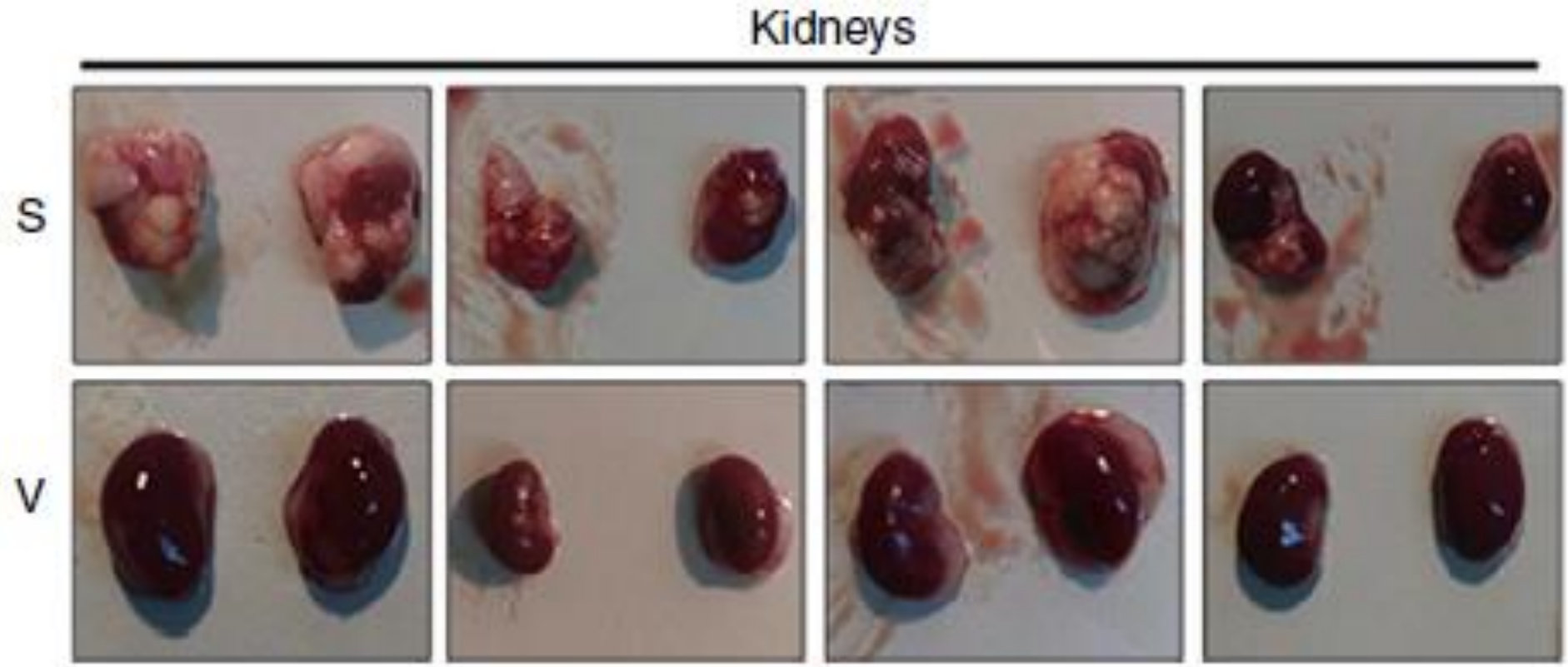

Ab
Ab
Δmurl1
Δmurl2
Pa
Pa
Δmurl
Sa
Sa Δmurl Δdat
10 mM
1.25 mM
0.1 mM
0 mM
20 mM
1.5 mM
0.1 mM
0 mM
20 µM

La vacuna protege frente a infecciones agudas letales causadas por *S. aureus*



Clon USA 300, cepas veterinarias de origen bovino, aviar

En experimentos donde no matábamos a los controles


Kidneys
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VIRULENCE, 2018
VOL. 9, NO. 1, 604–620
https://doi.org/10.1080/21505594.2017.1417723

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RESEARCH PAPER

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A D-Alanine auxotrophic live vaccine is effective against lethal infection caused by *Staphylococcus aureus*

Miriam Moscoso[a,#], Patricia García[a,#], Maria P. Cabral[a], Carlos Rumbo[a,b,c*] and Germán Bou[a]

Article

Cross-Protection against Acute *Staphylococcus aureus* Lung Infection in Mice by a D-Glutamate Auxotrophic Vaccine Candidate

Patricia García [1], Maria P. Cabral [1,2], Alejandro Beceiro [1,3], Miriam Moscoso [1,3] and Germán Bou [1,3,*]

Article

A New Live Auxotrophic Vaccine Induces Cross-Protection against *Klebsiella pneumoniae* Infections in Mice

Miriam Moscoso [1,†], Juan A. Vallejo [1,†], Maria P. Cabral [1,2], Patricia García [1], Víctor Fuentes-Valverde [1,3], Eva Gato [1,4,5], Jorge Arca-Suárez [1,3], Pablo Aja-Macaya [1] and Germán Bou [1,3,*]

Vaccines **2022**, *10*, 953. https://doi.org/10.3390/vaccines10060953

nature COMMUNICATIONS

ARTICLE

Received 4 Aug 2016 | Accepted 31 Mar 2017 | Published 26 May 2017 DOI: 10.1038/ncomms15480 OPEN

Design of live attenuated bacterial vaccines based on D-glutamate auxotrophy

Maria P. Cabral[1,*], Patricia García[1,*], Alejandro Beceiro[1], Carlos Rumbo[1], Astrid Pérez[1], Miriam Moscoso[1] & Germán Bou[1]

Brief Report

Double Auxotrophy to Improve the Safety of a Live Anti-*Pseudomonas aeruginosa* Vaccine

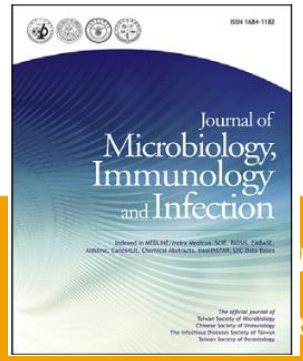
Víctor Fuentes-Valverde [1,2], Patricia García [1], Miriam Moscoso [1,2,*] and Germán Bou [1,2,*]

Journal of Microbiology, Immunology and Infection 56 (2023) 324—336

Original Article

A highly-safe live auxotrophic vaccine protecting against disease caused by non-typhoidal *Salmonella* Typhimurium in mice

Patricia García [a], Miriam Moscoso [a], Víctor Fuentes-Valverde [a,b], M. Rosario Rodicio [c,d], Silvia Herrera-León [e], Germán Bou [a,b,*]



PLOS | PATHOGENS

RESEARCH ARTICLE

A live auxotrophic vaccine confers mucosal immunity and protection against lethal pneumonia caused by *Pseudomonas aeruginosa*

Maria P. Cabral[1¤], Alexandra Correia[2,3,4], Manuel Vilanova[2,3,4], Fátima Gärtner[2,4,5], Miriam Moscoso[1], Patricia García[1], Juan A. Vallejo[1], Astrid Pérez[1], Mónica Francisco-Tomé[6], Víctor Fuentes-Valverde[1], Germán Bou[1*]

iii. Población diana o de riesgo

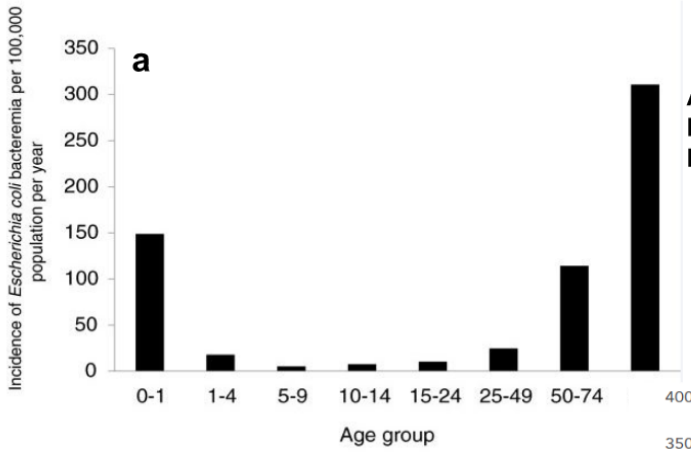
Target Populations

- Elderly
- Hospitalized
- Comorbidity
- Immune status

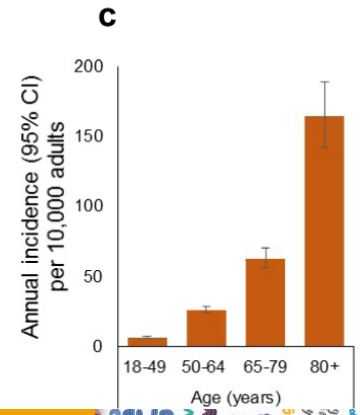
Age-related changes to the immune system

- Thymus involution
- Reduced haemopoietic bone marrow with reduced production of naïve cells
- Reduced number and functions of immune cell populations
- Proliferation of T memory cells and lowered capacity to respond to new antigens
- Imbalances in innate inflammatory mediators leading to chronic low grade inflammation

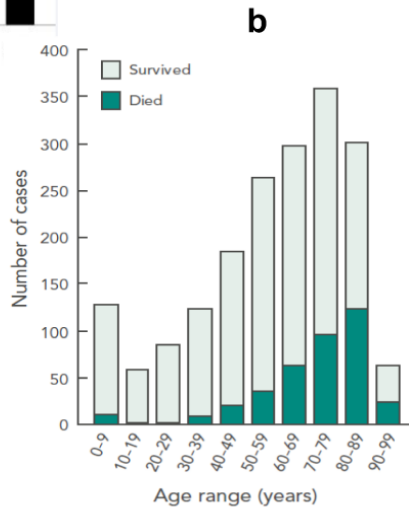
Increased susceptibility to bacterial infections



Age-specific *E. coli* bacteremia incidence New Zealand, 2005–2011



Age-specific *S. aureus* bacteremia incidence Australia & New Zealand, 2007–2008



Age-specific hospitalization incidence for community-acquired pneumonia United States, 2011-2012

<u>Target Populations</u>

- Elderly
- Hospitilized
- Comorbidity
- Immune status

<u>Clinical Trial Design</u>

- Target Population?
- Inclusion criteria?
- Endpoints?

<u>Implementation</u>

- Who?
- When?

Gracias!

XIV JORNADAS DE VACUNAS AEP

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