VACCINES AND INNOVATIONS IN FACILITY INFECTION CONTROL TO PREVENT NEONATAL SEPSIS

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FOUNDATION PERSPECTIVE ON ANTIMICROBIAL RESISTANCE

- Our interest in AMR relates to our current health strategies in developing countries
  - Focused on supporting the development of transformative tools to reduce mortality and disease burden among the world's most vulnerable populations
  - Appropriate antibiotic use has the power to save lives in these populations
- The threat of AMR reinforces the importance of prevention of infections – which is a core focus of foundation work

AMR STRATEGY: FOCUS AREAS FOR INVESTMENT

AMR Strategy Focus

- Focus on prevention of infections and the associated mortality through vaccines, monoclonal Ab, and microbiome approaches
  - Focus on neonatal sepsis
  - Continued vaccine development and delivery efforts for enteric disease, TB, HIV, malaria

Key Investments

- Surveillance and evidence generation to understand the etiologies and burden of illness
- Product development investments, including via CARB-X:
  - Vaccines ★
  - Monoclonal antibodies
  - Microbiome approaches
  - Innovations in infection prevention and control ★

BURDEN OF KLEBSIELLA PNEUMONIAE IN NEONATAL SEPSIS IN LOW AND MIDDLE INCOME COUNTRIES

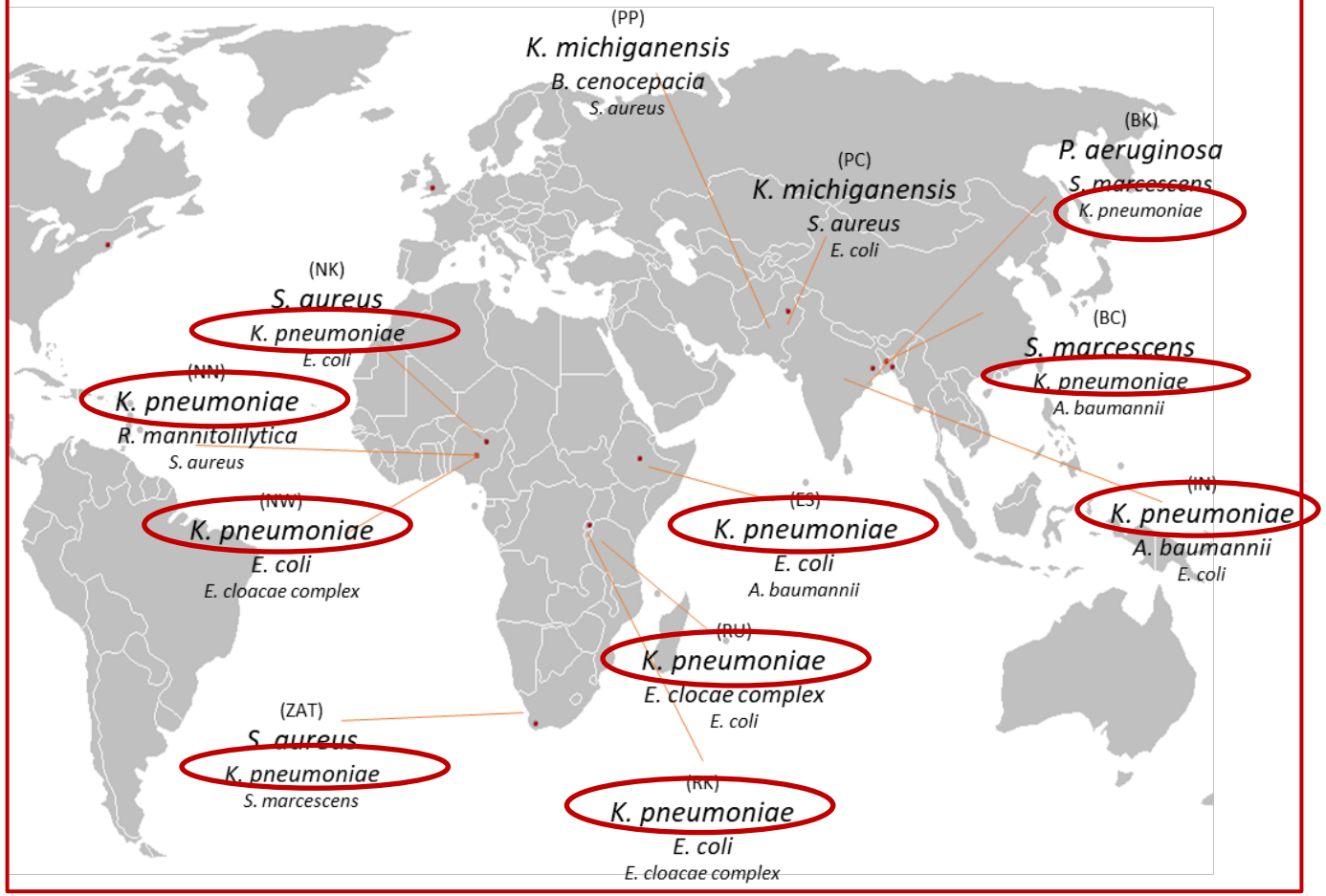
BARNARDS Study

- Enrolled 35,040 mothers at delivery at 12 sites in 7 countries
  - Nigeria, Rwanda, Ethiopia, South Africa, Pakistan, Bangladesh, India
- Of 36,348 enrolled infants, 2,311 infants had blood culture confirmed sepsis
  - *K. pneumoniae* most common organism isolated

CHAMPS Surveillance Platform

- *K. pneumoniae* accounts for:
  - 30% of neonatal infectious deaths
  - In causal chain of 16% of all neonatal deaths, and causes both early and late onset (hospital-acquired) illness

BARNARDS STUDY: Top Three Etiologies Identified at Each Site



BARNARDS: Burden of Antibiotic Resistance in Neonates from Developing Societies. CHAMPS: Child Health and Mortality Prevention Surveillance

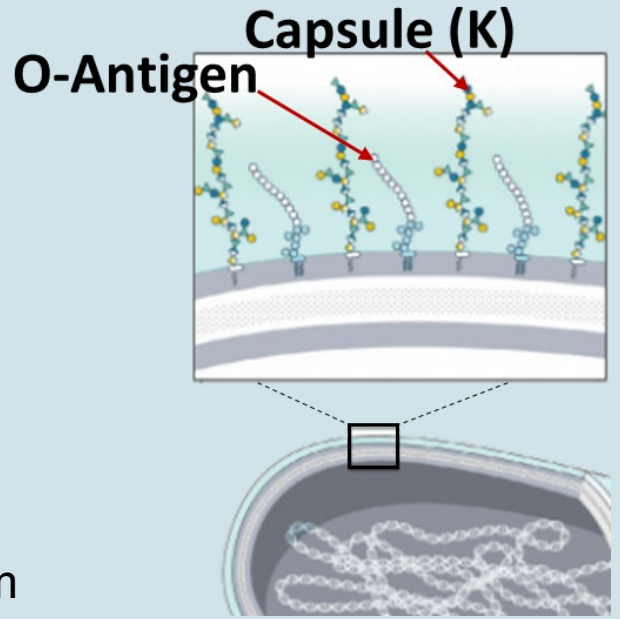
References: Sands, et al. BARNARDS Study, presented at ECCMID 2019

KLEBSIELLA PNEUMONIAE: POTENTIAL MATERNAL VACCINE TARGET TO PREVENT NEONATAL SEPSIS

- 8 lipopolysaccharide (LPS) O-antigens and 77 capsular K antigens are potential targets for conjugate vaccine

- Whole genome sequencing of 258 *K. pneumoniae* neonatal sepsis isolates from BARNARDS* study:
  - 98% of sepsis isolates from serogroups: O1, O2, O3, O4
  - 81% of isolates from 16 K serogroups

- <u>Key data gaps:</u>
  - Characterization of *K. pneumoniae* serogroups in neonatal sepsis from additional geographies
  - Evaluate for infant correlate of protection for *K. pneumoniae*



BARNARDS=Burden of Antibiotic Resistance in Neonates from Developing Countries

KLEBSIELLA PNEUMONIAE: A VACCINE TARGET IN OTHER POPULATIONS

- Most common O serogroups in adult nosocomial infections: O1, O2, O3, O5
- Target populations: Elective surgery patients, patients discharged to long-term care facilities

Type of Vaccine	Antigen
Conjugate vaccine	O1, O2, O3, O4 linked to *Pseudomonas aeruginosa* flagellin protein
	Bioconjugate vaccine targeting K1, K2
	Semi-synthetic conjugate vaccine targeting O1, O2
Multiple Antigen Presenting System (MAPS)	O1, O2, O3, O5, MrkA

- <u>Key questions:</u>
  - Do K antigens mask LPS O antigens? Is that a barrier to a vaccine targeting O serogroups?
  - Is a high valency conjugate vaccine required?
  - What is required for protective immunity in infants?

References: Feldman, PNAS 2019; Hegerle, PLOS One 2018; Vaxxilon website, 2019, Affinivax website

CONTAMINATED SURFACES CONTRIBUTE TO HEALTHCARE ASSOCIATED INFECTIONS, INDIA DATA

Rapid survey of environmental microbial burden in a neonatal ward – India: Results from one day in a month-long survey

Item sampled	Final culture results
Resuscitation mask	*Klebsiella, Proteus, Enterococcus*
Laryngoscope	*Acinetobacter, E. coli*
Thermometer	Coagulase negative (CN) *Staphylococcus*
Neonate bed surface	CN *Staphylococcus*, *Acinetobacter, Enterobacter, Klebsiella*
Weighing balance	No pathogen isolated
Oxygen hood	*Acinetobacter, Klebsiella,* CN *Staphylococcus*
Transportation trolley	*Klebsiella, Enterococcus,* CN *Staphylococcus*
Feed preparation surface	*Enterococcus*
Feeding tray	*Acinetobacter*
Stethoscope	No growth

Frequency of surface contamination correlates with frequency of hand and/or glove contamination of healthcare personnel

References: personal communication; Weber, *Curr Opin Inf Dis*, 2016; Dancer, *Clin Micro Rev*, 2014; Morgan, *Crit Care Med*, 2012

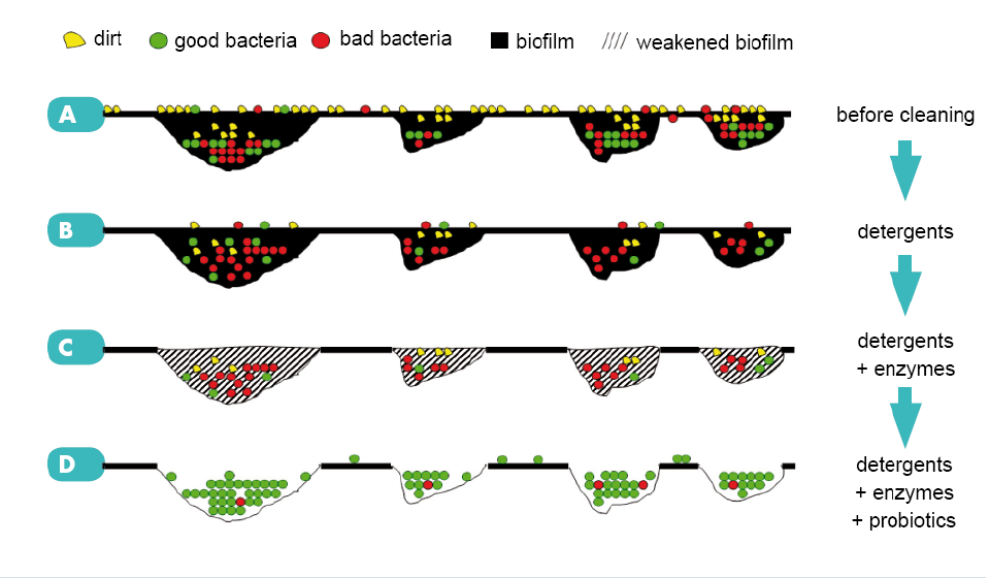
NOVEL APPROACHES TO HOSPITAL SURFACES

Approach	Category	Intervention	Mechanism	Challenges
Disinfect the surface differently	Manual disinfectants	Hydrogen peroxide	Oxidative cell death	Risk of burns
		Electrolyzed water	Free radical disinfection	Limited microbial reduction
	No touch disinfectants	UV light	Severs molecular DNA → microbicidal death	Cost, terminal cleaning only, surface must be in line of UV light
		High intensity narrow spectrum light	Stimulate intracellular porphyrins → cell death	Cost, light must remain on
		Ozone	Oxidative cell death	Limited and variable data
		Hydrogen peroxide mist	Oxidative cell death	Cost, injury risk, terminal cleaning only
Alter the surface	Nanocoatings	Organosilanes	Disrupt cell membrane	Needs applications every 3 months
	Metals	Silver, Copper	Toxic to microbes via multiple mechanisms	Cost, potential for resistance
	Topography	Ordered micropatterns	Prevent bacterial adhesion	Limits on types of materials
Don't disinfect the surface	Microbial management	Probiotic infection control	Non pathogenic bacteria reset the microbial environment	Requires manual application
		Bacteriophage	Targeted at specific pathogens	Focused application

PROBIOTIC INFECTION CONTROL

Approach:

- Use non-pathogenic probiotic bacteria to colonize hard surfaces
- Counteract proliferation of pathogenic species via the principle of competitive exclusion

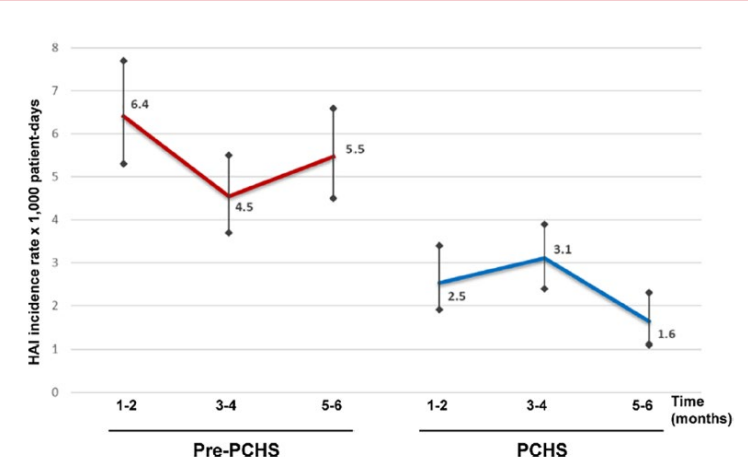


Product:

- Chrisal: detergent with food grade spores of *Bacillus pumilus* + *megaterium* + *subtilis*

Pre-post intervention trial in six hospitals in Italy, 2016-2017

- HAI incidence decreased from 4.8% to 2.3% (OR 0.44, 95% CI 0.35 - 0.54).
- Surface pathogen decreased 83%



Cluster Randomized Crossover Trial, Charite Berline, 2017-2018

- No significant difference in HAI rate between 3 arms
- Overall incidence much lower than expected (estimated 5%): study was likely underpowered.

Overall infection incidence rate	**1.7%**
Probiotic cleaning	1.9%
Disinfection cleaning	1.5%
Soap-based cleaning	1.6%

*Unpublished; Presented at ICPIC 2019, Geneva

References: Chrisal LLC, Belgium, Probiotic Cleaning Manual; Vandini, *PLOS One,* 2014; Caselli, *PLOS One,* 2016; Caselli, *PLOS One,* 2018. HAI= healthcare associated infection. Chrisal Solution: probiotic spores are included at a fixed quantity of 5 x 10^7 CFU /mL product concentrate; diluted 1:100 when used on hard surfaces.


THE WORK IS
COMPLICATED.
WHY WE DO IT IS NOT.