Current Opinion in Infectious Diseases

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--Manuscript Draft--

Manuscript Number:	
Full Title:	The current state of immunisation against Gram-negative bacteria in children: review of the literature
Article Type:	Review Article
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The current state of immunisation against Gram-negative bacteria in children: a review of the literature

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Keywords: Gram negative bacteria, immunisation, public health, antibiotic resistance, maternal immunisation

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Abstract

Purpose of review

Gram-negative bacteria (GNB) are a major cause of infection worldwide and multidrug resistance in infants and children. The major pathogens include *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. With new antibiotic options limited, immunisation is likely to play a critical role in prevention. This review discusses their epidemiology, the current state of vaccine research, and potential immunisation strategies to protect children.

Methods

A comprehensive review of the literature, conference abstracts along with web searches was performed to identify current and investigational vaccines against the major GNB in children.

Recent findings

Phase 1-3 vaccine trials have been undertaken for the major Gram-negative bacteria, but not in infants or children. *E. coli* is a common infection in immune competent children, including neonatal sepsis. Several vaccines are in late-phase clinical trials, with some already licensed for recurrent urinary tract infections in women. *Klebsiella* spp. causes community- and hospital-acquired infections, including sepsis in neonates and immunocompromised children although no vaccine trials have extended beyond early phase II trials. *P. aeruginosa* is a common pathogen in patients with cystic fibrosis. Phase I-III vaccine and monoclonal antibody trials are in progress, although candidates provide limited coverage against pathogenic strains. *Enterobacter spp. and A. baumannii* largely cause hospital-acquired infections with experimental vaccines limited to phase I research.

Summary

The current immunisation pipelines for the most prevalent GNB are years away from licensure. Similar to incentives for new antibiotics, global efforts are warranted to expedite the development of effective vaccines.

Introduction

The rising burden of sepsis caused by Gram-negative bacteria (GNB) and rapidly increasing antimicrobial resistance rates present major challenges because of a lack of effective treatments (1). In infants and young children, Gram-negative infection is not only a major cause of community-acquired sepsis but also of multidrug-resistant (MDR) bacterial disease and hospital-acquired infections, and is associated with high rates of morbidity and mortality worldwide, especially in lower- and middle-income countries (LMIC) (2). Given the high rates of MDR infections and lack of new antibiotics being developed (3), there is an urgent need to prioritise preventive strategies against these infections, focusing on passive and active immunisation. This review discusses the epidemiology, current state of research into active and passive immunisation, and potential immunisation strategies to protect high-risk children against GNB.

1. Burden of GNB disease

Gram-negative bacteria include a diverse range of species and subtypes, with five priority pathogens representing a significant global clinical burden: *Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Enterobacter* spp. and *Acinetobacter baumannii* (2) (see table 1). These are identified as high-priority pathogens by the World Health Organization (4) which has encouraged health institutes and researchers to find effective vaccines and treatments (4,5). GNB contain intrinsic antibiotic resistance mechanisms including decreased membrane permeability, efflux pumps and broad-spectrum-β-lactamases (3,6). A 2015 systematic review of paediatric (0-16y) sepsis across a range of LMIC found the level of resistance to third-generation cephalosporins in Gram-negative bacteria to be 84% in Asia and 50% in Africa (7). Up to 30% of neonatal sepsis deaths globally are caused by multi-drug-resistant pathogens (8).

Invasive bacterial sepsis due to GNB in childhood is associated with high morbidity and mortality, with one-third of patients developing progressive organ dysfunction and 17% of survivors experiencing at least moderate disability on discharge (2). Although case fatality rates have fallen, the odds of dying from sepsis remain more than four times higher in LMIC settings compared to high-income countries (10). Some children are at higher risk, especially

born premature, with underlying comorbidities such as malignancy, immunosuppression, or impaired host-barrier defences in cystic fibrosis and burns.

Neonates

A recent study estimated an annual global incidence of 3 million neonatal cases of sepsis (9-11). In neonates, Gram-positive bacteria, particularly Group B Streptococcus (GBS), remain a common cause of sepsis, especially in high-income countries, although the proportion of GNB has been increasing rapidly, with rising rates of *E. coli* infections reported in up to 29% of positive neonatal cultures (0.28 per 1000 live births) in both high-income and low-income countries (11–16). A recent systematic review of available data on microbiologically confirmed invasive bacterial infection in neonates from African countries since 1980, showed that *Klebsiella sp* accounted for 21% of culture-proven infections, second only to *Staphylococcus aureus* (25%), with *E.coli* accounting for 10% (8–10). Of note, *Klebsiella* infections have increased over time, from 15% (1980-2007) to 21% (2008-18).

Healthy children

In older children in high-income countries, GNB have been identified as causing more than 50% of paediatric sepsis (10), but their contribution in LMICs is less certain and more variable, ranging between 21% (10) to 67% (7,17). Published reviews, however, report different pathogen distribution in LMICs, and the most prevalent pathogen is *K.pneumoniae* compared to *Pseudomonas* spp. in high-income countries, possibly representing differences in the characteristics and risk factors of children presenting to hospital. A recent systematic review found *K. pneumoniae* was the predominant pathogen causing sepsis in LMICs, accounting for 50% of all GNB in children <16years, although this was limited by significant heterogeneity (7). Community-acquired infections in LMICs are also commonly caused by GNB including *Klebsiella* spp. (11,17-18). Analysis of global data on pathogens causing severe sepsis in paediatric intensive care units (PICUs), some of whom had comorbidities, reported the most prevalent being *Pseudomonas* spp. (7.9%), *Klebsiella* spp. (6.4%), *E. coli* (5.6%), *Enterobacter* spp (3.0%) and *Acinetobacter* spp. (2.5%) (2).

Immunocompromised children

Immunocompromised children, including those with cancer, on chemotherapy or receiving immunosuppressive medications, are also at high risk of GNB infection (33). In one UK

study, 80% of infections in paediatric cancer patients were associated with the presence of a central venous catheter and a quarter of culture-confirmed cases were due to GNB (34). GNB infection in immunocompromised children is also associated with high MDR rates; in one Brazilian paediatric oncology intensive care unit, MDR was detected in 50.0% of *E. coli*, 46.6% of *K. pneumoniae* and 36.4% of *A. baumannii* causing sepsis in children with haematological malignancy (35).

Hospital-acquired infections

Children in intensive care are disproportionately represented among reports of hospital-acquired GNB infections. In PICU, GNB infections are highly prevalent and associated with invasive devices such as intravascular catheters, ventilators, tracheostomies, nasogastric tubes, multiple antibiotic use and prolonged hospital stays (2,20,21). In neonates, low birth weight and premature infants are at risk, due to use of invasive devices, including ventilators, prolonged hospital stays and regular antibiotic exposure (14,22,23). Paediatric burn survivors are at risk due to disruption of the skin barrier, translocation across the gut mucosa and immunosuppression, with GNB responsible for half of deaths in some burns units (24-27) (24-30). Among childhood trauma, infection-related deaths have been reported due to *A. baumannii* (34.9%), *Pseudomonas* spp. (19.1%), *K. pneumoniae* (18.5%) because of tissue barrier disruption, invasive catheters and multiple antibiotic use (31-32).

Treatment

Inadequate stewardship, increased travel (with subsequent transmission of bacteria and resistant genes), limited antibiotic development, and intrinsic mechanisms contribute to rising multi-drug-resistant GNB (36-37). WHO guidelines for empiric antibiotic therapy of neonatal sepsis recommend gentamicin plus benzylpenicillin or ampicillin, with third-generation cephalosporins as second line (38-39), yet the majority of responsible pathogens are now resistant to these recommendations in African and Asian countries (18). Empiric antibiotic therapy is, therefore, increasingly based on local resistance; in South Asia, carbapenems are used as first-line empiric treatment for neonatal sepsis (2,8). Polymyxins are used as last-resort for carbapenem-resistant GNB (40), despite lack of safety or dosing data in infants (3).

Colistin-resistant *Enterobacteriaceae* infection has been reported in adults; with few paediatric data (41). New antibiotics in development with activity against MDR GNB include fosfomycin, cefiderocol, eravacycline and aztreonam-avibactam (40).

2. Vaccine research and development

Gram-negative bacteria included in this review share a three outer membrane structure. Early research focused on lipopolysaccharide (LPS), also known as endotoxin, a highly immunogenic component of the outer membrane complex (39). LPS contains three components. The outer O polysaccharide antigen is highly immunogenic and the outermost surface-exposed component, therefore making an excellent target for antibiotics, host and synthesised antibodies, but it varies widely between species and is responsible for the range of serotypes. Lipid A, the innermost region, is a highly conserved disaccharide with fatty acids. Considered the toxin component, it causes an inflammatory cascade, high fever and coagulopathy in sepsis (43). These are connected by an oligosaccharide on the outer surface of the cell wall core that binds the O antigen and Lipid A. LPS is the main trigger for systemic symptoms associated with sepsis (44).

Table 2 outlines the current status of GNB vaccine research. Use of such vaccines will depend on the target population and immunisation strategies will require knowledge of natural immunity and an assessment of patient needs and strategic priorities (Table 3).

E. coli

Disease targets

There are more than 160 *E. coli* serotypes but few are pathogenic in humans. The main targets for the disease would be serotypes causing invasive disease including neonatal sepsis and meningitis, in addition to those causing less severe disease including diarrhoeal disease and urinary tract infections (Table 1). Consequently, a multi-valent vaccine targeting a limited serotypes might be sufficient to prevent invasive disease without affecting carriage of benign serotypes (45). This is an important consideration because the majority of *E. coli* that colonise the human gut are non-pathogenic (46).

Virulence factors of *E. Coli*

An *E. coli* vaccine will need to act on multiple and diverse virulence factors common to the range of pathogenic *E. coli*; such specific virulence factors are less well-defined than in other pathogens (48). Moreover, *E. coli* infection is not immunogenic and the humoral response is short-lasting, suggesting previous infection may provide only partial immunity, further hindering vaccine development (47,49). Key virulence factors that enable immune evasion include the LPS O antigen and K antigen, with K1 and K5 virulent due to adhesins and toxins that facilitate colonisation and tissue penetration (50). The K1 antigen is a major cause of meningitis, whilst the K5 antigen, associated with neonatal sepsis, presents high heterogeneity, which is a major barrier to vaccine development (51) .

Vaccines against different disease targets

Vaccines for preventing *E. coli* sepsis have been developed with varying success. A phase 1 pilot study of an *E. coli* vaccine conjugated to *Pseudomonas* LPS was found to be safe and immunogenic; this vaccine covered 12 *E. coli* serotypes (O1, O2, O4, O6-O8, O12, O15, O16, O18, O25, O75) and significant increases in post-vaccination antibody titres were observed for most of the serotypes with demonstration of functionally active opsonophagocytic antibody that paralleled quantitative antibody responses (52). Attempts have been made to improve this vaccine by conjugation with other proteins; to date only a minimal additional increase in antibody titres in animal studies has been observed (59).

Vaccines against colonisation

There are licensed *E. coli* vaccines directed towards urinary tract carriage and infection in adults, including whole-cell/lysate-based vaccines, for symptomatic *E. coli* urinary infection. The most successful is Urovac (53), which has demonstrated some effect in reducing recurrent urinary tract infection in women. The vaccine has been licensed by the FDA in the United States, is administered by vaginal pessary and requires regular boosters; there are, however, no data on prevention of systemic infections (54). Such a vaccine has the potential to protect neonates against local and systemic *E. coli* infections by reducing maternal vaginal colonisation, and includes serotypes K1 and K5 which are large contributors to neonatal disease, but protection against neonatal disease is not discussed, and little work has been done on use in children or acceptability of pessaries in children/teenagers. Phase 1 research of oral lyophilized vaccines has been conducted in adults and found to reduce gastrointestinal carriage; other licensed *E. coli* vaccines also target secondary prevention of urinary tract infection; Uro-Vaxom (OM Pharma, Switzerland), an oral lyophilized protein vaccine from

18 *E. coli* serotypes, has demonstrated efficacy against UTI recurrence in adults, but requires daily administration for 3 months (55). Trials with the same vaccine have found no impact (56).

Passive immunisation

Attempts to derive monoclonal and polyclonal antibody therapies based on the vaccines above demonstrated conflicting results but most recently no significant impact was observed in phase 1 trials (43,52,57,58). Further monoclonal antibodies are in development (60).

Klebsiella pneumoniae

Disease targets

Important disease targets in *Klebsiella pneumoniae* include neonatal sepsis, hospital-acquired infections, and urinary infections (76,77).

Virulence factors

Virulence factors in *K. pneumoniae* include: 77 K capsular polysaccharide antigens, which have formed the predominant vaccine target; eight O LPS antigens; as well as a range of fimbriae (type 1 and 3) that promote biofilms and adhesion; siderophores that upregulate iron uptake by the bacteria (78).

Vaccines against disease

Vaccination against *K. pneumoniae* has been pursued for several decades with little success (78). Studies have investigated killed whole cell preparations, cell lysates, proteins and purified polysaccharides (and PS-protein conjugates). Several immunisation strategies have focused on the polysaccharide capsule, but with a large range of serotypes, obtaining sufficient coverage has been challenging (79), and wide geographical variation in serotype distribution presents further difficulties in developing an effective vaccine.

A 24-valent capsular polysaccharide vaccine demonstrated good IgG and IgA antibody responses in a phase 1 trial, and caused minimal toxicity, although this vaccine covered only 50% of pathogenic strains in some geographical regions thereby minimising its utility (79). Partly due to its limited coverage and complexities, no further research beyond phase 1 trials

has been performed. To date, the authors are not aware of any vaccines targeting pregnant women or neonates, and therefore no vaccines targeting neonatal sepsis (78).

Vaccines against colonisation

Other vaccine targets have included lipopolysaccharides as they play a greater role in urinary tract colonisation and only have 8 serotypes (80). These and others targeting outer membrane proteins have, however, not yet been developed beyond preclinical research (80,81). The lyophilized protein vaccine, Urovac, contains one strain of *Klebsiella* spp., and along with a similar vaccine, Urostim (82), have been shown to reduce the risk of urinary tract infection caused by the included strains, but with no cross-protection against other *Klebsiella* serotypes.

Passive immunisation

One trial of passive immunisation used hyperimmune pooled IVIG, specific for *Klebsiella* taken from donors who had generated immunoglobulin to the vaccine above (73). Passive immunisation was trialled as prophylaxis in intensive care patients in a phase I trial but stopped because of a lack of efficacy.

Pseudomonas aeruginosa

Disease targets

Disease targets include children with comorbidities, such as cystic fibrosis, cancer, as well as critically unwell children in the context of trauma, burns or ventilator- associated pneumonia (61). In cystic fibrosis, up to 45% may carry *P. aeruginosa* in the respiratory tract due to impaired mucociliary clearance and formation of biofilms, with MDR resistance rates of 8% (19).

Virulence factors

Immunisation against *P. aeruginosa* is difficult because of diverse virulence mechanisms. A number of different immunisation approaches have been taken in preclinical and early clinical trials, including lipopolysaccharide O antigens, live attenuated vaccines, outer membrane protein vaccines, and passive immunisation approaches (62–64). Since there are

20 serotypes and 30 subtypes of *P. aeruginosa* with little or no cross-protection between serotypes, vaccines based on the LPS O antigen need to incorporate at least 10 or more common serotypes and, potentially, other *P. aeruginosa*-specific antigens in order to ensure cross-reactivity and breadth of protection (61). Toxins and flagella further increase its ability to evade and suppress host cilia, and immune cell function (65,66).

Vaccines against disease targets

A phase two randomised controlled trial conducted in adults admitted to intensive care incorporating a recombinant (OprF/I) protein and aluminium hydroxide adjuvant demonstrated a significant increase in antibody titres in the vaccine group and was well tolerated (63). However, a subsequent phase three trial adopting the same vaccine and population demonstrated no difference in clinical outcomes including pneumonia, bacteraemia or mortality (63,67). Further vaccines including intranasal live vaccines are in development (68,69).

Vaccines against colonisation

Among the recent *P. aeruginosa* vaccine candidates, the most successful candidate was shown to reduce lung colonisation (albeit with borderline statistical significance (p=0.05)), with no effect observed for strains with non-vaccine flagella types. To our knowledge the company responsible has discontinued further work on this vaccine (70).

Passive immunisation

In recent years, passive immunisation against *P. aeruginosa* has received greater attention, especially because of the recognition that underlying immunocompromising conditions (71) may render active immunisation approaches ineffective (72). Older trials of hyperimmune immunoglobulin had no protective effects (73). More recently, two passive immunisation approaches have demonstrated potential, with phase 2 trials in progress for a monoclonal antibody prophylaxis (74). Mouthwash-based immunoglobulin prophylaxis is in phase 3 clinical trial(s) aiming to decolonise and therefore prevent infections; this follows promising data that it can prolong the interval between infections (75).

Acinetobacter

Disease targets

The focus of *A. baumannii* is largely hospital acquired infection and neonatal intensive care although community acquired infections have been reported (Insert ref to Hu 2010).

Immunisations

Obstacles to development of a vaccine against *A. baumannii* include the propensity of the bacterium to evade immune surveillance and the large number of strain types (83). This pathogen exhibits a high degree of antigen variability due to selective immunological pressure, which makes it difficult to identify conserved antigens across strains (84). Further logistical problems include its widely varying prevalence rates, which complicate clinical trial design (83). No vaccines against *A. baumannii* have progressed beyond phase 1 clinical trials (84). Potential targets include outer membrane vesicles, outer membrane protein A, auto-transporter, biofilm-associated protein, K1 capsular polysaccharide, and poly-(beta-1,6)-N-acetyl glucosamide (85). Experimental vaccines based on several targets have been shown to be immunogenic and confer protection against *A. baumannii* in animal models (86). A monoclonal antibody against K1 capsular polysaccharide was shown to be protective in-vivo; however, there are almost 40 recognised LPS serotypes, and the antibody only recognised 13% of the tested strains (87). An outer membrane protein Omp22, delivered using an *E. coli*-derived outer membrane vesicle, protected mice from lethal *A. baumannii* challenge (88).

Enterobacter

Enterobacter infections are largely hospital acquired, in neonatal intensive care and children with immune deficiency. Vaccines against *Enterobacter* spp. are by far the least developed of all GNB, and current research is limited to a small number of pre-clinical studies focusing on identifying capsular polysaccharide targets such as poly-(beta-1,6)-N-acetyl glucosamide (88,89).

Pooled immunoglobulin

In a meta-analysis of published literature, use of pooled IVIG to induce passive immunity in premature neonates has been demonstrated to reduce all-cause sepsis by 3%, with no data on deaths. The lack of cost-effectiveness meant that this has not been widely adopted (42).

3. Future immunisation strategies against GNB

Neonatal sepsis

Since GNB are a major cause of infant sepsis early protection – ideally from birth – is likely to be critical. In light of the success of antenatal immunisation in preventing neonatal tetanus and pertussis, emphasis is being placed on antenatal vaccination as a potential strategy (90,91). Passive immunity via maternal immunisation and placental transfer of antibodies is appealing given the high burden of neonatal and early infant disease (2). IgG antibodies to GNB have been demonstrated to transfer from mother to baby and are hypothesised to be protective, therefore this could be an approach for the future, in line with other maternal vaccination programmes (92,93). In pre-clinical trials, maternal vaccination of animal models did confer antibody rise in the offspring against GNB (94,95), including *Klebsiella* spp., *E. coli* and *Pseudomonas* spp. (92,96).

So far, however, there have been no human trials of maternal vaccination for any of the major GNB. Such a strategy could potentially have the greatest impact in reducing the burden of neonatal sepsis. The protection offered through passive foeto-maternal transfer of vaccine-induced antibodies would be short-lived but should protect infants during their period of highest risk. An important consideration, however, would be whether the vaccine could be administered early enough in pregnancy to provide adequate protection for infants born prematurely. Adolescent vaccination may provide another strategy if the vaccine is long-lived, with a view to it also providing immunity during subsequent pregnancies.

Routine infant and childhood immunisation

Developing vaccines that can be incorporated into routine infant and childhood immunisation programmes has obvious implementation benefits, especially if the vaccine provided long-term protection. Unlike current vaccines, such vaccines may only provide direct protection to vaccinated children without providing any indirect (herd) protection to those around them, as nosocomial infections present a greater source of transmission than children, although further research would be needed. Additionally, this approach is limited because it would not protect the major high-risk groups, especially neonates, and children whose immunity had been reduced by disease or active immunosuppression. So far, prevention of GNB through vaccination is far from realisation since few studies have progressed past phase 2 clinical trials.

Active and passive immunisation for high-risk groups

High-risk groups for GNB are likely to benefit from targeted immunisation strategies, either through passive or active immunisation. Passive immunisation with pathogen-specific antibodies after birth in premature neonates or at the time of neonatal infection, once the causative pathogen is identified, may be a successful strategy. High-risk older children include those with cancer, cystic fibrosis, receiving immunosuppressive therapy and those admitted to intensive care, requiring prolonged hospitalisation or with severe trauma (Table 3). Whilst potentially much more costly, in the case of passive antibody-based therapy, this approach has the benefit of providing direct and rapid immune protection against specific pathogens during the child's period of highest risk. With early-phase trials of active immunisation demonstrating evidence of protection in acutely unwell adults (52) and the rapid expansion of monoclonal antibodies (5), targeted immunisation of high-risk groups seems the most promising option for immunisation against these pathogens.

Conclusion

The growing burden of GNB sepsis in high-risk paediatric populations, including neonates, children with chronic conditions and those requiring intensive care, as well as rapidly increasing rates of multidrug resistance to antibiotics urgently necessitates new preventative strategies. Past research has focused predominantly around active immunisation, especially targeting LPS on the surface of GNB, although research into passive immunisation using pathogen-specific monoclonal antibodies is expanding. Whilst there is a focus amongst global health research funders and policymakers on passive antibody administered against specific pathogens during the acute illness, the benefits of other approaches including antenatal immunisation must be considered and developed to protect additional risk groups such as neonates and premature infants, especially in lower- and middle-income countries.

Key Points

- The growing burden of GNB sepsis in high-risk paediatric populations, alongside rising resistance, necessitates new preventative strategies.

- Five major GNB: *Klebsiella pneumoniae, Escherichia coli, Enterobacter* spp., *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, have trials in phase 1-3 but licensure for children, particularly neonates seems years away.
- There is a focus on passive immunisation, but alternative potential future strategies for immunisation include passive immunity via maternal vaccination, and vaccination of high risk groups.

Acknowledgements

Additional sources of funding: None
Conflicts of interest: None

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Table 1 (original): Microbiological, clinical, and epidemiological features of the most prevalent Gram-negative bacteria

Table 2 (original): Immunisations against Gram-negative bacteria, by current research stage

Table 3 (original): Future targeted immunisation strategies

References of special interest with annotations

*Special literature
**Outstanding literature

Tan B, Wong JJ-M, Sultana R, Koh JCJW, Jit M, Mok YH, et al. Global Case-Fatality Rates in Pediatric Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis. 2019 Feb 11; **

In their outstanding systematic review, Tan and colleagues systematically review global data, providing useful data and analysis on global case fatality rates, including lower, middle and high income countries alike. This enormous data pool provides the opportunity for cross-country comparison and enables meaningful interpretation of risk to children with sepsis and septic shock. More broadly, this highlights the challenges facing the management of sepsis in low income settings.

Adlbrecht C, Wurm R, Depuydt P, Spapen H, Lorente JA, Staudinger T, et al. Efficacy, immunogenicity, and safety of IC43 recombinant Pseudomonas aeruginosa vaccine in mechanically ventilated intensive care patients—a randomized clinical trial. Crit Care. 2020;24(1):1–10. **

In this outstanding randomised controlled trial, Adlbrecht and colleagues present data from a phase 2 trial of a recominant *Pseudomonas aeruginosa* vaccine, IC43 in ICU patients. Whilst this a phase 2 trial, the lack of clinical benefit is an important demonstration of the difficulties in developing immunisations against *Pseudomonas aeruginosa*, although the vaccine was well tolerated and immunogenic.

Choi M, Tennant SM, Simon R, Cross AS. Progress towards the development of Klebsiella vaccines. Expert Rev Vaccines [Internet]. 2019 Jul 3;18(7):681–91. Available from: https://doi.org/10.1080/14760584.2019.1635460*

In this reference which we have identified as special, Choi and colleagues review data on *Klebsiella. Pneumoniae* vaccine. One strength of this review is the authors comprehensive discussion of different vaccine platforms, including polysaccharide vaccines, LPS, antigen and the consideration of future nanoparticle and liposome platforms.

Table 1

Table 1 (original): Microbiological, clinical, and epidemiological features of the most prevalent Gram-negative bacteria

Pathogen	**Microbiological features**	**Clinical features** (97,98)	**Epidemiology**
Escherichia coli	Type species of the genus *Escherichia* (97) Most common species of the *Enterobacteriaceae* family (102) Contains a variety of strains, ranging from commensal to highly pathogenic (23)	**Respiratory** Can cause hospital-acquired infections and neonatal sepsis and meningitis. **Genitourinary** Frequent cause of community UTIs and uncomplicated pyelonephritis **Gastrointestinal** *E. coli* commonly presents with profuse watery or bloody diarrhoea, low grade fever and potentially fatal haemolytic uraemic syndrome **Neurological** Neonatal meningitis, with higher risks of adverse neurological disabilities compared to other bacteria **Other** Cause of severe clinical chorioamnionitis and subsequent neonatal sepsis	**High income** In USA, *E. coli* most common cause of early onset neonatal sepsis (15) Most significant Gram-negative pathogen in pre-term infants (15,16) (37) Most common cause of mortality in early-onset neonatal sepsis (14) Greater survival of VLBW infants may also be a factor accounting for the increasing proportion of EOS caused by *E. coli* (14) **Low- and middle-income** In Eastern Mediterranean region, principal Gram-negative cause (and 2nd most common overall) of EOS (103)
Pseudomonas aeruginosa	Aerobic Gram-negative bacilli, glucose non-fermenter (40)	**Respiratory** Colonisation or acute cough and purulent green	**High-income** Globally, most common Gram-negative isolate in

	Ubiquitous, particularly in hospital environments (97) Low intrinsic virulence: causes opportunistic infection (97)	sputum **Genitourinary and GI** Causes gastroenteritis, and recurrent and catheter-associated urinary tract infections. **CNS** Cause of meningitis and brain abscess post-trauma, mastoiditis and sinusitis **Skin, bone, soft tissue** Cause of necrotic ulcers, paronychia (green nail syndrome), septic arthritis/osteomyelitis **Other** Cause of neonatal sepsis, necrotizing otitis externa, chronic mastoiditis, endophthalmitis.	hospital acquired infection (2); resistance to Carbapenems noted (40) (101) Caused 4% of neonatal sepsis in U.S.(15) Caused up to 15% paediatric sepsis in referral hospitals in Italy (3) **Low- and middle-income** In India, caused highest case fatality rate among neonates (99) , and caused 2% of neonatal sepsis (Gupta 1993) Caused 9% of neonatal sepsis in low birth weight infants in Brazil (100)
Klebsiella Pneumoniae	Klebsiella is a genus of *Enterobacteriaceae* (102) Usually harmless gut commensals (97) Most infections are due to *K. Pneumoniae subspecies pneumoniae,* followed by *K.Oxytoca* (102)	**Respiratory** Cause of lung abscesses, and necrotising pneumonia, with 'redcurrant jelly' sputum and multiple lung abscesses. **CNS** Cause of meningitis. Associated with nosocomial bacterial sinusitis secondary to head trauma, diabetic ketoacidosis and prolonged intubation **Genitourinary and GI**	**High income** Second most common Gram-negative organism causing paediatric severe sepsis (6.4%) (2) (37) **Low- and middle-income** Accounted for 49.8% of all Gram-negative bacteria in children with sepsis in resource-limited countries (7) In neonates in Asia, most common Gram-negative organism and cause of most deaths (17)

		Causes UTIs, peritonitis in children with chronic liver disease and pyogenic polymicrobial liver abscesses **Eyes and ears** Cause of chronic suppurative otitis media and hearing impairment **Neonatal sepsis**	In Eastern Mediterranean regions, main Gram-negative cause of late-onset neonatal sepsis (104) Accounts for one in five cases of neonatal sepsis in LMIC, including 21% in African countries (18)
Acinetobacter baumanii	Strictly aerobic non-fermentative coccobacillary Gram-negative bacilli (40) Acinetobacter is a genus of *Gammaproteobacteria* and contains around 19 genospecies (97,102) *Acinetobacter baumannii* is the commonest infectious species (105) Has few virulence factors: causes opportunistic infection as found in water (97)	**Respiratory** Associated with nosocomial pneumonia, ventilator-associated pneumonia. **Cardiovascular** May cause endocarditis **Eyes** May cause superficial infections of the periorbital area	**High income** 2.5% of cases of global paediatric severe sepsis (2) In a US paediatric population, isolated from 6.8% of patients (106) **Low- and middle-income** Predominant pathogen in neonatal sepsis in India, with high levels of multidrug resistance (99) Common Gram-negative organism in LMICs (107)

Enterobacter sp.	Genus of *Enterobacteriaceae*. Includes species *E. Aerogenes, E.Cloacae, E. sakazakii* (97) Common human gut commensals (97) *E. Sakazakii* is a cause of severe neonatal meningitis (97)	**Respiratory** Cause of pneumonia and nosocomial pneumonia. **CNS** Specifically, *E. sakazakii* has been implicated in severe neonatal meningitis (mortality rate 40–80%) **GI and Genitourinary** Cause of UTIs and acute pyelonephritis	**High income** 3% of cases of global paediatric severe sepsis (2); with widespread carbapenem resistance (36)(109–112) (108) Cause of 16.7% of paediatric bloodstream infections in US (106) **Low- and middle-income** Accounted for 4% of neonatal sepsis in Delhi (99)

Table 2

Table 2 (original): Immunisations against Gram-negative bacteria, by current research stage

	Research			**Post licensure ***
Pathogen	**Preclinical/ Phase 1**	**Phase 2**	**Phase 3**	
E coli	Maternal vaccination in animal models showed antibody response in offspring (Matias (17), Luis (15), Rabinowitz(16). (52) 12 Valent LPS vaccine led to good antibody response and little toxicity, but was not developed further (52). ExPEC4V does not reduce UTI recurrence but minimal side effects (RR 0.82, 95% CI 0.62–1.10) (119)	Phase 2 in children monoclonal antibody therapy against E coli toxins, minimal effect seen but no toxicity (52)	(Uro-vaxom) Phase 3 recurrent UTI reduced reinfection rate (120).	Uro-Vaxom (oral bacterial strain vaccine, 3 month duration prevents UTI (55) Uroimmune oral lysed bacterial vaccine daily prophylaxis prevents UTI (121) (Urovac) Lysed whole cell vaccine administered via vaginal pessary of 10 strains of pathogens reduced reinfection rate, with greater effect seen in context of boosters (54). (Urostim) Lysed bacterial cells via oral tablet, reduced UTI symptoms at 1 year in children and adults with recurrent UTI (82)
Pseudomonas aeruginosa	LPS- based vaccine prevented death in adults with solid cancer (113) and adults with burns (62), but high toxicity. No impact on children with leukaemia. Specific monoclonal antibodies against Pseudomonas and Klebsiella had non-significant effect on infection and more adverse reactions (73) (Medimmune) Monoclonal antibody MEDI3902 led to good antibody immune response (114)	IC34 OprF membrane protein based vaccine, seroconversion seen with >4-fold rise in antibodies. Well tolerated without safety concerns (63) 16- valent polysacharide vaccine demonstrated minimal difference in lung function compared to placebo in children with cystic fibrosis, no difference in time to infection and work discontinued (115) KB001 Passive monoclonal antibody, non-significant lower mortality in treatment group in	IC34 OprF membrane protein based vaccine, seroconversion seen but no clinical infection rate difference was seen. Discontinued (63,67) Flagella-based vaccine. Small, borderline statistically significant reduction in frequency of infection in cystic fibrosis patients (p=0.05), production discontinued. (118)	**Nil**

		ventilated patients, no difference in bacterial load (64). In cystic fibrosis patients no difference in bacterial density or symptoms, but lower inflammatory markers and neutrophils in sputum (116). (Medimmune) Monoclonal antibody, led to antibody response and adequate safety profile (117)	Mouthwash of passive IgY antibodies to delay time until infection - ongoing trial (75)	
Klebsiella Pneumoniae	Vaccine Phase 1 only, toxic side effects but >four-fold antibody rise (123) O Polysaccharide Conjugate vaccine led to antibody rise in burn survivors with minimal toxicity, and in healthy volunteers (79,124) IVIG passive antibodies against Pseudomonas and Klebsiella administered had non-significant effect on infection and more adverse reactions (73)	N/a	N/a	(Urovac) Lysed whole cell vaccine administered via vaginal pessary of 10 strains of pathogens reduced reinfection rate, with greater effect seen in context of boosters (54)
Acinetobacter baumanii	Monoclonal antibodies have protected mice against infection. Active vaccines developed but none effective beyond phase 1 (88)	Nil	Nil	Nil
Enterobacter sp.	Passive injection of PNAG antibody in mice generated protection against Enterobacter infection (89) Toxin injection generated neutralizing antibodies in animal studies (122)	Nil	Nil	Nil

* only active immunisation against *E. coli* recurrent urinary tract infections have been licensed

Table 3 (original): Future targeted immunisation strategies

Potential target populations	**Target pathogen(s)**	**Proposed immunisation approach**	**Considerations**
Maternal vaccination	*E coli, Klebsiella, Enterobacter,*	Passive immunity for the newborn via maternal active vaccination	Protection for mother and during highest-risk period for neonate
Neonatal immunisation	*E coli, Klebsiella,*	Active immunisation and passive antibody immunisation	Premature infants may not be protected early enough through active immunisation at birth
Routine childhood	*No targets yet*	Active immunisation	Childhood immunisation could be successful if the vaccine provided long-term immunity and/or indirect (herd) protection
Cancer patients	*Klebsiella, Enterobacter, Pseudomonas aeruginosa, Acinetobacter*	Vaccinating prior to initiating immunosuppressive therapy, active non-live immunisations or passive immunisation	Leaky gut and immunocompromise after chemotherapy, high risk of nosocomial infection
Chronic disease including cystic fibrosis	*Pseudomonas aeruginosa*	A combination of active and passive immunisation	High risk of nosocomial infection, impaired clearance mechanisms
Immunosuppressed groups	*Klebsiella, Enterobacter, Pseudomonas aeruginosa, Acinetobacter*	Vaccinating prior to initiating immunosuppressive therapy, active non-live immunisations or passive immunisation	Existing immunity may be ineffective
Acutely unwell patients/ trauma/ burns in intensive care	*Klebsiella, Enterobacter, Pseudomonas aeruginosa, Acinetobacter*	Vaccinating prior to initiating immunosuppressive therapy, active non-live immunisations or passive immunisation	Reduced barriers to invasive infection