Vaccines against antimicrobial resistance (AMR) in *Enterobacteriaceae*

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Introduction

Enterobacteriaceae is a family of gram-negative, facultatively anaerobic, non-spore-forming bacillus that make up a small proportion of intestinal microbiota but are major human pathogens whose steadily increasing antibiotic resistance poses a significant health threat. This group of nosocomial pathogens can colonize various sites and cause serious infections among individuals with severe comorbidities or significant underlying susceptibility factors. Multidrug-resistant microorganisms (MDRs) have been reported in this order of bacteria.

There is a near static pipeline with only few antibiotics being approved by regulatory agencies in recent years; however, these are subjected to the appearance of resistance and almost none of them targets MDRE. In the absence of effective treatment against enterobacterial infections, **non-traditional strategies**, such as **vaccines** may be a feasible option to address this health problem. Prophylactic vaccines can address AMR though the following mechanisms:

Indirectly

- Preventing bacterial infections, thus, reducing the need for antibiotic prescriptions and minimizing the selective drug pressure.

Directly

- Reducing occurrence and spread of resistant serotypes.
- Decreasing infection rate of resistant strains closely related (cross-reactivity).

Objectives

In this work we review the threat to public health caused by multi-drug resistant *Enterobacteriaceae* (MDRE) and assess the role of vaccines as a possible strategy to prevent infection and decrease the spread of resistance in the selected pathogens.

Methodology

Critical priority *Enterobacterales*

Escherichia coli, Klebsiella pneumoniae, *Enterobacter spp., Serratia spp., Proteus spp., Providencia spp., Citrobacter spp. and Morganella spp.*

E. coli and ***K. pneumoniae*** pose the greatest concerns because they have a higher burden of disease and high levels of resistance to **third generation cephalosporins (3GC)**, **β-lactam** antibiotics, **carbapenems (CR)**, **fluoroquinolones** and **colistin** respectively; and at the same time, both species are part of the normal flora of the gastrointestinal tract.

Criteria used to include vaccine projects:

1. Vaccine projects that are in **clinical trial**, prioritizing those in advanced stages of development.
2. Selection of some **preclinical projects**, including as much as possible, representation for all the bacteria studied and reflecting innovative techniques in vaccinology.

AMR in *Enterobacteriaceae*

E. coli

PATHOLOGIES: urinary tract, bloodstream, intra-abdominal, skin and soft tissue, foodborne infections and meningitis in neonates.

AMR: fluoroquinolone resistance, ESBLs, 3GC, NMD-1/5, MCR-1, CTX

K. penumoniae

PATHOLOGIES: pneumonia, bloodstream, surgical site, and urinary tract infections.

AMR: fluoroquinolone resistance, ESBLs, KPC, OXA-48, TEM

! plasmids can co-express several resistance genes

Mechanisms of resistance:

- **Hydrolysing enzymes**
- **Target modification**
- **Permeability alterations**

AMR in enterobacteria: **acquired:** horizontal transfer; **intrinsic**

Incidence of resistant strains in sanitary settlements

(data extracted from EPINE 2019 report)

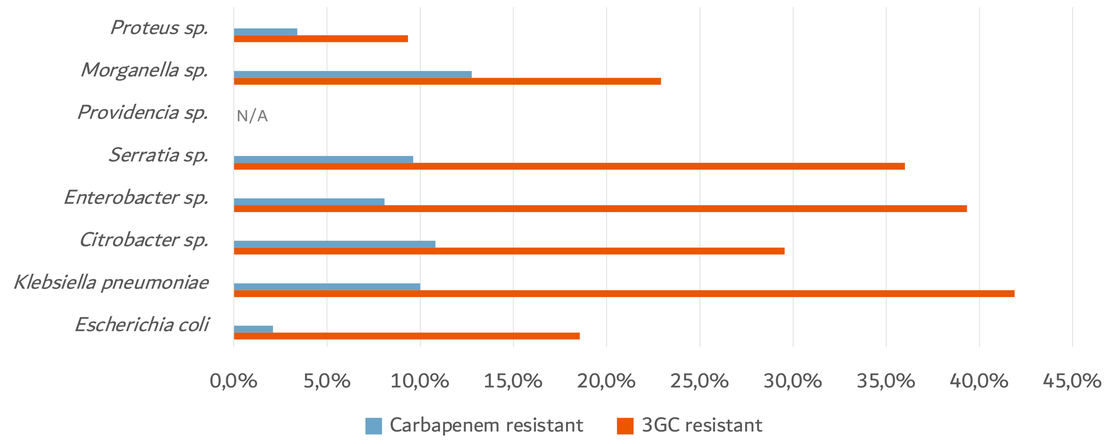

Figure 1: Incidence of resistant critical enterobacteria registered by EPINE 2019 report.

Vaccine strategies

Immunological mechanisms to elicit vaccine-mediated protection:

- Opsonophagocytosis of infecting pathogens
- Modulation of T cell immunity
- Neutralization of toxins

CLINICAL

Table 1: Vaccines in clinical development for critical *Enterobacteriaceae* pathogens.*

	Targeted pathogens	Key component	
Phase 2	***E. coli*** **(urinary)**	**Multivalent bioconjugate** ExPEC4V	prophylactic
Phase 2	***E. coli*** **(enteric)**	**Live attenuated**, oral vaccine ACE527 with dmLT (mucosal adjuvant)	prophylactic
Phase 2	***E. coli*** **(enteric)** and *Shigella*	ETVAX: **inactivated recombinant** *E. coli* strains over-expressing colonization factors (CFs) and the heat labile toxoid LCTBA	prophylactic
Phase 2	***E. coli*** **(enteric)** and *C. jejuni*	**Monoclonal antibody**-like recombinant protein, LMN-101 targeting FlaA (flagellin filament protein)	therapeutic
Phase 2	***E. coli*** **(enteric)**	O-specific polysaccharide of EHEC conjugated with recombinant exotoxin A of *P. aeruginosa* (O157-rEPA)	prophylactic
Phase 2	***E. coli*** **(enteric)**	LT toxin using skin patch	prophylactic
Phase 1	***E. coli*** **(enteric)**	ACE527 ETEC, **attenuated live** complex	prophylactic
Phase 1	***E. coli*** **(urinary)**	FimH (type 1 fimbrin D-mannose specific adhesin) antagonist, GSK3882347	prophylactic
Phase 1	***E. coli*** **(enteric)**	**Antibodies** cαStx1B and cαStx2A (Shiga-toxin based vaccine)	therapeutic

PRECLINICAL

Table 2: Summary of promising vaccine candidates in preclinical development for critical *Enterobacteriaceae.**

Targeted pathogens	Key component	
E. coli **(urinary)**	Antigens from uropathogenic *E. coli* (UPEC) combined with a Th1-skewing adjuvant	prophylactic
E. coli **(urinary)**	dmLT with two surface-exposed receptors, Hma or IutA	prophylactic
K. pneumoniae	**mAb therapy** targeting the outer polysaccharide capsule (CPS) of *K. pneumoniae*	therapeutic
K. pneumoniae	**Bioconjugate vaccines**, enzymatically produced in glycoengineered *E. coli* cells, against the 2 predominant hypervirulent *K. pneumoniae* serotypes, K1 and K2	prophylactic
K. pneumoniae, *A. baumannii* and *P. aeruginosa*	Inactivated LPS-null (endotoxin free) **whole-cell** *A. baumannii* vaccine displaying at the cell surface multiple conserved antigens *from P. aeruginosa* and *K. pneumoniae.* KapaVax (VXD-005)	prophylactic
K. pneumoniae	CPS2 antigen from a carbapenem-resistant *K. pneumoniae* strain (ST258)	prophylactic
Proteus mirabilis	**Multi-peptide vaccine** of MrpA, UcaA and Pta factors in combination with AddaVax adjuvant	prophylactic
Proteus mirabilis	Vaccine based in MrpA and Flagellin as an adjuvant, proposing the fusion protein MrpA.FliC as promising vaccine	prophylactic

*References are available upon request.

Discussion

1. These are facultative pathogens that affect subjects with previous medical conditions and co-morbidities.
2. Identification of an adequate population target to develop prophylactic vaccines is challenging.
3. Development of previous prophylactic vaccine candidates has been haltered due to low incidence in hospital settings and difficulties in finding a suitable target.
4. Prophylactic vaccines have to overcome the economic and logistic barrier of introducing new vaccines in the health care system.

Prophylactic vaccines

- Generate **active immunity.**
- Licensed prophylactic vaccines can help to **reduce the incidence of bacterial infection** in certain population groups at risk and indirectly **ameliorate antibiotic stewardship**.
- Incorporation of new technologies in vaccinology and the identification of new targets will allow reassessment of prophylactic vaccines against enterobacteria.
- Many challenges still pending.

Therapeutic vaccines

- Therapeutic vaccines (with mAb) are already in the pipeline for *E. coli.*
- Generate **passive immunity.**
- Require the **pathogen to be identified before treatment**, which can take several days and thus poses risks to the patient
- **Feasible and promising** approach.
- In **early-stage of development** and will not reach the clinical phase for some years.

Other non-traditional antimicrobial agents: **bacteriophage therapy**

Conclusions

Advances in vaccinology techniques, together with the identification of new targets, may allow a change in the vaccine design strategy, towards a more **resistant-strain-specific approach**. Prophylactic vaccines that are already in advanced stages of development may be worth pursuing, however, there are still many challenges directly related to the opportunistic nature of this pathogens which make this antimicrobial treatment a less feasible option to address AMR in comparison to other alternative treatments with a therapeutic approach (e.g., mAb vaccines).

Most relevant references

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