

Extraintestinal Pathogenic *Escherichia coli*, a Common Human Pathogen: Challenges for Vaccine Development and Progress in the Field

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Extraintestinal pathogenic *Escherichia coli* (ExPEC) is the most common gram-negative bacterial pathogen in humans. ExPEC causes the vast majority of urinary tract infections (UTIs), is a leading cause of adult bacteremia, and is the second most common cause of neonatal meningitis. Increasing multidrug resistance among ExPEC strains constitutes a major obstacle to treatment and is implicated in increasing numbers of hospitalizations and deaths and increasing healthcare costs associated with ExPEC infections. An effective vaccine against ExPEC infection is urgently needed. The O antigen, a component of the surface lipopolysaccharide, has been identified as a promising vaccine target. With the availability of a novel bioconjugation technology it is expected that multivalent O antigen conjugate vaccines can be produced at industrial scale. Clinical proof of concept of a 4-valent O antigen conjugate vaccine is ongoing. An ExPEC vaccine effective against strains that are associated with major diseases and resistant to multiple drugs could be routinely delivered to individuals at risk of developing severe *E. coli* infection, such as elderly people, individuals undergoing abdominal surgery and prostatic biopsy procedures, and persons at risk of recurrent and/or complicated UTI.

Keywords. *Escherichia coli*; extraintestinal pathogenic *Escherichia coli*; vaccine; O antigen; disease burden; antimicrobial resistance; urinary tract infection.

Extraintestinal pathogenic *Escherichia coli* (ExPEC) is the most common gram-negative bacterial pathogen, causing a diverse range of clinical diseases that affect all age groups. ExPEC is the most common cause of bacteremia, which primarily affects older adults, and is a frequent cause of meningitis in neonates [1]. The majority of urinary tract infections (UTIs) in young healthy women are caused by ExPEC [1]. Global morbidity and mortality rates due to ExPEC infections are substantial and increasing. The worldwide emergence of the multidrug-resistant (MDR) *E. coli* sequence type (ST) O25b:ST131 clone represents a major challenge for prevention and management of *E. coli* infections [2]. As yet, no prophylactic vaccine against ExPEC exists. Despite promising results during early investigations of candidate vaccines in human trials during the 1990s [3], vaccine development did not progress, largely because of technical issues associated with vaccine production. In this review, we highlight the importance of ExPEC as a human pathogen of global significance. Although there is an urgent need for an

effective ExPEC vaccine, only 1 vaccine manufacturer is currently performing clinical investigations in humans.

Classical serological typing of *E. coli* is based on the O, H, and K surface antigens, first described by Kauffman in the 1940s and developed by Frits and Ida Orskov, who made seminal contributions to *E. coli* typing [4]. The ‘O’ designates “ohne Hauch” and refers to nonspreading growth on agar; ‘K’ is for “Kapsel,” and ‘H’ is for “Hauch.” The O antigen forms part of the *E. coli* lipopolysaccharide (LPS), which comprises a membrane anchoring lipid A domain linked to a core oligosaccharide with repeating O antigen subunits that show marked variability between strains, with >180 distinct O antigens described [5]. Despite this variability, typing studies dating back to the 1940s show that O antigens have remained remarkably stable over time [4, 6, 7]. O antigens are only present in strains displaying smooth-colony morphology; strains displaying rough-colony morphology do not express O antigens and cannot be serotyped on the basis of the O antigen. The K antigen is the *E. coli* polysaccharide capsule, of which there are >80 distinct types known [8], and the H antigen is the flagellum, of which there are >50 types [9]. O, K, and H antigens can be present in any combination, leading to an enormous number of strains that differ in their immunological profile.

ExPEC: A Major Human Pathogen

ExPEC has the potential to invade many tissues and to cause infection in any age group. Although the most common ExPEC infections are UTIs and bacteremia, ExPEC is also isolated from persons with infections in areas such as the respiratory tract,

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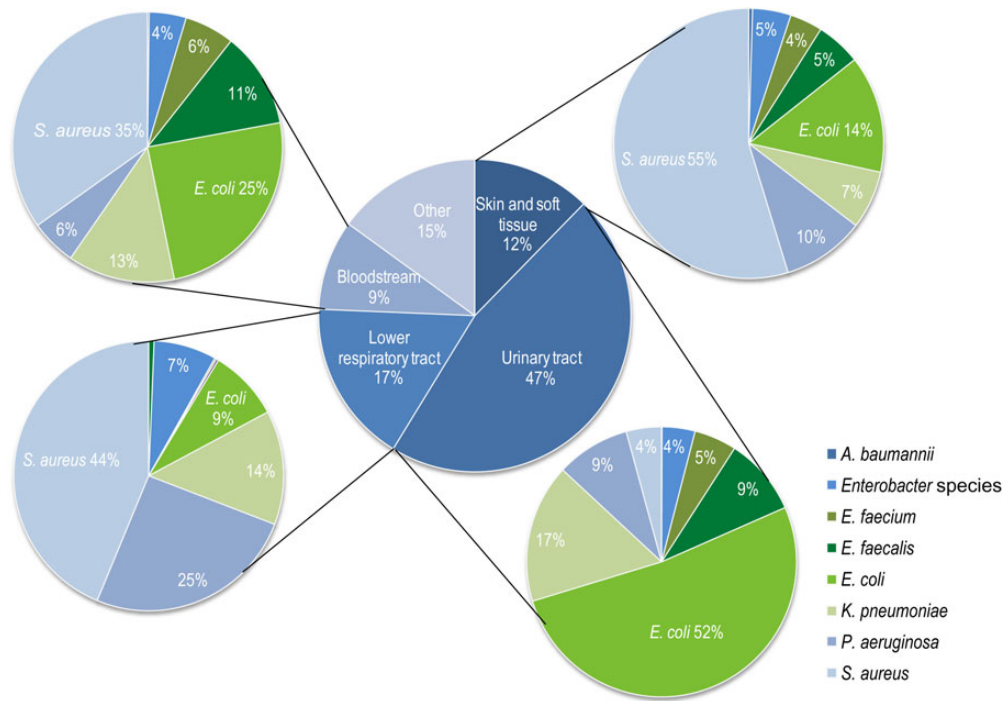


Figure 1. Distribution of pathogens among isolates from 80 089 hospital admissions in 19 US hospitals between 2007 and 2010 [10]. Abbreviations: *A. baumannii*, *Acinetobacter baumannii*; *E. coli*, *Escherichia coli*; *E. faecalis*, *Enterococcus faecalis*; *E. faecium*, *Enterococcus faecium*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*.

skin, and soft tissue (Figure 1). Along with Group B Streptococcus, ExPEC is a leading cause of neonatal meningitis [1] and a frequent cause of prostatitis, peritonitis, and pneumonia [1].

UTIs

In the United States, UTIs account for approximately 0.9% of all outpatient and emergency department visits and nearly 8% of all hospitalizations [11, 12]. Catheter-associated UTIs are the second most common cause of healthcare-related infections in the United States [13]. The vast majority of uncomplicated infections, recurrent UTIs, and cases of pyelonephritis, and around one third of catheter-associated infections in the United States are caused by ExPEC (Table 1).

Rising prevalence of strains that are resistant to first-line oral agents such as trimethoprim-sulfamethoxazole, ampicillin, and fluoroquinolones has been documented globally among *E. coli* UTI isolates [14]. Hospital admissions for UTIs increased by 50% in the United States between 2000 and 2009 [12]. However, hospital admissions caused by extended-spectrum β -lactamase (ESBL)-producing *E. coli* increased by 300%, illustrating the growing burden and healthcare-related costs due to ExPEC and the urgent need for effective interventions [12].

E. coli Bacteremia

E. coli is a leading cause of bacteremia worldwide [15, 16]. The most common source of bacteremia in adults is the urinary tract [17]. Between 2% and 6% of patients who undergo transrectal

prostate biopsy develop infectious complications, which can include bacteremia [18]. In this population, fluoroquinolone-resistant ExPEC strains colonizing the rectum are the most common source of infections [19].

The overall annual incidence of *E. coli* bacteremia in adults ranges between 30 and 50 cases/100 000 population but increases markedly with age (Figure 2A) [15, 20]. Among adults aged ≥ 65 years, the incidence of community-acquired ExPEC bacteremia

Table 1. Burden of Extraintestinal Pathogenic *Escherichia coli* Urinary Tract Infection (UTI) in the United States

Disease	Incidence or Risk	Burden		
		Cases due to <i>E. coli</i> , %	Cases, Annual No.	Annual Cost (Year)
UTI	>50% lifetime risk in women [11]	85–95 [1]	10.5 million office/ED visits [11]	2.3 billion (2010) [11]
CAUTI	4-fold increased risk [11]	25–35 [1]	1 million–1.5 million [1]	170–350 million (2000) [1]
Pyelonephritis	59.0 cases/10 000 women, 12.6 cases/10 000 men [11]	90 [1]	250 000 admissions [1]	2.14 billion (2000) [11]

Abbreviations: ED, emergency department; CAUTI, catheter-associated urinary tract infection; UTI, urinary tract infection.

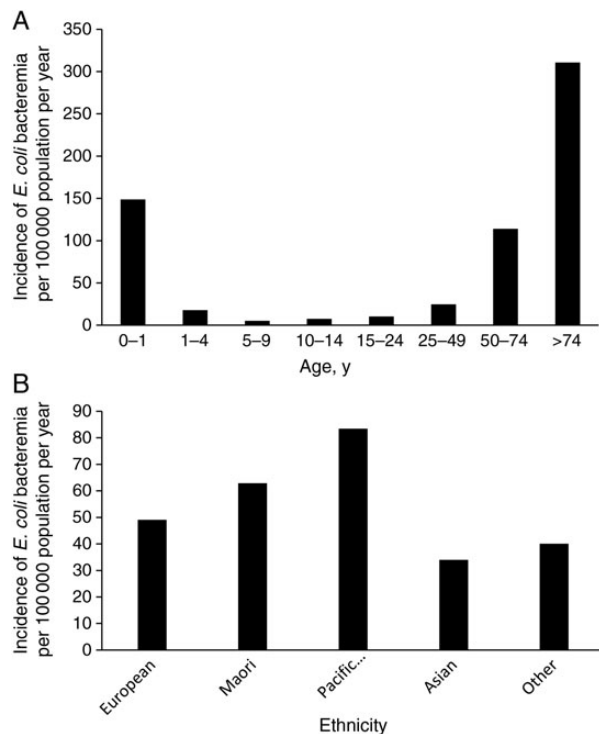


Figure 2. A, Incidence of *Escherichia coli* bacteremia, by age, in Auckland, New Zealand, between 2005 and 2011. The figure is reproduced from the article by Williamson et al [20]. B, rising numbers of *E. coli* bacteremia isolates reported to the European Antimicrobial Resistance Surveillance System between 2002 and 2008. Data are from the article by De Kraker et al [16]. Abbreviations: *E. coli*, *Escherichia coli*; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*.

was 150 cases/100 000 person-years (1998–2001 in the United States) and 452 cases/100 000 person-years in individuals aged ≥ 85 years [17]. Case-fatality rates for bacteremia are between 13% and 19% but may be much higher (up to 60%) in elderly persons with nosocomial infections [21]. In 2001, it was estimated that, in the United States, severe *E. coli* sepsis caused approximately 40 000 deaths [1]. All-cause septicemia-related hospitalizations in the United States increased by approximately 8% annually between 2000 and 2008 and by 4% between 2008 and 2009 [22]. Assuming that the rate of increase has continued at 4% and that the proportion of sepsis due to *E. coli* and the case-fatality rate has continued unchanged over that time, we estimate that there may have been >85 000 deaths due to *E. coli* sepsis in 2014 in the United States alone. Hospitalizations associated with sepsis were the most costly reason for hospitalization in the United States in 2008, making up 4% of all inpatient costs [22].

Similar trends have been observed in Europe: the number of cases of *E. coli* bacteremia increased by 8.1% annually between 2002 and 2008 (Figure 2B), accompanied by a 30% annual increase in third-generation cephalosporin-resistant isolates [16]. A retrospective 15-year evaluation of bacteremia in Denmark (during 1992–2006) also showed an increasing incidence of

gram-negative bacteremia, with the majority of community-acquired, nosocomial, and healthcare-related bacteremia caused by *E. coli* and the majority occurring in elderly individuals [23]. In the United Kingdom, the incidence of *E. coli* bacteremia increased by almost 70% between 1999 and 2011, largely driven by infections with antibiotic-resistant strains, which increased 7-fold over the study period [24]. Thus, *E. coli* bacteremia is a costly, potentially lethal, and increasingly frequent problem exacerbated by societal aging and increasing prevalence of antibiotic-resistant strains.

ANTIMICROBIAL RESISTANCE: AN IMMINENT GLOBAL EMERGENCY

Resistance mechanisms to all major antibiotic classes exist among *E. coli* strains. These include the production of ESBLs, including TEM, SHV, CMY, and CTX-M types, and carbapenemases (NDM-1 and OXA-48 types). Currently, CTX-M-15 is the most prevalent ESBL among ExPEC [2]. Resistance to fluoroquinolones and aminoglycosides occurs via plasmid- or chromosomally encoded transferases or via mechanisms that reduce antimicrobial uptake into the cell. Rapid dissemination of newly resistant ExPEC clones, including *E. coli* O25b:ST131, are known to lead to localized outbreaks of extraintestinal disease.

Antibiotic-resistant *E. coli* strains are increasingly prevalent. In Europe, the population-weighted mean percentage of resistant *E. coli* isolates was 11.8% for third-generation cephalosporins and 22.3% for fluoroquinolones (data are from 2012) [25]. MDR (resistance to ≥ 3 antibiotic classes) made up 4.4% of all European isolates in 2012. In the United States, 31.3% of *E. coli* isolates among hospitalized patients (during 2007–2010) were fluoroquinolone resistant [10]. In India, the prevalence of MDR *E. coli* has been reported to be as high as 76% among inpatients with UTIs [26].

Antibiotic resistance frequently leads to treatment failure; increased rates of hospitalization, morbidity, and mortality; and increased associated healthcare and societal costs. Increasing antimicrobial resistance coupled with the current lack of truly novel antimicrobial agents is rapidly emerging as a major threat to human health and development, with direct effects on global productivity [27]. A United Kingdom Prime Minister review committee estimated that 50 000 deaths in the United Kingdom and United States are caused by antibiotic-resistant infections annually [27]. Antibiotic-resistant *E. coli* infections already account for one half of the estimated global burden caused by antibiotic resistance [27]. Antibiotic-resistant ExPEC is fueling increases in hospitalization rates for UTI and increases in infectious complications after prostatic biopsy and is a risk factor for poor outcome in patients with bacteremia [28, 29]. Increasing rates of infectious complications after prostatic biopsy documented in several countries are thought to be due, in part, to increasing *E. coli* antibiotic resistance [28].

ST131 EPIDEMIC

The ST clonal group known as ST131 is a virulent, antibiotic-resistant *E. coli* strain found in community and healthcare settings and within the environment. The ST131 strain is frequently associated with CTX-M-15 and is usually fluoroquinolone resistant [2]. Within the ST131 clonal complex are several sublineages that show specific virulence traits and antibiotic resistance profiles. A ST131 clonal subtype known as H30 (fimH-based lineage) emerged a little more than a decade ago and now predominates among ST131 strains worldwide. H30 is characterized by fluoroquinolone resistance due to point mutations in *gyrA* and *parC* and by a distinct set of virulence factors [2]. The H30 sublineage is more prevalent than other clones among patients with recurrent or persistent UTI and patients with bacteremia [30].

The vast majority of ST131 strains exhibit serotype O25b:H4, but recent work has identified an O16 ST131 subset: a virulent, usually fluoroquinolone sensitive clade thought to comprise around 5% of all *E. coli* isolates worldwide [31]. The O16 subclone and an H22 subclone are the second most prevalent ST131 clades [31].

ST131 contributes substantially to *E. coli* resistance among clinical isolates. ST131 comprises approximately 70% of fluoroquinolone-resistant strains in the United States and >50% of MDR isolates [32]. The prevalence of *E. coli* fluoroquinolone resistance was 16% in Europe (during 2002–2008) [16] and 31.3% in US hospitals (during 2007–2010) [10]. The H30 subclone is the most prevalent MDR subclone among nosocomial ExPEC infections [33]. Hospital outbreaks of ST131 strains have been described with evidence of potential for wide dissemination among inpatients and residents of long-term care facilities [34].

IMPORTANCE OF THE O ANTIGEN

The O and K antigens are well-described virulence factors that contribute to *E. coli* survival through evasion of host defenses [35]. The O antigen and, to a lesser extent, the K-capsular polysaccharide inhibit phagocytosis and complement-mediated killing and contribute to bacterial survival in human serum.

The importance of the O antigen in conveying serum sensitivity and contributing to virulence suggests that the effects of O antigen could be hampered by antibody. Immunoglobulin G (IgG) antibodies to *E. coli* surface antigens develop during childhood and increase through adolescence [36]. Levels of IgG antibody to surface antigens increase in patients with bacteremia [36], and the antibody response is largely directed at the O antigen [35]. O-specific and K-specific antibodies have been shown to promote phagocytosis and to confer protection against homologous lethal challenge in animal models [37]. Nevertheless, infection can occur in individuals with circulating anti-O antibodies [36], and in some cases, anti-K antibodies may confer a higher degree of protection than anti-O antibodies

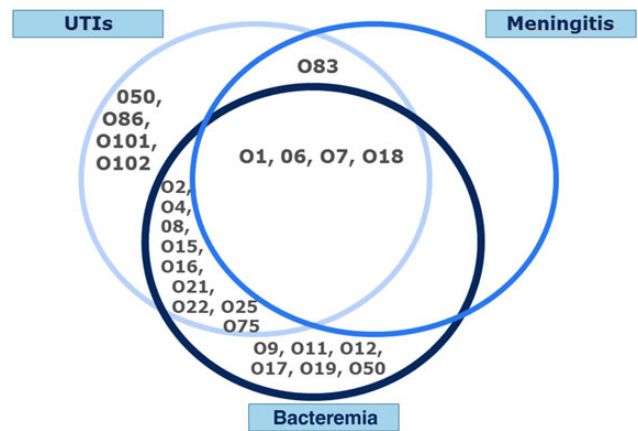


Figure 3. *Escherichia coli* O serotypes causing extraintestinal infections. Data are from the article by Orskov et al [41]. Abbreviation: UTIs, urinary tract infections.

[37]. As for O antigens, a relatively small number of K antigens predominate among ExPEC strains, with K1 being the most common capsular type [38, 39]. While vaccines containing K1 have been considered, the K1-antigen is identical to the capsular polysaccharide of *Neisseria meningitidis* serogroup B and resembles sialylated glycoproteins found in human neural tissue [40]. Owing to concerns about their potential for cross-reactivity with human tissue, early attempts at *E. coli* vaccine development primarily focused on the O antigen [3].

The distribution of ExPEC strains can be influenced by age, the site of infection, and setting. While there are >180 O serotypes currently described [5], only a subset of these are associated with the majority of ExPEC infections, with limited geographic variation (Figure 3) [41]. Between 10 and 12 O serotypes account for approximately 90% of meningitis isolates and >60% of bacteremia isolates [3].

PAST ATTEMPTS AT ExPEC VACCINE DEVELOPMENT

Attempts to develop *E. coli* vaccines targeting O antigens began decades ago but proved unsuccessful [39]. This is because LPS activates Toll-like receptor 4, inducing severe local and systemic reactions, and therefore requires detoxification before it can be administered to humans. Detoxification is achieved by removing lipid-A via hydrolysis. While this improves the reactogenicity profile, detoxification also reduces the immunogenicity of the polysaccharide [39]. The limited immunogenicity of some O polysaccharides also requires either protein conjugation or adjuvant to induce an adequate immune response.

An O18-polysaccharide-protein conjugate vaccine that used *Pseudomonas aeruginosa* exoprotein A (EPA) as the carrier protein was immunogenic, promoted opsonophagocytic killing (OPK) in mice and humans, and provided protection in mice against lethal O18 challenge [42]. Subsequently, Cross et al published a clinical trial of an O polysaccharide conjugate vaccine

containing purified polysaccharide from 12 O serotypes conjugated to EPA [3]. Healthy adults received 1 vaccine dose containing 25 µg of each of the 12 polysaccharides. A 4-fold increase in antibody as compared to baseline was observed for at least 4 of 12 serotypes in every subject (except one individual, who was a complete nonresponder). However, the percentage of individuals with 4-fold rises in enzyme-linked immunosorbent assay antibody titers appeared to be dependent on the prevaccination concentration for 9 of 12 serotypes, whereas for serotypes O16, O25, and O75, preexisting immunity did not influence the postvaccination response. Different serotypes appeared to have different immunogenic potential (O1 and O6–O8 being more immunogenic than O4, O12, O16, and O25), and the susceptibility of individual serotypes to OPK also differed. Previous exposure to EPA in one subject who was a complete nonresponder is suggestive of carrier-induced immune suppression (CIES) [3].

Despite the success of chemical conjugation techniques in progressing vaccine development, the process of combining multiple individually conjugated serotypes in a single vial is technically challenging and costly [43]. In addition, the O

antigen is much harder to purify as (delipidated) polysaccharide, compared with, for instance, meningococcal and pneumococcal capsular polysaccharides. These limitations, as well as the imperative for a multivalent vaccine to successfully influence ExPEC-associated disease, have delayed ExPEC vaccine development.

BIOCONJUGATION: A NEW OPPORTUNITY FOR MULTIVALENT ExPEC VACCINE DEVELOPMENT

The technique of in vivo bioconjugation is an important advance with implications that may be as far reaching as that of the original development of conjugation technology. Bioconjugation refers to the biosynthesis of polysaccharide and carrier protein within *E. coli* cells and their subsequent in vivo coupling by use of the oligosaccharyltransferase PglB from the N-linked protein glycosylation system originally identified in *Campylobacter jejuni* and subsequently transferred to *E. coli* [43]. In the bioconjugation process, PglB acts to transfer diverse O polysaccharides to a protein carrier (eg, EPA) present in the periplasm, from which the resulting bioconjugate is subsequently harvested using a generic purification process (Figure 4) [44]. Thus, the

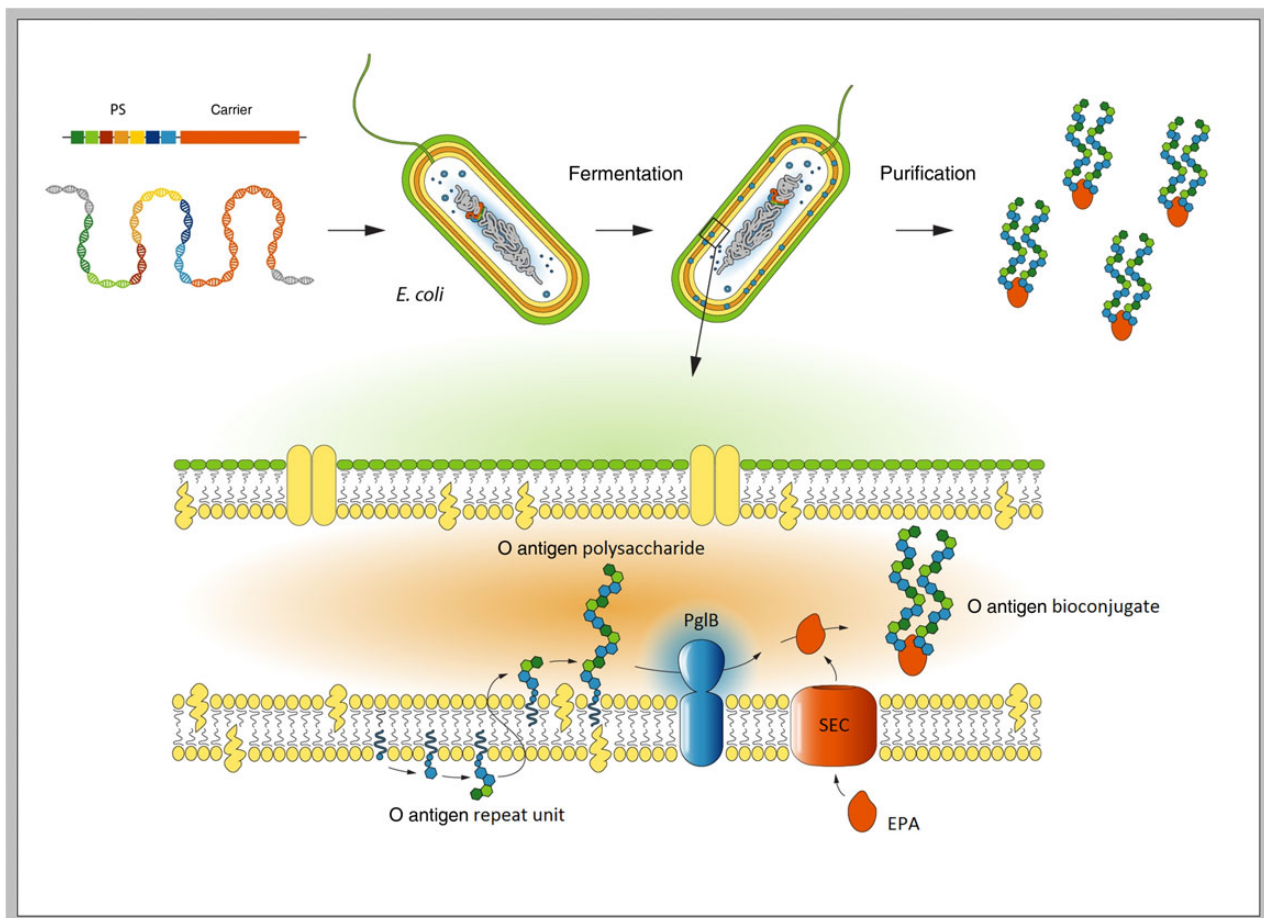


Figure 4. Process of in vivo bioconjugation, using recombinant *Escherichia coli*. *Campylobacter* oligosaccharyltransferase (PglB) transfers selected O polysaccharides (devoid of lipids) to the *Pseudomonas aeruginosa* exoprotein A (EPA) protein carrier present in the periplasm. Abbreviation: SEC, secretory pathway.

bioconjugation process allows for in vivo conjugation of multiple specific O polysaccharides to specific sites of any protein carrier and removes the requirement for chemical detoxification of LPS. Polysaccharide-protein conjugate molecules developed by this process have a well-defined and homogenous structure and do not suffer from loss of epitopes, which may occur during chemical conjugation processes [45]. The resulting bulk is of high purity with very low levels of free polysaccharide. The potential for large-scale production has been demonstrated [44].

A 4-valent prototype *E. coli* bioconjugate vaccine (EcoXyn-4V; GlycoVaxyn) is being evaluated in a phase 1 study (clinical trials identifier NCT02289794), with results expected at the end of 2015.

CHALLENGES AHEAD

Advances Are Needed in Molecular Typing Methods

The availability of a low-cost test capable of rapid detection of specific clades based on O serotypes or other combinations of antigens, such as CH typing (*fumC* and *fimH*), could have important clinical implications for treatment of ExPEC infections [30]. The use of inappropriate antibiotics has been associated with persistent or recurrent UTI [30] and is a risk factor for mortality in patients with bacteremia [29]. Rapid testing for clonal groups associated with antibiotic resistance has been proposed as a means by which to reduce the chance of inappropriate antibiotic administration prior to the availability of culture results [30].

Strain Selection

Because of its contribution to virulence and immunodominance, the O antigen appears to be a suitable antigen for development of an ExPEC vaccine. Up to date, systematically collected data describing serotypes implicated in antibiotic resistance and serotype distribution by disease (UTI, meningitis,

and bacteremia), age, and region are needed for serotype selection (Figure 5).

Vaccine manufacturers also need to consider whether a candidate ExPEC vaccine should be for general use, indication specific (such as different vaccines for prevention of UTI and bacteremia), or strain specific (such as targeting strains known to be highly antibiotic resistant; Figure 5). O serotype 25b, being strongly associated with ST131, will need to be included in any ExPEC vaccine that enters the market. Updated information on predominant serotypes and technical considerations, such as the number of bioconjugated serotypes that can be successfully included in a single vaccine, will drive these decisions. Nevertheless, given current knowledge, the marked overlap of ExPEC O serotypes causing UTIs, meningitis, and bacteremia (Figure 3) and the fact that the urinary tract is the most common entry point to the bloodstream suggest that a single, multivalent ExPEC vaccine will likely have an impact on all forms of ExPEC-associated disease, particularly if given routinely to older adults.

Demonstration of Efficacy

In the absence of a serological correlate of protection, and because it is not known whether vaccine efficacy will be similar for different indications and within different target age groups, serotype-specific efficacy of a candidate ExPEC vaccine in preventing each target disease in each target population may need to be demonstrated (Figure 5). Efficacy studies with definitive outcomes should be achievable in certain diseases and populations, given the frequency of disease caused by ExPEC.

Ultimately, identification of a serological correlate of protection may be achievable, as has been the case for vaccines against *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *N. meningitidis*, although the protective threshold may differ according to O serotype, indication, and age group. For example, prevention against bacteremia is likely to rely on circulating antibodies capable of binding to O antigen and promoting opsonophagocytosis. Mechanisms of protection against UTI are less well understood and may differ, such as for simple uncomplicated UTI versus persistent or recurrent UTI or for UTI in individuals with indwelling catheters. It is not known whether protection of the urinary tract would be conveyed through vaccine-induced immunoglobulin A (IgA) or IgG or whether urinary tract antibody levels are important. Thus, it is conceivable that high serum antibody levels that transudate into the mucosal tissues may be needed to achieve protection against recurrent or complicated UTI, in which biofilm formation can impede access of antibody. A similar situation proved to be the case for pneumococcal diseases, in which lower antibody concentrations appeared necessary to prevent invasive pneumococcal bacteremia, compared with pneumococcal otitis media. In the case of pneumococcal otitis media, a link between efficacy

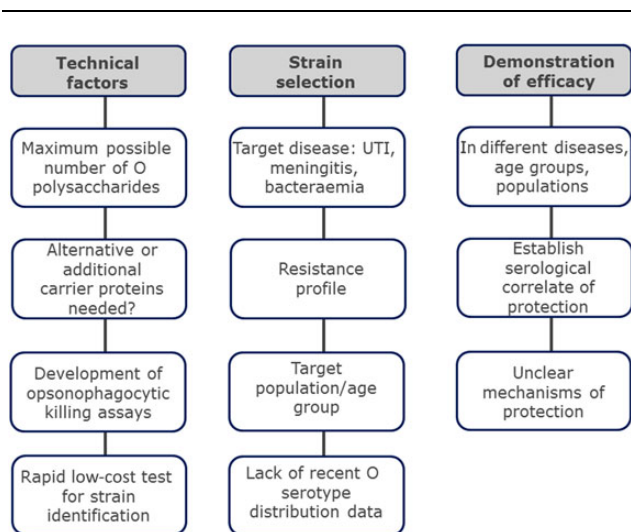


Figure 5. Challenges to extraintestinal pathogenic *Escherichia coli* vaccine development. Individual challenges to vaccine development need to be surmounted to achieve successful technical development, appropriate strain selection, and demonstration of efficacy in the target population. Abbreviation: UTI, urinary tract infection.

and serum IgG but not mucosal IgA was observed, suggesting that transudating IgG is most important for protection [46].

The immune response to vaccination typically decreases with age, and specific assessment of immunogenicity and efficacy will be needed to evaluate vaccination in elderly people, who are at highest risk of ExPEC bacteremia. Other worthwhile investigations could include duration of protection, the need for booster doses, and the effect of vaccination on gastrointestinal flora. Analysis of the human microbiome indicates that *E. coli* constitutes <1% of intestinal flora overall, with even lower representation of the 10–12 candidate vaccine O serotypes [47]. Thus, while vaccination against 10–12 O serotypes (of >180) would be unlikely to have any substantial impact on gastrointestinal and/or urogenital flora or result in serotype replacement [39], the impact of vaccination on carriage of the target strains could help to predict the likelihood of recurrence (eg, for UTIs) of disease due to specific O serotypes. By eliminating specific serotypes from the gastrointestinal tract, vaccination could induce a herd effect.

Validated assays are needed to assess immunogenicity and to support efforts to establish a serum correlate of protection. Assessment of functional antibodies, using OPK assays, will likely yield the most clinically relevant information.

Carrier-Induced Epitopic Suppression

Studies in mice using a 12-valent *E. coli* LPS-EPA-conjugated vaccine showed that the immunogenicity of multiple serotypes on the same carrier protein was reduced as compared to the separate evaluation of monovalent vaccines after multiple immunizations, suggesting CIES and a potential limit to the amount of carrier protein able to be administered [48]. CIES is observed for some other carrier proteins, notably tetanus toxoid in infants after multiple immunizations [49]. Whether the bioconjugation process will minimize CIES when used to produce multivalent *E. coli* vaccines is not yet known. The use of alternative carrier proteins, potentially with direct activity against *E. coli*, could circumvent this issue. On the other hand, the use of a single immunization in adults is unlikely to be sensitive to CIES.

CONCLUSION

ExPEC is a global pathogen causing a spectrum of diseases that affect all ages. The increasing incidence and associated costs of disease caused by ExPEC and the burgeoning problems associated with the emergence and spread of MDR ExPEC strains means that an effective vaccine against ExPEC infection is urgently needed. The O antigen is a feasible vaccine target that has been shown to be immunogenic in humans, with induction of opsonophagocytic antibodies demonstrated, and has conveyed protection against lethal challenge in preclinical models. For the first time, the technique of bioconjugation has opened up the possibility for the development of a multivalent O antigen-based bioconjugated ExPEC vaccine. It may be desirable

that an effective ExPEC vaccine could be routinely implemented in adults >50 years of age along with existing influenza and pneumococcal strategies in this age group. Targeted vaccination of other specific groups at risk of invasive *E. coli* infections, such as patients undergoing prostate needle biopsy or abdominal/genitourinary surgery, residents of long-term healthcare facilities, individuals with indwelling catheters, and those at risk of recurrent or complicated UTIs, could potentially provide benefits to these groups. Most importantly, wider implementation of an ExPEC vaccine could potentially reduce infections due to resistant strains, impacting positively on patterns of antibiotic use, the spread of resistant clones, healthcare costs, and, potentially, future global productivity.

Notes

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