Vaccine Pipeline for Prophylactic Antimicrobial Resistance Prevention

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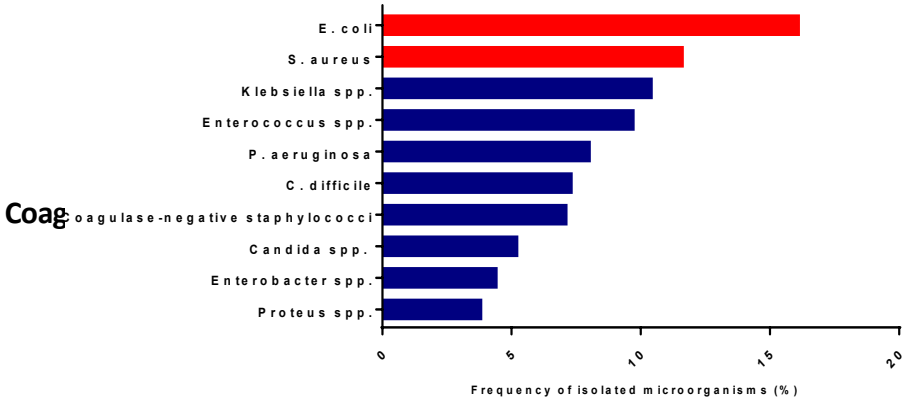
Extraintestinal Pathogenic *E. coli* (ExPEC) and *S. aureus* are key pathogens that occur frequently & are associated with bloodstream infection and high mortality

Top 10 most frequently isolated microorganisms of reported HAI in EU/EEA study (2016-2017)



Suetens et al., Surveillance and outbreak report (EU/EEA), 2018

ESKAPE pathogens:

Enterococcus

Staphylococcus

Klebsiella

Acinetobacter

Pseudomonas

Enterobacter

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E. coli/ExPEC & S. aureus are the leading pathogens associated with healthcare-associated infections (HAI) in largest USA HAI epidemiology study

Distribution and rank order of the most frequently reported pathogens across all types of adult HAI - NHSN, 2015-2017

Pathogen[a]	No. (%) Pathogens	Rank
Escherichia coli	**62,571 (17.5)**	**1**
		2
Selected *Klebsiella* spp	31,530 (8.8)	3
Pseudomonas aeruginosc	28,513 (8.0)	4
Enterococcus faecalis[b]	28,236 (7.9)	5
Coagulase-negative stap	24,199 (6.8)	6
Enterobacter spp	16,568 (4.6)	7
Enterococcus faecium[b]	13,687 (3.8)	8
Proteus spp	11,463 (3.2)	9
Candida albicans[b]	11,043 (3.1)	10

Modified from Weiner et al., Infect Control & Hosp Epidemiol, 2019

Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the National Healthcare Safety Network, 2015–2017

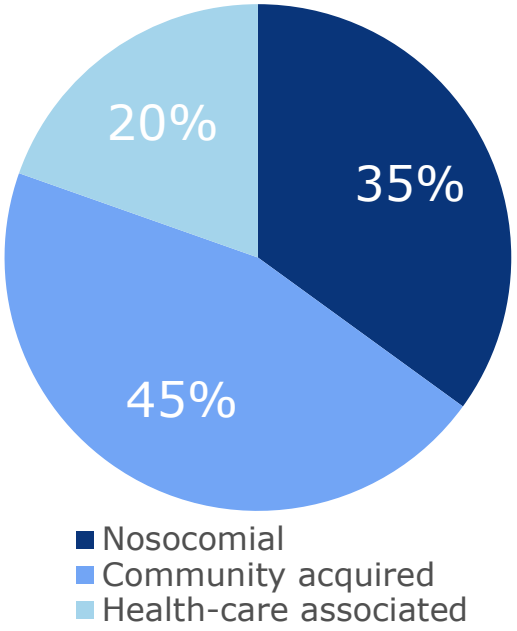
Weiner et al., Infect Control & Hosp Epidemiol, 2019

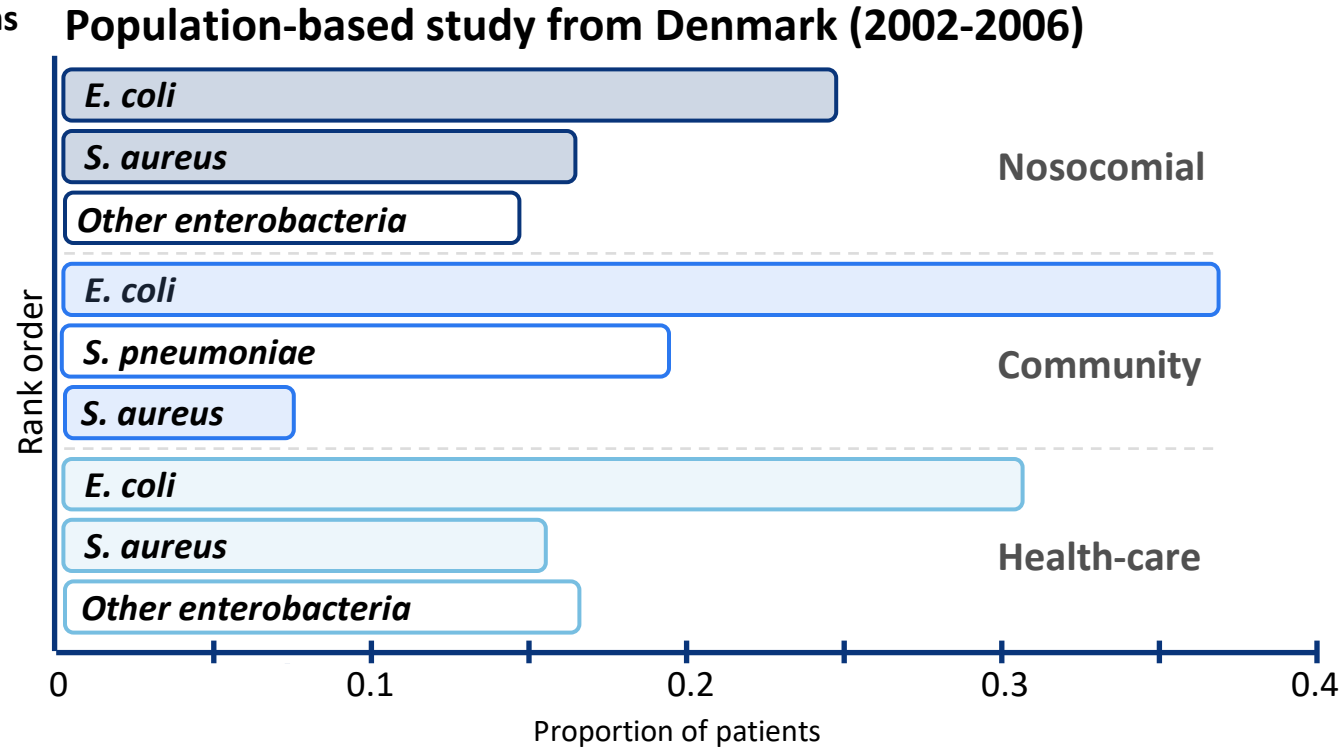
National Healthcare Safety Network (NHSN):

- **Managed by Centers for Disease control and prevention (CDC)**
- **The largest and most widely used electronic surveillance system for tracking HAI in the United States**
- **Over 25,000 healthcare facilities participate in the NHSN by entering and analyzing data on HAIs**

E. coli/ExPEC & *S. aureus* are the leading causes of community-onset and HAI related bacteremia in population-based study Denmark

Percentage of bloodstream infections by acquisition place and pathogen





Søgaard et al., CID 2011
Weiner et al., Infection Control & Hospital Epidemiology 2016

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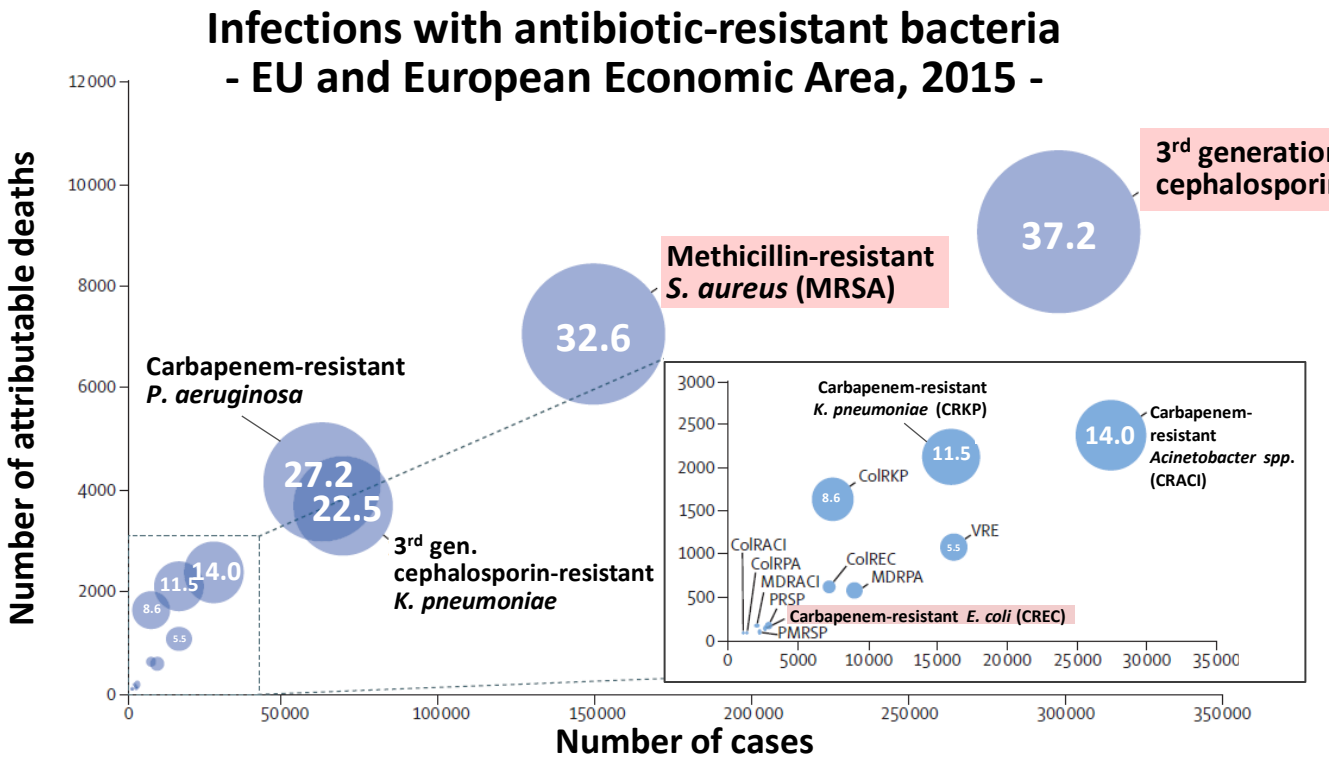
Burden of antibiotic-resistant *E. coli*/EXPEC & *S. aureus*/MRSA infections outnumbers other AMR infections in EU and EEA



WHO list of priority AMR pathogens

Priority 1 – critical

- Carbapenem-resistant *Acinetobacter baumannii*
- Carbapenem-resistant *P. aueruginosa*
- Carbapenem- and third generation cephalosporin-resistant (ESBL) Enterobacteriaceae (predominantly ExPEC and *K. pneumoniae*)

Priority 2 – high

- Methicillin-resistant *S. aureus* (MRSA)/vancomycin-resistant *S. aureus*
- …

Cassini et al., Lancet Infect Dis 2019 – data from EARS-Net collected between Jan 1, 2015 – Dec 31, 2015;

WHO Pathogens Priority List Working group, Tacconelli et al., Lancet Infect Dis 2018

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The *Staphylococcus aureus*-vaccines field: a history of failures

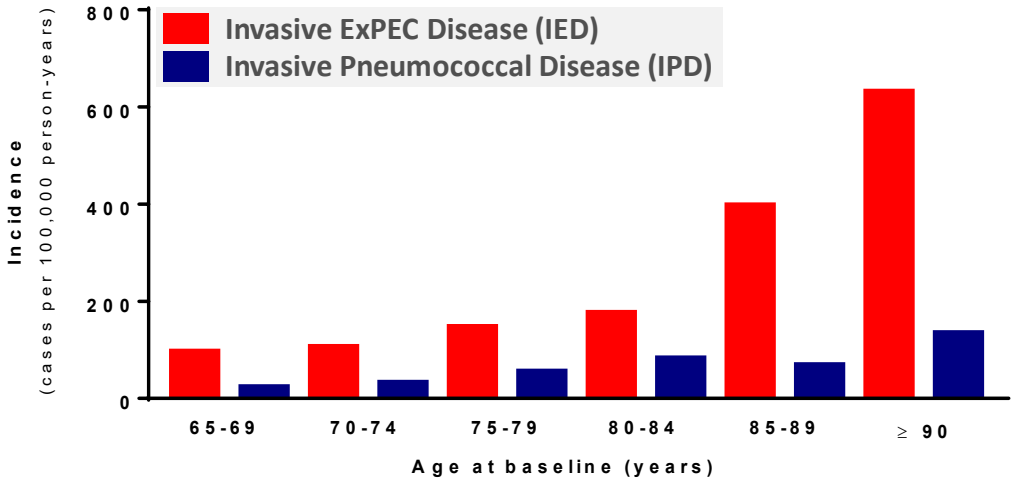
Reasons to believe that it is possible to beat this bug:

- **Misled by mice** in absence of accepted mode of actions
  - ➢ More human-like surgical-site-infection model needed
- **Focus on capsules and surface proteins and opsonophagocytosis** whilst *S. aureus* primarily aims at immune escape mechanisms
  - ➢ Focus on key specific *S. aureus* virulence factors/immune escape mechanisms
- **Absence** of **adjuvant**:
  - ➢ Use of a strong Th1 adjuvant, induction of high antibody levels and CD4 bystander T cell immunity

E. coli/ExPEC bacteremia outpaces pneumococcal bacteremia in seniors

INCIDENCE OF COMMUNITY-ONSET BACTEREMIA (U.S.)

Cohort of 46,238 non-institutionalized Group Health cooperative members ≥65 years of age; followed from 1998–2001



Jackson et al., JID 2005

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Active Bacterial Core surveillance (ABCs)

- *Bordetella pertussis*
- Group A *Streptococcus*
- Group B *Streptococcus*
- *Haemophilus influenzae*
- *Legionella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

➢ **Would be good to add *E. coli* /ExPEC on CDC's ABC list of pathogens**

https://www.cdc.gov/abcs/pathogens/pathogen-links.html

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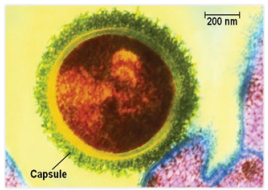
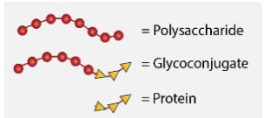
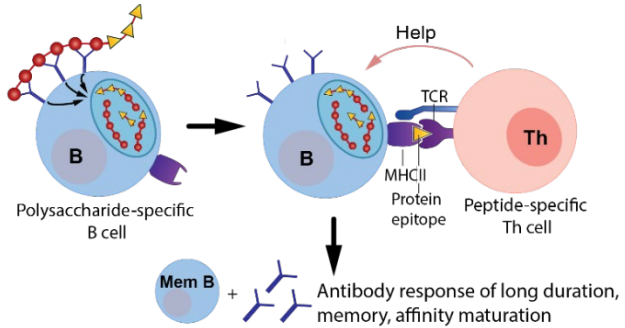
The development of ExPEC10V, a glycoconjugate vaccine: combination of a proven mechanism of protection and a breakthrough bioconjugation technology

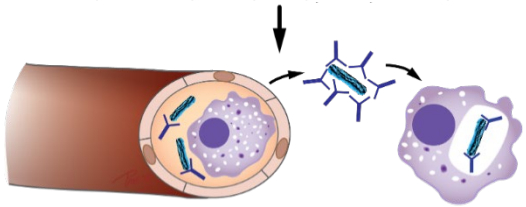
Low threshold serum levels of opsonophagocytic antibodies correlate with protection against diseases caused by encapsulated bacteria





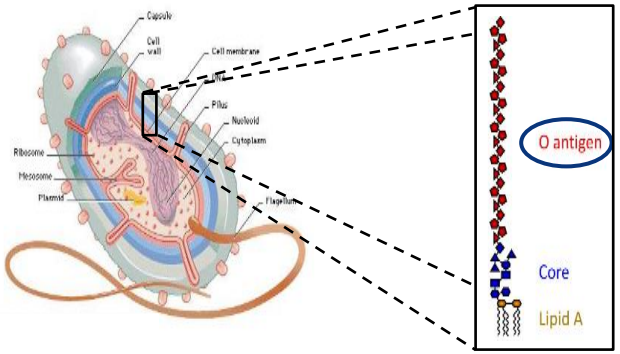


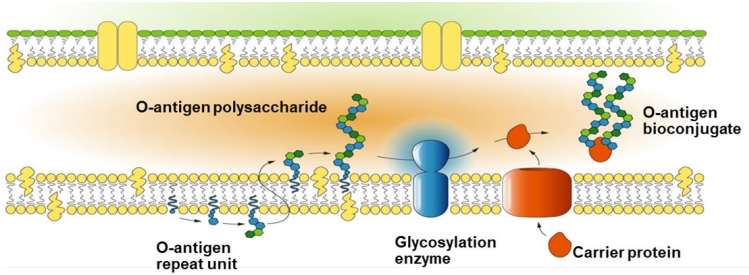
Opsonophagocytic killing



Adapted from Peeters et al., Vaccine protocols, 1996; Rappuoli & De Gregorio, Nature, 2011

In-licensed breakthrough bioconjugation technology enables production of multivalent ExPEC conjugate vaccine





Poolman J, et al. J Infect Dis. 2016

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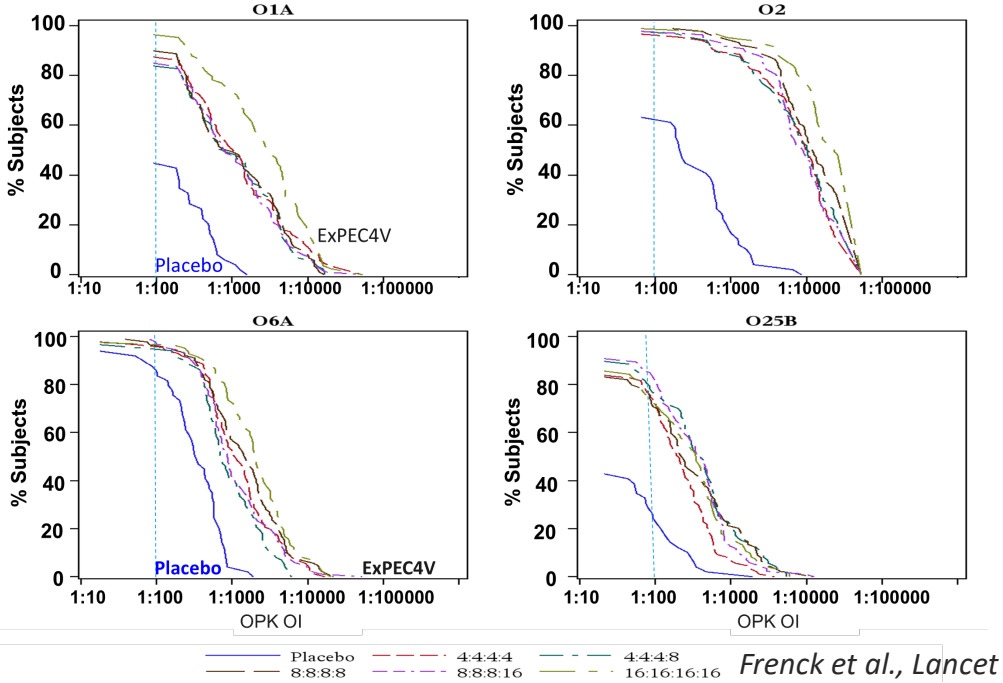
Janssen's ExPEC10V vaccine in Phase 1/2a, aiming for all-60+ use

ExPEC4V Phase 2 dose-finding study in seniors
Robust Ab response with opsonophagocytic killing activity (OPA) in over 90% of subjects



Frenck et al., Lancet Infect. Dis., 2019

OPA DATA: immunological PoC
- REASON TO BELIEVE -

OPA responses comparable to Prevnar in seniors[#]

[#] Van Deursen et al., Clin Infect Dis, 2017; Bonten et al., N Engl J Med, 2015

Phase 1/2a ExPEC10V ongoing – aiming for all 60+ use

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Conclusions, where can vaccines help to address the AMR issue?

- Vaccines can prevent the consequences of AMR:
  prevent acute life-threatening invasive bacterial diseases in a situation where the first antibiotic regimen needs to be the right one
- Prevention of invasive bacterial disease with surface polysaccharide protein conjugate vaccines have a successful track record, this is particularly promising for *E. coli*/ExPEC invasive disease, the nr. 1 cause of invasive disease in adults
- *S. aureus*/MRSA vaccines have failed in Phase 3 trials so far
- To prevent the use of antibiotics, vaccines would need to impact mucosal bacterial diseases such as urinary tract infections, skin and soft tissue infections, pneumonia, etc; this requires enhanced immune responses, a need for CD4 bystander T-cell immunity in addition to strong antibody responses (adjuvant)


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