The vaccine in the battle against *E. coli* infection

Maricarmen Rojas-López[1,2]
[1.]GSK, Via Fiorentina 1, 53100, Siena, Italy. [2.]INRA, UR454 Microbiologie, F-63122 Saint-Genès Champanelle, France.

Escherichia coli, a bacterium commonly found as a commensal in the human microbiota, possess a plasticity of their genome that have allowed them to evolve into pathogenic strains able to cause clinically important disease and syndromes in humans and animals. Pathogenic *E. coli* are mainly gathered into two groups depending on the disease localization: extraintestinal pathogenic *E. coli* (ExPEC) and intestinal pathogenic *E. coli* (InPEC). While ExPEC strains are associated mainly with neonatal meningitis (NMEC) and urinary tract infections (UPEC); InPEC strains, related to diarrheal disease, are subdivided into at least 6 well-known pathotypes: enteropathogenic *E. coli* (EPEC), enterohemorrhagic *E. coli* (EHEC, that also belong to the Shiga toxin-producing *E. coli* group (STEC), enteroinvasive *E. coli* (EIEC), enteroaggregative *E. coli* (EAEC), diffusely adherent *E. coli* (DAEC), and enterotoxigenic *E. coli* (ETEC).

Nowadays, diarrheal diseases are one of the major burdens in public health worldwide and are caused by several etiological agents, for example *Shigella, Norovirus,* as well as InPEC. Without a vaccine, diarrheal diseases are a big issue in low-mid income countries (Asia, Africa and Latin America) and cause an increase in disability-adjusted life years (DALYs) [1], and even raise the cost in health care. While EPEC and ETEC pathotypes are mainly endemic in developing countries, other pathogens such enterohemorrhagic *Escherichia coli* (STEC) O157:H7 and non-O157 STEC, are responsible for large outbreaks around the world, mainly in developed countries, causing not only diarrheal disease but bringing clinical complications like hemorrhagic colitis, and hemolytic uremic syndrome (HUS, a rising issue in Latin-American countries like Argentina (reviewed [2]. Uniquely, enteroaggregative *E. coli* pathotype has been involved in diarrheal diseases in developing and industrialized countries [3]. More recently, an uncommon EAEC of serotype O104:H4 that is multidrug-resistant and is able to express the Shiga-like toxin (Stx) was responsible of the large outbreak in Europe in 2011. With 3816 reported cases, this outbreak led to 845 cases of hemolytic–uremic syndrome and 54 deaths, [4, 5].

Although the use of antibiotics is an important key strategy to treat the infections, at the present time there is an increase in antibiotic resistant strains that have become a problem in public health and that also restricts treatment of infections caused by pathogenic bacteria.

Overall from i) increases in the public health burden caused by disease; ii) endemic ETEC and EPEC cases in developing countries; iii) infections with STECs and increased numbers of HUS cases; iv) increased annual costs for the healthcare system; v) emergence of antibiotic resistant strains, arises the need for an effective treatment. One of the most suitable strategies would be the existence of a vaccine; however, to date there is not a universal or specific licensed vaccine against InPECs or any of the pathovars.

The genomic plasticity of *E. coli* leads to rapid exchange of genetic material – such as virulence factors and loci– among the different pathotypes. Consequently, there exists a large diversity of lineages and genetic elements [6, 7], delaying the development of an effective treatment and vaccine. The virulence factors (encoded in genes) that differentiate diverse InPECs as well as the disease evolution and host-pathogen interactions vary among each pathotype and even among strains.

Nonetheless, advances in whole genome sequencing and genomic analysis have opened new horizons in vaccine development. Innovative approaches like Reverse Vaccinology, based on genomic analysis of pathogens, can be used for identification of potential antigens by bioinformatic tools. This has allowed the identification of prospective antigens and development of a safe and broad protective vaccine against *Neisseria meningitidis* serogroup B. The same approach has been successfully applied to many other pathogens including extra intestinal pathogenic *E. coli* (ExPEC) for which a number of promising antigens have been identified (reviewed [8, 9]. In particular, the genome sequence analysis of a neonatal meningitis isolate (NMEC) allowed the identification of 230 potential antigens. The most protective antigens discovered were an adhesin (FdeC, a broadly conserved adhesin) and a secreted and surface-associated lipoprotein from *Escherichia coli* (SslE, a conserved zinc metallopeptidase). These antigens confer cross protection in three different murine models: intestinal, urinary and sepsis models [10-12].

Vaccine candidates for ExPEC and InPEC identified so far are reported in Table 1.

Table 1. Vaccine candidates for vaccine development.

Pathotype	Antigens/Model	Selection	Reference
ExPEC	SslE and FdeC. major protective antigens (sepsis animal model) and broadly conserved in ExPECs	Reverse Vaccinology approach	[11]
ETEC	YghJ, pAT, Ag43, EaeH, EtpA, EatA, LT, ST, CF's antigens. Protective in mouse models. ACE527 ETEC complex, human trials.	Immnunoproteomincs, In sillico and other approaches	[13-16]
EHEC (DNA vaccine)	65 antigens identified: 2 more protective effect. pVAX56.2, pVAX10, pVAX12 and pVAX41. Mouse model	In silico model approach	[17, 18]
EHEC	EspA, Tir, Intimin, StxB.	In sillico approaches *Immunoproteomics.	[19-23]
EPEC	EspA, EspB, BfpA	Detection of human antibodies in maternal milk and stools.	[24-26]

As previously mentioned, the battle to develop an effective vaccine able to protect against InPEC infection, has not been easy. Nonetheless, by applying the new approaches including, genomics, proteomics and immunoproteomics allowed the identification of vaccine candidates able to elicit an immune response following infection.

In recent years, there have been important efforts towards vaccine development by different research groups, worldwide, and at present, the most effective strategy is to reinforce collaboration among scientists and create synergies between the different programs such as the Global Burden of Disease (GBD by Health Metrics and Evaluation, 2010) and Child Health Epidemiology Reference Group (CHERG by World Health Organization) [27], focused on estimation of cause-specific disease morbidity-mortality and specific ethology agent responsible of different diseases including the diarrheal ones.

Recently, it has been proposed that multidisciplinary research, collaboration and partnerships should adopt the One Health concept, as done in Latin America [28]. In particular, this concept states that there is a interdependence between human health and the environment, animals and human beings to achieve this objective, research should be extended to animal pathogenic strains. Examples of this are E. coli research studies in animal reservoirs [29]. Although the vaccine field is advancing very fast, and new sophisticated approaches are being applied for the identification of new and effective antigens, the battle against InPEC infections is still open and only multidisciplinary research efforts in the field of microbiology, immunology, epidemiology, medicine, clinical, veterinary and public health, could allow to understand the disease in different settings and the design of new preventive strategies.

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Conflict of Interest Statement

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