ARTICLE IN PRESS

Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Vaccine value profile for *Klebsiella pneumoniae*

Ziyaad Dangor [a,*], Nicole Benson [b], James A. Berkley [c,d], Julia Bielicki [e,f], Merijn W. Bijsma [g,h], Jonathan Broad [i], Ed T. Buurman [j], Alan Cross [k], Erin M. Duffy [j], Kathryn E. Holt [l,m], Pui-Ying Iroh Tam [n], Mark Jit [o], Konstantinos Karampatsas [e], Michael Katwere [p], Gaurav Kwatra [q,r,a], Ramanan Laxminarayan [s], Kirsty Le Doare [e,t,u], Robert Mboizi [o], Francesca Micoli [v], Catrin E. Moore [e], Eve Nakabembe [w], Nichola R. Naylor [t,x], Seamus O'Brien [y], Courtney Olwagen [a], Denasha Reddy [a], Charlene Rodrigues [l,z,aa], David A. Rosen [ab], Manish Sadarangani [ac,ad], Padmini Srikantiah [b], Sharon M. Tennant [k], Mateusz Hasso-Agopsowicz [ae], Shabir A. Madhi [a]

[a] South Africa Medical Research Council Vaccines and Infectious Diseases Analytics Research Unit, University of the Witwatersrand, Johannesburg, South Africa
[b] Global Health Division, Bill & Melinda Gates Foundation, Seattle, WA, USA
[c] KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya
[d] Centre for Tropical Medicine & Global Health, University of Oxford, UK
[e] Centre for Neonatal and Paediatric Infection, St George's, University of London, UK
[f] Paediatric Research Centre (PRC), University of Basel Children's Hospital, Basel, Switzerland
[g] Amsterdam UMC, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Meibergdreef, Amsterdam, the Netherlands
[h] Amsterdam UMC, University of Amsterdam, Department of Pediatrics, Amsterdam Neuroscience, Meibergdreef, Amsterdam, the Netherlands
[i] Croydon University Hospital, London, UK
[j] CARB-X, Boston University, Boston, MA 02215, USA
[k] Center for Vaccine Development and Global Health, University of Maryland School of Medicine, Baltimore, MD, USA
[l] Department of Infection Biology, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
[m] Department of Infectious Diseases, Central Clinical School, Monash University, Melbourne, Victoria 3004, Australia
[n] Paediatrics and Child Health Research Group, Malawi-Liverpool Wellcome Programme, Blantyre, Malawi
[o] Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
[p] Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda
[q] Division of Infectious Diseases, Department of Pediatrics, Cincinnati Children's Hospital Medical Center and University of Cincinnati, Cincinnati, OH, USA
[r] Department of Clinical Microbiology, Christian Medical College, Vellore, India
[s] One Health Trust, Bangalore; Princeton University, Princeton, NJ, USA
[t] UK Health Security Agency, Porton Down, UK
[u] World Health Organization, Geneva, Switzerland
[v] GSK Vaccines Institute for Global Health, Italy
[w] Department of Obstetrics and Gynaecology, School of Medicine, Makerere University College of Health Sciences, Upper Mulago Hill Road, P.O. Box 7072 Kampala, Uganda
[x] Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London, UK
[y] Global Antibiotic Research & Development Partnership (GARDP), Geneva, Switzerland
[z] Dept of Paediatrics, Imperial College Healthcare NHS Trust, London, UK
[aa] Pathogen Genomics Programme, UK Health Security Agency, London, UK
[ab] Department of Pediatrics and Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, MO, USA
[ac] Vaccine Evaluation Center, BC Children's Hospital Research Institute, Vancouver, BC, Canada
[ad] Department of Pediatrics, University of British Columbia, Vancouver, BC, Canada
[ae] Department of Immunization, Vaccines & Biologicals, World Health Organization, Geneva, Switzerland

ARTICLE INFO

ABSTRACT

Klebsiella pneumoniae causes community- and healthcare-associated infections in children and adults. Globally in 2019, an estimated 1.27 million (95% Uncertainty Interval [UI]: 0.91–1.71) and 4.95 million (95% UI:

* Corresponding author.
E-mail address: Ziyaad.Dangor@wits.ac.za (Z. Dangor).

https://doi.org/10.1016/j.vaccine.2024.02.072

Keywords:
Vaccine
Klebsiella pneumoniae

3.62–6.57) deaths were attributed to and associated with bacterial antimicrobial resistance (AMR), respectively. *K. pneumoniae* was the second leading pathogen in deaths attributed to AMR resistant bacteria. Furthermore, the rise of antimicrobial resistance in both community- and hospital-acquired infections is a concern for neonates and infants who are at high risk for invasive bacterial disease. There is a limited antibiotic pipeline for new antibiotics to treat multidrug resistant infections, and vaccines targeted against *K. pneumoniae* are considered to be of priority by the World Health Organization. Vaccination of pregnant women against *K. pneumoniae* could reduce the risk of invasive *K. pneumoniae* disease in their young offspring. In addition, vulnerable children, adolescents and adult populations at risk of *K. pneumoniae* disease with underlying diseases such as immunosuppression from underlying hematologic malignancy, chemotherapy, patients undergoing abdominal and/or urinary surgical procedures, or prolonged intensive care management are also potential target groups for a *K. pneumoniae* vaccine.

A 'Vaccine Value Profile' (VVP) for *K. pneumoniae,* which contemplates vaccination of pregnant women to protect their babies from birth through to at least three months of age and other high-risk populations, provides a high-level, holistic assessment of the available information to inform the potential public health, economic and societal value of a pipeline of *K. pneumoniae* vaccines and other preventatives and therapeutics. This VVP was developed by a working group of subject matter experts from academia, non-profit organizations, public–private partnerships, and multi-lateral organizations, and in collaboration with stakeholders from the WHO. All contributors have extensive expertise on various elements of the *K. pneumoniae* VVP and collectively aimed to identify current research and knowledge gaps. The VVP was developed using only existing and publicly available information.

1. The global public health need for a vaccine

Globally in 2019, *Klebsiella pneumoniae* (*K. pneumoniae*) was ranked as the fourth highest cause of infection related deaths across all-age-groups, with an estimated 790,000 (95 % Uncertainty Interval [UI]: 682,000–1,010,000) deaths [1]. Furthermore, *K. pneumoniae* was the second leading cause of global deaths attributable to antimicrobial resistant (AMR) pathogens, and leading (19.9 %; 95 % UI: 15.1–25.4) cause in sub-Saharan Africa [2]. There are two priority groups in whom the burden of *K. pneumoniae* is most concerning and thus the focus of this Vaccine Value Profile (VVP); namely: (i) neonates and young infants, and (ii) vulnerable children, adolescents and adult populations at risk of *K. pneumoniae* disease. Table 1 summarizes the key epidemiological features of invasive *K. pneumoniae* disease.

(i) Neonates and infants*:* *K. pneumoniae* is one of the most common causes of multidrug resistant hospital-acquired infections and the leading etiology of neonatal sepsis, globally [2–4]. Overall, given the slower decline in global neonatal mortality than in older children [5], the ongoing healthcare resource limitations in many regions, the lack of new antimicrobial agents in the pipeline and increasing AMR, a maternal vaccine against *K. pneumoniae* is a highly attractive prospect. A safe, effective, and affordable vaccine delivered during pregnancy, which results in transplacental transfer of protective antibody could reduce the risk of invasive *K. pneumoniae* disease morbidity and mortality in young infants, and also reduce antimicrobial usage. Furthermore, vaccination against *K. pneumoniae* could contain the spread of AMR bacteria and reduce the costs of hospitalization to families and the health system. Vaccinating pregnant women could protect against both early-onset sepsis (disease occurring within the first 72 h of life) which could be a consequence of *K. pneumoniae* acquisition *in utero*, during delivery from the mother's vaginal microbiota or from environmental sources. Furthermore, infants could also potentially be protected beyond 72 h of age (i.e., late-onset sepsis) which could be due to community or hospital-acquired infections. Modelling suggests that a *K. pneumoniae* vaccine targeted at pregnant women, could avert approximately 80,000 deaths and 400,000 neonatal sepsis cases, predominantly in sub-Saharan Africa and South Asia [4].

(ii) Vulnerable populations: *K. pneumoniae*, particularly multidrug resistant hospital-acquired strains have a high mortality in at-risk vulnerable children, adolescents and adult populations, including but not exclusive to those with/ requiring:

- severe acute malnutrition
- anticipated prolonged hospital stay,
- invasive intensive care management,
- abdominal and/or urinary surgical procedures,
- at risk of surgical site or device-associated infections,
- chronic obstructive airway disease,
- primary or secondary immunodeficiency,
- hematological or other malignancy,
- long-term acute care facility admission, or
- adults over 65 years of age.

The VVP does not address the "Hypervirulent *K. pneumoniae*" strain which predominantly occurs in healthy adults from Southeast Asia and typically presents as community-acquired pyogenic liver abscess [6].

1.4. Current methods of surveillance, diagnosis, prevention, and treatment

1.4.1. Surveillance

K. pneumoniae is commonly included in hospital-based surveillance for AMR and/or healthcare associated infections, and human blood and urine isolates are included in the WHO Global Antimicrobial Resistance (AMR) and Use Surveillance System (GLASS) [71]. *K. pneumoniae* is not typically included in formal surveillance programs in community settings, nor in non-human settings. Examples of formal AMR surveillance programs that include *K. pneumoniae* are:

- Africa CDC Anti-Microbial Resistance Surveillance Network; AMRSNET; https://africacdc.org/download/africa-cdc-framework-for-antimicrobial-resistance/;
- Antimicrobial Use and Resistance in Australia Surveillance System (AURA); https://www.safetyandquality.gov.au/our-work/antimicrobial-resistance/antimicrobial-use-and-resistance-australia-surveillance-system/about-aura-surveillance-system.
- English Surveillance Programme for Antimicrobial Utilization and Resistance; ESPAUR; https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report;
- European Antimicrobial Resistance Surveillance Network; EARS-Net; https://www.ecdc.europa.eu/en/about-us/networks/disease-networks-and-laboratory-networks/ears-net-data.
- European CDC Central Asian and European Surveillance of Antimicrobial Resistance; CAESAR; https://www.who.

Table 1
Summary of epidemiology and potential indirect public health impact.

Feature	Summary and evidence
1.1 Epidemiology	
Reservoir	• *As a commensal bacterium, K. pneumoniae causes opportunistic human infections. K. pneumoniae* colonization *is most frequent in the gastrointestinal tract (5–38 % of stool samples), but may also colonize the nasopharynx, genital tract, vagina and skin of humans* [7–10]. • *Gastrointestinal K. pneumoniae* colonization is *a risk factor for invasive disease, with carriers four times more likely to develop invasive disease compared with non-carriers* [8,11]. *Human carriage rates are also higher in hospitalized patients (77 % of stool samples), primarily thought to be related to the effect of use of antibiotics on the gastrointestinal microbiome* [7,12]. • *The carriage rates of K. pneumoniae* may vary in *ethnic groups from different settings, such as K. pneumoniae being identfied from stool samples of 19 % of healthy Chinese adults in Japan compared with 88 % of healthy Chinese in Malaysia* [13]. • *K. pneumoniae is also ubiquitous in the environment, having been found in several ecological niches such as soil, water, plants, different animals (insects, birds, reptiles and the intestine of mammals) and food* [14–16] • *There is a paucity of information on the specific niches. Further understanding of the different reservoirs and transmission of K. pneumoniae from wider environmental and animal niches are needed globally.*
At-risk populations	• *K. pneumoniae has the highest incidence in the extremes of life, predominantly affecting neonates and the elderly.* • *K. pneumoniae is especially important as a hospital-acquired pathogen in neonates, in all age-groups admitted to high dependency and intensive care facilities (which includes premature, small for gestational age, and sick term infants), and in individuals with intra-vascular devices or on mechanical ventilation support.* • *In a multi-center study across seven sub-Saharan African and South Asian countries between 2015* and *2017, K. pneumoniae was reported as the leading cause (24.9 %) of neonatal sepsis. Overall, more than 80 % of Gram-negative bacilli were resistant to third generation cephalosporins and 13–15 % resistant to carbapenems* [17]. • *Early-onset neonatal sepsis due to K. pneumoniae is often rapidly fatal and may be difficult to identify due to lack of appropriate blood sampling or microbiology infrastructure. Furthermore, K. pneumoniae is even more difficult to isolate from newborns born prematurely or of low birth weight, or following birth asphyxia* [18,19]. • *Epidemiological surveillance studies often do not stratify invasive K. pneumoniae based on whether infection was community acquired or hospital associated* [20].

Mortality	• *Deaths attributable to AMR are highest in sub-Saharan Africa, likely because of a high burden of infections and inadequate laboratory and clinical care resources to effectively diagnose and treat cases. Consequently, a large potential burden of invasive disease due to AMR pathogens, including K. pneumoniae, are undetected in routine practice in resource constrained settings.*
	• *Globally, in 2019, carbapenem and third-generation cephalosporin-resistant K. pneumoniae were estimated to have caused approximately 50,000 deaths each* [2]. *Resistance to cephalosporins is more frequent in early-onset sepsis than late-onset neonatal sepsis* [17].
	• *A global neonatal sepsis observational cohort study (NeoOBS) examined sepsis, antimicrobial usage and microbiology in 11 countries from 2018 to 2020* [19]. *Approximately 37 % of the Gram-negative organisms were K. pneumoniae, mostly resistant to WHO-recommended regimens (ampicillin/penicillin + gentamicin) and to carbapenems (33 %). The 28-day case fatality risk for invasive K. pneumoniae* disease was *21 %.*
	• *Through minimally invasive tissue sampling (post-mortem needle biopsies) to determine causes of death on deceased children as part of the Child Health and Mortality Prevention Surveillance program in seven low- and middle-income countries (LMICs) in sub-Saharan Africa and Southeast Asia:*
	  ○ *40 % (590/1458) of neonatal deaths were attributed to an infectious syndrome when examined postmortem, with K. pneumoniae being the leading bacterial cause (45.4 %). Thirty-seven percent of the deaths in neonates attributed to K. pneumoniae were late onset (7–27 days) cases* [21].
	  ○ *K. pneumoniae was also common (24.5 %) in the causal pathway of all childhood deaths in the 1–59 month of age-group, with 80 % of deaths associated with K. pneumoniae in the causal pathway being due to hospital-acquired infections* [22].

Morbidity	• *There is no data specifically detailing the rate of occurrence or severity of neurodevelopmental impairment (NDI) for patients following invasive K. pneumoniae disease.* • *Most data on NDI stem from cohort studies evaluating the morbidity impacts of neonatal sepsis. In a meta-analysis of 14 studies, blood culture-proven neonatal sepsis in very preterm infants was associated with greater than three-fold increase in substantial risk of NDI (including cerebral palsy and neurosensory deficits) compared with neonates who did not develop sepsis* [23]. • *Cohort studies in the US, Europe and Asia have also identified an association between early or late-onset neonatal sepsis and NDI, but with smaller effect sizes and variably affected cognition and motor development* [24–26]. • *There is a paucity of data on the association between neonatal sepsis and NDI from low- and middle-income settings. Studies from Brazil reported that prevalence of NDI was greater in very low birth-weight infants with sepsis than non-affected infants, mostly for neuromotor development (33.7* vs. *9.3 %; aOR 2.5, 95 %CI 1.2–5.1) at 12 months of age for early or late onset sepsis* [27,28]. • *In survivors of invasive Group B Streptococcal (GBS) disease during early infancy, moderate or severe NDI was predicted in 2020 to occur in 37,100 (14,600–96,200) children* [29]. *There is an increased risk of NDI in both high-income countries (HICs; 4.6 %) and LMICs (38.1 %) in survivors of invasive GBS disease compared with healthy controls (2.5 and 21.7 %, respectively)* [30,31]. • *Sequelae of sepsis on cognition resulting in functional disability is also increasingly being recognized in adults. With each patient serving as his or her own control, severe sepsis was associated with a 3.3-fold (95 %CI 1.5–73) progression to moderate/severe cognitive impairment from 6.1 % to 16.7 %, in the US* [32].
Geographical and seasonal distribution	• *The greatest burden of morbidity and mortality from K. pneumoniae infections is in LMICs, particularly in sub-Saharan Africa and South Asia* [1].*Nevertheless, there remain critical data gaps on the burden and sequelae of invasive K pneumoniae disease in LMIC.* • *Studies from HICs suggest that K. pneumoniae bloodstream infection incidence rates, including among neonates, are highest during the warmest months of the year* [33–36]. *There is limited data available on the seasonality of K. pneumoniae infections from LMICs.* • *In adults, community acquired infection caused by a hypervirulent K. pneumoniae strain was most frequently reported in South-East Asia* [6].
Gender distribution	• *Overall, there is no difference in the sex distribution of deaths attributed to K. pneumoniae* [1]. • *In a neonate intensive care unit in Pakistan, male sex was associated with a 9.2 (95 % CI 1.3–66) higher adjusted odds of K. pneumoniae sepsis and mortality* [36].
Socio-economic status vulnerability(ies) (equity/wealth quintile)	• *K. pneumoniae contributed to a greater proportion of deaths in sub-Saharan Africa than HICs* [2].

(continued on next page)

Table 1 (*continued*)

Feature	Summary and evidence
	• *In resource constrained settings, neonatal sepsis is managed with limited understanding and confirmation of the bacterial cause with extremely low rates of bacterial culture confirmation, due to lack of a culture to take samples together with a lack of accessibility to blood culture equipment and high-quality laboratory culture facilities. The involvement of certain key bacterial species and resistant pathogens is provided by the microbiological culture results available due to neonatal clinical research studies and from neonatal unit surveillance microbiology* [17,19].
Natural immunity	• *Innate immune responses against K. pneumoniae infection mainly involve the complement system and phagocytosis* [37,38]. • *Cellular and humoral adaptive immune responses to K. pneumoniae have been described in animal model and human studies* [39]. *Cell-mediated and humoral immunity play a protective role against K. pneumoniae disease* [39]. • *The capsular polysaccharide (CPS)-mediated resistance to phagocytosis can be overcome by opsonization using a specific antibody combined with serum complement, and possibly through surface phagocytosis (non-antibody-mediated phagocytosis by adherent leucocytes)* [37,40].
Pathogenic types, strains, and serotypes	• *CPS, designated as the K-antigen, is a key virulence factor of K. pneumoniae which promotes resistance to phagocytosis by macrophages, neutrophils and monocytes* [37,38,41,42] • *Nearly 80 immunologically-distinct K-antigen serotypes have been identified by sero-immuno assays, and a further 82 are proposed on the basis of unique gene content in the CPS biosynthesis locus* [43,44]. • *Blood isolates show a similar K-antigen distribution to those found colonizing the human gut* [45]. • *In a multi-center study on neonatal sepsis in seven LMICs, 13 of the top-20 most common CPS loci identified (KL2, KL15, KL23, KL24, KL25, KL39, KL54, KL62, KL64, KL102, KL112, KL117, KL122) were also amongst the top-20 CPS loci identified from bloodstream infections from adults in Asian countries* [17,46]. • *The most common lipopolysaccharide (LPS) O-antigen serotypes are O1, O2, O3, O4 and O5* [44,47]. *O1 to O4 serotypes accounted for 97 % of all neonatal sepsis cases in a multi-centered study in LMICs, as well as 93 % of bloodstream isolates from adults in Asian countries* [17,43]. *Serotypes O1, O2, O3, and O5 accounted for 90.1 % of invasive K. pneumoniae strains across all age groups in a multi-country collection across Asia, Africa, Europe and the Americas* [47]. *Notably, there are subtypes within O2 and O3, and it is not clear whether antibodies generated against particular subtypes would cross-react with other subtypes.* • *Other species in the K. pneumoniae complex, primarily K. quasipneumoniae and K. variicola, may also cause neonatal sepsis* [44,48,49]. • *Hypervirulent K. pneumoniae, most commonly associated with K1, K2 and K5 serotypes, are characterized by hypermucoidy, enhanced siderophore production, and lethality in a mouse pneumonia model. Hypervirulent K. pneumoniae are uncommon in hospital-acquired infections in neonates and immunocompromised adults* [6]. • *Hundreds of discrete K. pneumoniae sublineages are defined by core-genome variation* [50]. *Within most sublineages, CPS loci are not stable and can be exchanged via recombination* [51].
1.2 Potential indirect impact	
Anti-microbial resistance (AMR) threat	• *K. pneumoniae is considered to be a critical-priority AMR pathogen threat by WHO* [52], *being one of the AMR pathogens with the highest mortality due to invasive disease* [2]. *The rapid emergence of AMR, particularly extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing strains limits therapeutic options, leading to increased mortality* [53]. • *K. pneumoniae are intrinsically resistant to ampicillin due to the presence of the SHV-1 penicillinase in their chromosome* [14]. • *Most acquired resistance in K. pneumoniae results from the acquisition of AMR genes via horizontal gene transfer, aided by plasmids and other mobile genetic elements* [14]. *Hundreds of mobile AMR genes have been found in K. pneumoniae. Many AMR genes were first identified in Klebsiella before their dispersal amongst other clinically relevant Gram negative organisms* [14]. • *Historically there was an inverse relationship between the presence of AMR genes and hypervirulence genes. There are fewer AMR genes in the more invasive Klebsiella strains compared with isolates that mainly caused healthcare associated infections. Nevertheless, a carbapenem-resistant strain of hypervirulent K. pneumoniae was identified in 2015 in Asia* [54], *and there has been a convergence of multi-drug resistant and hypervirulent K. pneumoniae with global spread* [53].
Epidemic and outbreak potential	• *K. pneumoniae is a common cause of outbreaks within hospital settings, including neonatal units* [55,56]. • *To date, there is no indication that K. pneumoniae can cause outbreaks in community settings.*
Transmission route/potential	• *Transmission of K. pneumoniae is common within hospitals and has been associated with persistence in a range of contaminated sources including hospital plumbing, medical devices, and reagents. Colonization studies suggest that transmission often results in asymptomatic carriage, progressing to clinical infection in a fraction of colonized individuals* [8,57]. • *Evidence for transmission of K. pneumoniae from environmental or animal reservoirs to humans is scarce* [58–63]. *Nevertheless, there limited sporadic transmission has been reported between a small number of domestic animals and humans* [63–65].
Acquired/herd immunity	• *The CPS and LPS induce humoral immune responses through a T-cell independent mechanism, without inducing the formation of memory cells* [37]. • *There is a paucity of studies on the role of cell-mediated immunity against K. pneumoniae* [37]. • *There is no evidence whether infection or vaccine induced immunity would confer indirect protection to others, or herd immunity.*
Co-associated mortality	• *Case fatality risk of invasive K. pneumoniae disease is higher in adults with comorbidities such as heart disease (51 %), diabetes (31 %), chronic lung disease (28 %), chronic kidney disease (26 %), and liver disease (15 %)* [66]. • *It has been proposed that K. pneumoniae expressing polyketide synthase (also known as colibactin) is associated with colorectal cancer* [67].
1.3 Economic burden	
Health facility costs/out of pocket costs/ productivity costs	• *The estimated annual economic burden of neonatal sepsis and its sequelae is estimated at $469 billion for sub-Saharan Africa alone, although the estimates are based on limited data collected prior to the recent shift towards healthcare facility-based deliveries and improved neonatal care for preterm births in LMICs* [68]. • *Reducing associated neonatal deaths is likely to save many "working life years".* • *To understand the economic value of a prophylactic intervention such as a vaccine for K. pneumoniae, requires a greater understanding of the economic burden of disease at the population, hospital, community and patient/family level. There needs to be clear data demonstrating the attributable and associated mortality, morbidity and related healthcare and socioeconomic cost related to a target pathogen before the impact of the intervention can be assessed. The context for such an evaluation will be informed by the target population and the outcomes that are anticipated. Reduction in mortality and morbidity will have different health economic impacts compared to more general AMR outcomes for example.*

(*continued on next page*)

Table 1 (*continued*)

Feature	Summary and evidence
	• Economic evaluations of *K. pneumoniae* vaccines should incorporate *ecological externalities related to reducing AMR and preventing large hospital outbreaks, as well as the impact on financial burden of households and particularly across socio-economic subgroups* [69]. • *In adults, carbapenem-resistant K. pneumoniae infections were associated with increased medical costs above the cost of antimicrobial therapy* [70].

int/europe/groups/central-asian-and-european-surveillance-of-antimicrobial-resistance-(caesar).

- India's Antimicrobial Resistance Surveillance & Research Initiative; https://iamrsn.icmr.org.in/;
- Latin American and Caribbean Network for Antimicrobial Resistance Surveillance; ReLAVRA+; https://www.paho.org/en/topics/antimicrobial-resistance/latin-american-and-caribbean-network-antimicrobial-resistance.
- Mapping antibiotic resistance across northern Australia: https://amr-hotspots.shinyapps.io/amr-hotspots/.
- Philippines' Antimicrobial Resistance Surveillance Program; https://arsp.com.ph/;
- Regional (US) and national Canadian surveillance of carbapenem-resistant *K. pneumoniae* [72]; https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-report-2022.html#a2.3.
- UK Health Security Agency; https://www.gov.uk/government/publications/escherichia-coli-bacteraemia-surveillance-form.
- 2020 Animal Pathogen AMR Data; https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/2020-animal-pathogen-amr-data.

1.4.2. Diagnosis

K. pneumoniae are Gram-negative, lactose fermenting aerobic coliforms which can be readily cultured in standard agar, e.g., blood agar, nutrient agar or MacConkey agar. Morphologically, *K. pneumoniae* colonies appear as ~ 2 mm circular, mucoid, and translucent/opaque. The string test can be performed on the colonies that demonstrates a hypermucoviscous phenotype, a recognized virulence feature. The diagnosis of invasive *K. pneumoniae* disease requires microbiology laboratory diagnostic methods applied to sterile samples including blood, urine, cerebrospinal fluid, fluid aspirated from infected pleura, pericardium, peritoneum, synovium or abscesses.

On identification of a colony that is morphologically representative of *K. pneumoniae*, further biochemical testing would demonstrate that *K. pneumoniae* are lactose fermenting, H_2S (hydrogen sulphide)-negative and indole-negative, has positive Voges-Proskauer (VP) reaction, is capable of growth in KCN (potassium cyanide), uses citrate as a sole carbon source, and is incapable of growth below 10 °C. In middle- and high-income settings, matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry (MS) is used for bacterial identification and speciation. MALDI-TOF can adequately identify many *Klebsiella* species if the full spectra are used to distinguish the many closely-related species within the *K. pneumoniae* species complex, these are not routinely included in all MALDI-TOF databases so inaccurate species attribution can occur [73].

When culture methods are negative for growth, molecular methods can be used to detect *K. pneumoniae*, including polymerase chain reaction (PCR). Specific PCR are available in some settings to perform on sterile site samples to identify the presence or absence of *K. pneumoniae*, but with no information provided to determine antibiotic susceptibility. Broad-range PCR using the 16S ribosomal subunit can be used to detect the presence of bacteria including *K. pneumoniae* in a sample. By sequencing the PCR products, it is possible to identify the genus and sometimes species of the *Klebsiella* spp. Real-time PCR can be used to detect *K. pneumoniae* in environmental and stool samples, but is not recommended for diagnostic use [74,75].

1.4.3. Prevention

K. pneumoniae are ubiquitous in the environment, found in soil, plants, animals and humans. The human microbiome has identified *K. pneumoniae* in the gut, skin, mouth and vagina [14,76]. Therefore, hand hygiene is important in the context of prevention of transmission of *K. pneumoniae* from one person to another, particularly in healthcare settings to prevent hospital-acquired infections. Environmental cleaning to prevent hospitalized patients acquiring *K. pneumoniae* is also important. Many infections that occur in hospitals develop from strains already present in the host's own microbiome, for which primary prevention strategies to prevent progression to invasive disease is less well defined [8]. One strategy used in high-dependency and hematology wards is screening for colonization on admission, to help identify at-risk patients and avoid inappropriate therapy should infections develop with resistant organisms. Antimicrobial stewardship interventions can prevent the development of AMR in colonizing *K. pneumoniae* and other resident flora, which can be transferred between different *Enterobacteriaceae* resulting in invasive disease with resistant or multi-drug resistant *K. pneumoniae*, which may be more difficult to treat.

1.4.4. Treatment

K. pneumoniae can be treated with a wide range of antibiotics but are intrinsically resistant to ampicillin, due to presence of SHV-1 penicillinase on their chromosome. Final antibiotic treatment regimens should be determined based on prevailing antimicrobial susceptibility profiles, preferably from the relevant setting.

For *K. pneumoniae* that are ESBL-producing, most cephalosporins and monobactams such as aztreonam are ineffective. Carbapenems are the drug class of choice, with meropenem being preferred to treat severe sepsis and central nervous system infection [77]. Ertapenem can be used in less severe infections and for adults or adolescent patients requiring outpatient antibiotic therapy.

K. pneumoniae that produce carbapenem-hydrolyzing beta-lactamases are further categorized into serine carbapenemases (KPC) and metallo-β-lactamases (NDM, IMP, VIM). Treatment options are far more limited and include colistin, tigecycline, and aminoglycosides, which can have significant side effects. Newer β -lactam-β-lactamase inhibitor combinations such as ceftazidime/avibactam can be used in adults but may need to be combined with aztreonam [78], but the evidence, availability and cost are limitations to treating infections in children and neonates, especially in LMICs.

1.5. Summary of research gaps in epidemiology, potential indirect public health impact and economic burden

- The majority of existing surveillance on the burden of invasive *K. pneumoniae* disease is performed via HIC networks and mainly in adults. More structured surveillance on the overall burden of *K. pneumoniae* disease is required from LMICs, which would require improving diagnostic laboratories at sentinel sites. A major challenge is the low blood culture sensitivity that hampers the ability to confirm *K. pneumoniae*, particularly in preterm neonates. The surveillance should include data on the geographic and seasonal burden of *K. pneumoniae* invasive disease. Incidence data will be required by national ministries of health, GAVI, and other groups to support the investment in vaccines. Furthermore, the surveillance should work towards delineating high-risk populations which could assist in determining who to target for prophylactic strategies such as vaccines and provide epidemiological data to assist in vaccine design.

- Ongoing (possibly enhanced) surveillance, including clinical and molecular epidemiology (including relevant typing) will be required before, preferably well in advance of, and after the introduction of a new vaccine to fully evaluate impact.
- The prevalence and persistence of *K. pneumoniae* colonization in different body sites (gut, skin, nasopharynx), and the role of the microbiome as a source of infection, needs to be more clearly defined.
- Further understanding of the different reservoirs and transmission from wider environmental and animal niches should be explored.
- There is a need for new and improved antimicrobials for treatment of AMR strains, including drugs that could be formulated for use in children.
- Better understanding of immune protection against *K. pneumoniae* is required, including role of systemic humoral and cell-mediated immunity and tissue immune responses. Identifying serological markers associated with risk reduction of invasive *K. pneumoniae* disease would contribute to vaccine development by providing proof of concept for candidate antigens.
- Transfer of *K. pneumoniae* antigen-specific antibody from pregnant women to the fetus and newborn, including transplacental transfer and via breast milk, needs to be evaluated.
- The impact of any maternal vaccine on the pregnant women's microbiome and future risk of invasive *K.* pneumoniae disease would also warrant investigation.
- A full economic evaluation is needed to consider vaccination of the mother or newborn (for a vaccine to be administered in pregnancy), or the individual (for adult administered vaccines), including healthcare burden, accounting for specific costs related to AMR infections, and societal costs.

Table 2
Overview of potential target and key population(s) and associated delivery strategy(ies).

Target and key population(s)	Delivery strategy(ies)
Pregnant women to protect the fetus and young infant	● Pregnant women from 24 to 36 weeks gestation in various HIC and LMICs. Tools to accurately determine gestational age are warranted in LMICs. ● All GAVI-eligible and transitioned countries, as well as LMICs that have never been GAVI-eligible. ● A single dose regimen is preferred. ● To be safely administered with other recommended and near future maternal vaccines (such as influenza, COVID-19, TT, Tdap, RSV and GBS vaccines) ● Requires established antenatal care platforms. Consideration needs to be given to countries with a high proportion of pregnant women not accessing antenatal care. ● Maternal immunization readiness platforms in Africa and Asia need to be strengthened. ● Increased number of doses or double dosing may be required for pregnant women living with HIV
Adolescents and adults	● 3 single-dose injections, 3–4 weeks apart (single dose would be preferred) ● Available in high-, middle- and low-income countries ● Vulnerable children, adolescents and adult populations at risk of *K. pneumoniae* disease: ○ severe acute malnutrition ○ anticipated prolonged hospital stay, ○ invasive intensive care management, ○ patients undergoing abdominal and/or urinary surgical procedures, ○ risk of surgical site or device-associated infections, ○ chronic obstructive airway disease (COAD), ○ immunocompromised, ○ hematological or other malignancy, and ○ residents of long-term acute care facilities, ○ possibly adults over 65 years of age.

2. Potential target populations and delivery strategies

There are currently two main target populations for *K. pneumoniae* vaccines, and the delivery strategies differ (Table 2). The first is pregnant women targeted in the second or third trimester of pregnancy to enhance the placental transfer of protective antibodies to the fetus thereby protecting young infants in the vulnerable neonatal period and first few months of life. Formative research for a vaccine targeted at pregnant women to protect neonates in LMICs is being funded by The Bill & Melinda Gates Foundation (section 4). The second strategy is targeted towards vulnerable children, adolescents and adult populations at risk of *K. pneumoniae* disease such as those with an anticipated prolonged hospital stay or residents of long-term acute care facilities, with chronic obstructive airway disease, risk of surgical site infections, device-associated infections, immunocompromised, hematological or other malignancy. Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is funding the development of a *K. pneumoniae* vaccine for use in adults and neonates (section 4).

Maternal immunization targeted for administration in the second or third trimester of pregnancy, to protect the mother, fetus (from adverse outcomes like stillbirth) and young infant has been used to reduce the risk of tetanus, pertussis, influenza, and COVID-19 during early infancy. The WHO recommends vaccination of pregnant women against tetanus, influenza, Covid-19 and pertussis. Recently, a maternal RSV vaccine has been approved by the US FDA and a GBS vaccine is entering phase-III trials. The GBS vaccines may achieve licensure benchmarked on a safety profile and thresholds associated with risk reduction probability of disease [79]. Similarly, studies are underway to determine serological anti-K and anti-O IgG thresholds associated with risk reduction of serotype-specific *K. pneumoniae* invasive disease.

3. *Klebsiella pneumoniae* and its consideration as a public health priority by global, regional or country stakeholders

K. pneumoniae causes community- and healthcare-associated infections in children and adults. *K. pneumoniae* was the second leading pathogen of an estimated 1.27 million (95 % UI: 0.91–1.71) deaths attributable to bacterial AMR globally in 2019 [2]. The major burden of invasive *K. pneumoniae* mortality is in neonates and infants. In sub-Saharan Africa and South Asia, K. pneumoniae was reported as the leading cause of neonatal sepsis (24.9 %), and infectious cause of neonatal mortality (45.4 %) [17,21]. This rising concern of multidrug resistant hospital-acquired infections and adverse neonatal outcome makes it a public health priority. Table 3 provides an overview of non-commercial stakeholders' interest and potential demand.

4. Existing guidance on preferences/preferred product attributes for vaccines against *Klebsiella pneumoniae*

The preferred product characteristics (PPC) for *K. pneumoniae* vaccines have not yet been developed by the World Health Organization (WHO). At the time of publication, the Bill & Melinda Gates Foundation (BMGF), which is funding the development of a vaccine targeted at pregnant women, has developed an intervention target product profile (iTPP) for a *K. pneumoniae* vaccine intended to protect neonates in LMICs as detailed in Table 4.1.

Table 3
Overview of non-commercial stakeholders engaged, their interest and potential demand.

Stakeholders engaged	Summary of position/interest	Potential demand and uptake
CDC https://stacks.cdc.gov/view/cdc/82532	CDC is monitoring AMR in the US through the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) https://www.cdc.gov/narms/index.html. CDC categorized AMR pathogens as a threat to human health. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-*ar*-threats-report-508.pdf	AMR ESKAPE *(Enterococcus faecium, Staphylococcus aureus, K. pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species)* pathogens represent a global threat to human health. Action Plan includes action items organized into four focus areas: Surveillance, Prevention and Control, Research, and Product Development. https://www.cdc.gov/drugresistance/pdf/public-health-action-plan-combat-antimicrobial-resistance.pdf
WHO https://www.who.int/news-room/events/detail/2018/10/25/default-calendar/global-conference-on-primary-health-care	WHO "priority status" list of pathogens (ESKAPE) for which new antimicrobial development is urgently needed. *K. pneumoniae* is among the ESKAPE pathogens. WHO GLASS program to guide national AMR surveillance [71].	WHO is working to implement a global action plan to tackle AMR by increasing awareness and knowledge, reducing infection, and encouraging prudent use of antimicrobials. Availability of Federal funding for ESKAPE pathogens [80] Recommends *K. pneumoniae* blood and urine isolates be included in formal surveillance programs.
NIAID	Research on AMR is central to the mission of the National Institute of Allergy and Infectious Diseases (NIAID).	Working in partnership with other federal agencies, industry, foundation partners, and foreign governments to fund basic and clinical research towards understanding, diagnosis, and treatment of infectious diseases [81].
NIH	Funding for Surveillance, Prevention and Control, Research, and Product Development including rapid diagnostic tests and vaccines.	
CARB-X	CARB-X is a global non-profit partnership accelerating antibacterial products to address drug-resistant bacteria, including *K. pneumoniae*. The CARB-X portfolio is the world's most scientifically diverse, early development pipeline of new antibiotics, vaccines, rapid diagnostics and other products. CARB-X is the only global partnership that integrates solutions for the prevention, diagnosis and treatment of life-threatening bacterial infections, translating innovation from basic research to first-in-human clinical trials. https://carb-x.org/about/overview/	

CARB-X is also funding the development of vaccines against *K. pneumoniae*, including carbapenem-resistant strains, to protect adults as well as neonates. It has also shared its guidance on a TPP for a vaccine intended for use in adults in both LMICs and HICs (Table 4.2). The goal is to create a single product that can prevent neonatal sepsis in LMICs by immunizing mothers, as well as to prevent invasive *K. pneumoniae* infections in adults in both HICs and LMICs. The HIC market would help attract investment for the product.

5. Vaccine development

5.1. Probability of technical and regulatory success (PTRS)

For licensure of a *K. pneumoniae* vaccine administered to pregnant women, a significant reduction in culture-confirmed invasive *K. pneumoniae* disease in the neonate or young infant of vaccinated women compared to unvaccinated women would need to be demonstrated. If a serologic correlate or surrogate of protection could be demonstrated through sero-observational studies, consideration may be given to licensure of *K. pneumoniae* vaccines on safety and immunological endpoint alone, followed by phase-IV vaccine effectiveness studies (Table 5).

A reduction in blood culture-confirmed *K.* pneumoniae bacteremia would need to be demonstrated in vulnerable children, adolescents and adult populations at risk of *K. pneumoniae* disease. Another potential endpoint may be vaccine efficacy against colonization (primarily gastrointestinal) among either hospitalized patients or in nursing homes, if this is demonstrated to be a mechanism through which the vaccines work.

5.2. *Overview of the* vaccine *candidates in the clinical pipeline*

Table 6 summarizes the paucity of *K. pneumoniae* vaccines in the clinical pipeline. Klebvax and the K2, K3, *K*10 and K55 mix are no longer in active clinical development. The *Kleb4V* which includes O-antigens, has not been targeted for maternal immunization to protect neonates and young infants. Notably, CARB-X and the BMGF are funding the development of vaccines against *K. pneumoniae* to protect adults and neonates. There is a multi-pathogen licensed vaccine that contains a strain of Klebsiella although it is not in widespread use and its main purpose is in the prevention of recurrent urinary tract infection in adults, and the included evidence suggests that it only protects against the strain that is included in the vaccine rather than wider cross-protection [87,88].

6. Health impact of a vaccine on burden of disease and transmission

A *K. pneumoniae* vaccine administered to pregnant women to protect neonates from invasive *K. pneumoniae* disease could reduce neonatal sepsis in LMICs and HICs significantly. Bayesian modelling of data from 3 global studies in 18 mainly LMICs (2,330 neonates who died with sepsis), from 2016 to 2020 was used to estimate the number of *K. pneumoniae* cases that would be averted if a vaccine with 70 % efficacy was given to pregnant women [4]. Globally, a maternal *K. pneumoniae* vaccine would avert almost 400,000 (Credible Interval [CI]: 334,523—485,442) neonatal sepsis cases annually, and 80,000 (CI: 18,084—189,040) neonatal deaths (Table 7).

Table 4.1
Summary of target product profile for *Klebsiella pneumoniae* maternal vaccines (from BMGF) to protect neonates in LMICs.

Product attribute	Minimal characteristic, if described	Preferential characteristic
Indication	Prevention of *K. pneumoniae* blood culture-confirmed sepsis and/or meningitis due to vaccine serotypes in infants up to three months of age through maternal immunization.	Prevention of *K. pneumoniae* blood culture-confirmed sepsis and/or meningitis due to vaccine serotypes in infants up to six months of age through maternal immunization.
Product	CPS + LPS non-live vaccine, without novel adjuvants	CPS + LPS non-live vaccine, unadjuvanted.
Target population(s)	Pregnant women age > 16 years, at 24–36 weeks gestation.	All pregnant women from 20 weeks gestation age, to address the high burden of hospital-acquired infections in preterm births.
Target Countries	All Gavi-eligible and transitioned countries.	All Gavi-eligible and transitioned countries as well as LMICs that have never been Gavi-eligible.
Outcome measure(s) and target efficacy	A 50 % reduction in blood culture-confirmed *K. pneumoniae* sepsis.	An 80 % reduction in blood culture-confirmed *K. pneumoniae* sepsis.
Duration of protection	Through to three months after birth.	Through to six months after birth.
Safety profile	No evidence of severe side effects or adverse birth outcomes; limited mild local reactions.	No evidence of severe side effects or adverse birth outcomes; limited mild local reactions.
Vaccine presentation	Single dose vial, liquid formulation.	Single and multi-dose vials. Innovative presentations to facilitate delivery are encouraged.
Number of doses and schedule	1 single-dose injection at 24–36 weeks gestational age.	1 single-dose injection at > 20 weeks gestational age.
Vaccine volume	0.5 mL	0.5 mL
Route of administration	IM	IM
Coadministration with other vaccines	• Can be safely administered with influenza, COVID-19, TT, Tdap and RSV vaccines in accordance with local recommendations. • No clinically significant blunting of immune response to infant vaccines.	• Can be safely administered with all maternal vaccines, which may include TT, Tdap, COVID-19, RSV, and influenza; consideration of combination with Tdap and RSV. • No blunting of immune response to infant vaccines.
Product stability and storage	Minimum shelf life of 2 years at 2 – 8 °C. • Vaccine vial monitor (VVM)-7. • If freeze sensitive, use of cryoprotectant formulation or allow the use of shake test or include other indicators of freezing.	Minimum shelf life of 3 years at 2 – 8 °C. • VVM-30. • Not freeze-sensitive. • Use of vaccine for a minimum period of 2 months when stored at a controlled temperature chain (CTC); i.e., stability of the vaccine outside the cold chain for a minimum of 3 days at temperatures up to 40 °C.
Cold chain volume required	Consistent with Vaccine Presentation and Packaging Advisory Group (VPPAG) Guidance, i.e., maximum 4.0, 6.5, 13.0, and 15.0 cm^3 per dose for 10-, 5-, 2-, and 1-dose vials, respectively.	Consistent with VPPAG Guidance.
Product Registration Path	Approval from at least one functional NRA, WHO prequalification and policy recommendation on vaccine use in LMICs, and local marketing authorization in priority markets.	Approval from at least one functional NRA, WHO prequalification and policy recommendation on vaccine use in LMICs, and local marketing authorization in priority markets.
Manufacturing Capacities	Sufficient to meet Gavi's demand.	Sufficient to meet demand from all Gavi and LMIC countries.
Primary Target Delivery Channel	Through existing antenatal care clinic programs.	Through antenatal care clinic or other channels such as national immunization days, child health days, etc.
Target Procurement Price	Accessible and affordable for LMICs.	Accessible and affordable for LMICs.

Cps – capsular polysaccharide; CTC – controlled temperature chain; HIC – high-income country; IM – intramuscular; LMIC – low- and middle income country; LPS – lipopolysaccharide; NRA – national regulatory authorities; RSV – Respiratory Syncytial Virus; VPPAG - Vaccine Presentation and Packaging Advisory Group; WHO – The World Health Organization.

6.1. Summary of research gaps in modelling health impact on disease burden and transmission

- Estimating the cost and impact that a vaccine could have on reducing antibiotic use and AMR, both in *K. pneumoniae* and in other bacteria.
- Estimating the benefit of a vaccine in reducing outbreaks in hospitals and the community, and hence alleviating the burden on healthcare systems.
- Accurate measurement of the herd (community) protection that different vaccination strategies could have.

7. Social and/or economic impact of a vaccine

Even though there is evidence to suggest potential utility gains through *K. pneumoniae* vaccination reducing drug resistant infections (~4 million DALYs attributable with AMR could have been averted globally), the implications of such illnesses on healthcare costs, productivity and economic growth are still largely unknown [93]. This highlights an important gap in the literature that needs to be filled by both empirical studies and modelling.

K. pneumoniae infections are associated with a substantial impact on healthcare resources, particularly around opportunistic nosocomial infections. These infections increase the overall cost of hospital procedures (e.g., by requiring both prophylactic and therapeutic antibiotic use), and may lengthen patients' hospital stay.

AMR *K. pneumoniae* infections impose high costs. The immediate impact is to elevate the costs of treatment, by necessitating the use of more expensive antibiotics, increased hospital stay and increased risk of expensive procedures such as intensive care unit admissions. In studies conducted in Israel, Italy, USA, and Germany, drug-resistant infections had relatively high average length of stay [94–98]. Whilst the incremental impact on length of stay of AMR, namely comparing third-

Table 4.2
Summary of target product profile for *Klebsiella pneumoniae* vaccines (from CARB-X) for adults in LMICs and HICs.

Product attribute	Minimal characteristic, if described	Preferential characteristic
Indication	Prevention of invasive infections due to circulating *K. pneumoniae* strains in hospitals or communities.	Prevention of invasive infections and pneumonia due to circulating *K. pneumoniae* strains in hospitals or communities.
Product	No preferred modality.	No preferred modality.
Target population(s)	Adolescents and adults at high risk of infection, e.g., affected by COAD, risk of surgical site infections, device-associated infections, residents of long-term acute care facilities etc.	Older adults (>65 years of age).
Target Countries	HICs and LMICs.	HICs and LMICs.
Outcome measure(s) and target efficacy	>60 % reduction in blood culture-confirmed *K. pneumoniae* bacteremia; >80 % reduction of antibiotic-resistant *K. pneumoniae.*	>80 % reduction in blood culture-confirmed *K. pneumoniae* bacteremia; >90 % reduction of antibiotic-resistant *K. pneumoniae*
Duration of protection	≥ 2 years.	≥ 5 years.
Safety profile	At least similar to licensed injectable vaccines for the age group.	At least similar to licensed injectable vaccines for the age group.
Vaccine presentation	Single dose vial, liquid formulation.	Single dose vial, liquid formulation.
Number of doses and schedule	3 single-dose injections, 3–4 weeks apart.	1 single-dose injection.
Vaccine volume	0.5 mL	0.5 mL
Route of administration	IM	IM
Co-administration with other vaccines	None	Can be safely administered with routine seasonal vaccines for the age group such as influenza or pneumococcus.
Product stability and storage	Minimum shelf life of 2 years at 2—8 °C.	Minimum shelf life of 3 years at 2—8 °C.
Cold chain volume required	Consistent with VPPAG Guidance.	Consistent with VPPAG Guidance.
Product Registration Path	Approval from at least one functional NRA	Approval from at least one functional NRA, WHO prequalification, local marketing authorization in priority markets.
Manufacturing Capacities		Sufficient to meet demand from all Gavi and LMICs countries.
Special Populations		HIV + population.
Target Procurement Price		<$2 per dose.

COPD – chronic obstructive pulmonary disease; IM – intramuscular; HIC – high-income countries; LMICs – low- and middle-income countries; NRA – national regulatory authorities; VPPAG - Vaccine Presentation and Packaging Advisory Group; WHO –World Health Organization.

generation cephalosporins and carbapenem resistant infections to their susceptible counterparts, appears to be significant, the impacts on hospital costs from payer/provider-perspectives are less conclusive [95,99–103]. For example, a study in the USA found community-onset AMR *K. pneumoniae* to be associated with an excess of $11,800 (95 % CI: -$10,500 to $34,200), with hospital-onset equivalents costing an excess of $13,200 (95 % CI: -$5,900 to $32,200) [104]. A study in Hong Kong found similar insights, with infection-related cost, though on average higher ($16,026 vs $11,602) was found to be insignificant (p-value = 0.382) [105]. However, both studies cite retrospective nature and small sample sizes as limitations, so these conclusions could be subject to Type 2 errors.

As well as the potential incremental cost of treating endemic AMR *K. pneumoniae* in hospitals, there is the wider threat of outbreaks of drug-resistant *K. pneumoniae*. An ESBL-producing 4-month outbreak in 2001 in neonates within the USA was costed at $341,751, with the largest costs attributable to healthcare worker time in direct patient care (2,489 h, $146,331) [106]. Between July 2014 and October 2015, an outbreak of carbapenemase-producing *Enterobacteriaceae* in England cost €1.1 m (range €0.9–1.4 m), with around €312,000 of actual expenditure, and €822,000 of opportunity cost [107]. During October–December 2015, a multidrug-resistant, New Delhi-metallo-β-lactamase–positive *K. pneumoniae* strain in the Netherlands had an estimated economic impact of $804,263, with the highest costs associated with hospital bed closures [108].

Beyond the healthcare system, families and caregivers also bear a wider array of costs, ranging from emotional distress to lost wages by patients and their caregivers to out-of-pocket payments for hospitalization and drugs. A study conducted in Brazil of patients with carbapenamase-producing *K. pneumoniae* found that direct medical costs per patient were $4,135.15, with the vast majority of these costs due to antimicrobial therapies, particularly systemic antimicrobials. Notably, the highest cost burden was incurred during the period of infection [109]. Similarly, a study conducted in China found higher antibiotic and treatment costs among patients with carbapenem-resistant *Enterobacteriaceae* compared to those with susceptible strains [110].

The long-term consequences of AMR *K. pneumoniae* may be far more dire. If *K. pneumoniae* develops resistance to current last resort antibiotics and no new antibiotics are brought to market, then certain medical procedures may become perilous due to the risk of untreatable infection, potentially rendering them too hazardous to perform [111]. This phenomenon could result in a rise in the prevalence of long-term disability stemming from the inability to conduct surgical interventions for conditions that are not life-threatening in nature, and the inability to treat surgical site infections when they occur [112].

An effective vaccine would reduce this burden through multiple mechanisms. Firstly, vaccines may reduce the overall carriage of and incidence of *K. pneumoniae* infections, thereby mitigating the strain on healthcare facilities and resources. Reducing deaths attributable to *K. pneumoniae* (particularly for neonatal-sepsis) could also increase the

Table 5
Overview of parameters that inform scientific feasibility of developing an effective vaccine for LMICs public market use.

Parameter	Issues and evidence
Diagnosis/case ascertainment	Diagnosis is through positive culture from the usually sterile infected site (e.g. blood, CSF) [17,47]. In LMICs the ability to diagnose invasive disease is often limited by the blood culture sampling of babies suspected to have sepsis or meningitis where the microbiology laboratory technology is available to identify invasive *K. pneumoniae* disease. Investment in improved diagnostic technology is needed [82].
Biomarkers/ Correlates of risk and/or protection	There is currently no immune surrogate or correlate for protection against invasive *K. pneumoniae* disease which could be used to infer protection or vaccine efficacy. Similarly, there are no established biomarkers. Work is ongoing to develop antibody binding (e.g. Luminex) and functional (e.g. serum bactericidal assay (SBA)/ opsonophagocytic killing (OPK)) assays, but these have yet to be standardized or correlated with protection [40].
Sero-epidemiological data	There are no sero-epidemiological studies on infection induced immunity following *K. pneumoniae* infection. More detailed investigation of K- and O-serotypes prevalent in different geographic areas are needed to inform potential vaccine formulation using these antigen targets [17,45–47,83]. In addition, there are highly conserved epitopes in the Gram-negative bacterial LPS core that may be potential vaccine targets.
Clinical endpoints	For *K. pneumoniae* vaccine studies, a clinical endpoint would be the prevention of invasive *K. pneumoniae* disease in the vaccinated group compared with a control group. Another secondary endpoint could be reduction of gastrointestinal colonization among either hospitalized neonates or in adult nursing homes, but further research is needed. Other secondary or exploratory endpoints include the prevention of all-cause neonatal sepsis, duration of hospitalization and all-cause mortality in the vaccinated group compared with a control group.
Controlled Human Infection Model (CHIM)	There are currently no human infection models. Human infection models depend on having a challenge strain that can induce clinical manifestations of infection without posing a threat to the human subject. While this has been achieved for some organisms, no such model has been established for an opportunistic pathogen and it is expected to be very challenging for *K. pneumoniae.*
Opportunity for innovative clinical trial designs	There is limited opportunity for innovative *K. pneumoniae* clinical trial designs. Large multicenter studies will be required for a reduction of invasive disease as an endpoint, particularly in settings with a low burden of disease. Sero-epidemiological studies are underway to establish an immune surrogate or correlate for protection against invasive *K. pneumoniae* disease. Unlike for GBS, these studies however need to be cognizant of the challenges in establishing a correlate for protection against invasive *K. pneumoniae* disease; for example, the data analysis will need to factor the multiple potential confounders in the control group, and stratify by prematurity as a large proportion of *K. pneumoniae* hospital-acquired cases occur in preterm neonates.
Regulatory approach(es), including potential	The goal of a *K. pneumoniae* vaccine would be (i) the prevention of invasive *K. pneumoniae* disease in neonates by targeted vaccination of pregnant women and (ii) the prevention of invasive *K. pneumoniae* disease targeted at vulnerable populations at risk of *K. pneumoniae* and/or the elderly. Licensure from at least one functional NRA, followed by WHO Strategic Group of Experts on Immunization (SAGE) adoption and prequalification for Gavi markets. This will be dependent on indication and selected priority markets.
Accelerated approval strategies	In the absence of data demonstrating a serologic correlate or a surrogate of protection, *K. pneumoniae* vaccines are unlikely to be approved based on safety and immunogenicity data alone. There are no CHIMs. Animal survival challenge model studies will need to be undertaken. Furthermore, sero-epidemiological studies measuring quantitative and OPA/ SBA antibody thresholds following natural infection will need to be established.
Potential for combination with other vaccines	A combination strategy is definitely feasible, especially with a maternal vaccination strategy, combining with different pathogens causing neonatal sepsis, combining with other vaccines recommended in pregnancy (e.g. Tdap) or combining with other nosocomial infections (e.g. in the elderly). A 24-valent *K. pneumoniae* CPS vaccine (Klebvax^{R}), administered concurrently with an 8-valent *Pseudomonas* vaccine, was well tolerated in studies from the 1990 s. Nevertheless, Klebvax was not introduced into routine clinical use (See Table 6). Combination vaccines which target additional ESKAPE pathogens is appealing for reducing the risks of invasive disease in neonates and high-risk adult groups. The safety of vaccine combinations must be determined. Also, the timing of co-administered vaccines must be considered, especially given the potential interaction with routine childhood immunization.
Feasibility of meeting presentation and stability requirements	Stable experimental *K. pneumoniae* vaccines have been developed, but to date these have required cold chains which are difficult in LMICs. A single dose vial is preferred to minimize wastage, but consideration needs to be given in the LMICs. Stability requirements are consistent with Vaccine Presentation and Packaging Advisory Group (VPPAG) guidance.
Vaccine platform	There are many *K. pneumoniae* vaccine platforms in development [84,85]. CPS (K-antigen)/LPS (O- antigen)-based vaccines are in preclinical development using well-established technologies, including bioconjugation, and the formation of nanoconjugates; all are feasible for large scale manufacturing, tech transfer and adaptable to alternative strains if needed. Complex multi-valent vaccines may be required for sufficient coverage of dominant circulating strains of *K. pneumoniae*. Use of technologies enabling low cost of goods is preferable. Various conjugation strategies or outer membrane vesicle (OMV) vaccines may be amenable to scale-up and adaptable to new strains [86]. OMV and live attenuated *K. pneumoniae* vaccines would need to ensure detoxification of the LPS to reduce reactogenicity. The use of live attenuated vaccines is unlikely to be an option for vaccination of pregnant women. Some technologies, such as semi-synthetic oligosaccharide synthesis, would be difficult to produce at large scale. Vaccines directed at the highly conserved Gram-negative bacillus LPS core may also protect against preclinical *K. pneumoniae* infection.
Large scale Manufacturer capacity / interest	GlaxoSmithKline (LimmaTech Biologicals AG) has tested a tetravalent bioconjugate vaccine including O-antigen-polysaccharides in a Phase 1 clinical trial (NCT04959344). Inventprise is working on combination multivalent K and O-antigen based conjugate vaccine against *K. pneumoniae*. GlaxoSmithKline is developing a multi-valent *K. pneumoniae* vaccine through Multiple Antigen Presentation System (MAPS) technology acquired by Affinivax. There may well be developing interest from other multi-national companies, but this would depend on the availability of both immunogenicity and functional activity of the proposed vaccine. Many vaccines in development have not published functional data.

Table 6
Overview of vaccine candidate in clinical trials.

Candidate	Antigen platform	Developer/ manufacturer	Phase of development, population, and location	Route of administration, no. of doses, schedule	Presentation and stability
Kleb4V /GSK4429016A (NCT04959344)	*P. aeruginosa* exotoxin protein A recombinant bioconjugates of O1, O2a, O2afg, O3b w/wo AS03	LimmaTech Biologicals AG/ GSK	Ph1/2; 18–40 years and older adults (55–70 years) Germany;completed September 2022	Two doses given IM; two months apart	Liquid formulation with and without adjuvant (ASO3); target and low dose tested
Klebvax* [89–91]	24 V K-Ag unconjugated from *K. pneumoniae* and *K. oxytoca* (2, 3, 5, 9, 10, 15–18, 21, 22, 25, 28, 30, 35, 43, 52, 53, 55 and 60–64)	SSVI and WRAIR	Ph1, 2 and made into H-IVIG; adult volunteers and ICU patients (VA Coop Study-4), Baltimore, US.	1,200 μg of polyvalent CPS vaccine injected IM along with 200 μg of Pseudomonas conjugate into the other arm.	Vaccine lyophilized and reconstituted prior to use.
K2, K3, *K*10 and K55 mix* [92]	CPS, unconjugated	SSVI and WRAIR	Ph1; 22–62 years; UK	25 or 50 μg of each antigen; SC; 1 immunization	Vaccine was lyophilized and reconstituted in water before administration

Abbreviations: PH = Clinical phase; GSK = GlaxoSmithKline; IM = intramuscular; CPS = capsular polysaccharide; H-IVIG = hyperimmune immunoglobulin for intravenous use; SSVI = Swiss Serum and Vaccine Institute; WRAIR = Walter Reed Army Institute of Research; SC = subcutaneously. *No longer in active clinical development.

labor pool through increased working-life-years available, reducing associated productivity losses [4]. Additionally, by reducing infection incidence, vaccines would reduce the need to use higher-tier antibiotics, consequently diminishing the selection pressure on *K. pneumoniae* and potentially delaying the development of AMR. Furthermore, reducing antibiotic usage through vaccination could potentially have benefits on other pathogens, as the use of non-specific antibiotics might also decrease, contributing to a decline in resistance among other microorganisms [113].

8. Policy considerations and financing

The development and deployment of a vaccine against *K. pneumoniae* presents critical policy considerations and financing challenges, particularly in LMICs and HICs. Given the substantial burden of disease associated with *Klebsiella* infections in both LMICs and HICs, equitable access to the vaccine is imperative. In Gavi-eligible countries, financial support from Gavi will be pivotal in ensuring access to the vaccine. However, in non-Gavi markets, policymakers must carefully assess the local context, considering factors such as disease prevalence, potential impact, and cost-effectiveness when deciding on the introduction of Klebsiella immunization. Furthermore, to secure funding from Gavi, the vaccine must meet the rigorous prequalification standards set by the WHO, and a policy decision made by the WHO SAGE is essential. These interlinked considerations and financing mechanisms will play a pivotal role in the global effort to combat *K. pneumoniae* infections (Table 8).

9. Access and implementation feasibility

The feasibility and implementation of *K. pneumoniae* vaccines are examined in this chapter, with a focus on maternal immunization to prevent neonatal and infant sepsis, as well as immunization for vulnerable children, adolescents and adult populations at risk of *K. pneumoniae* disease. It is suggested that the potential integration of these vaccines into existing delivery systems shows moderate promise, particularly when utilizing platforms established for other vaccinations (Table 9). The identification of a viable target population and the commercial viability are moderately attractive, with a higher potential noted in high-income countries due to the rise of AMR. The clarity of the licensure path and policy decisions is presented as variable, necessitating novel strategies for vaccine efficacy assessment. Financing mechanisms and the ease of uptake are discussed, indicating a moderate expectation of interest from global funders and a high likelihood of incorporation into clinical guidelines (Table 9).

10. Conclusion

The global threat posed by invasive *K. pneumoniae* disease, particularly hospital-acquired multidrug resistant strains affecting neonates and young infants, and vulnerable children, adolescents and adult populations at risk of *K. pneumoniae* disease warrant immediate vaccination strategies. In this VVP for *K. pneumoniae,* we described the potential public health and economic value of vaccines targeted against *K. pneumoniae.* We highlight the limited vaccine pipeline and call on funders to develop vaccines targeted against *K. pneumoniae.*

Based on limited surveillance estimates, a *K. pneumoniae* vaccine with 70 % efficacy administered to pregnant women to protect neonates would avert almost 400,000 neonatal sepsis cases yearly, and 80,000 neonatal deaths. More data from LMICs and a full economic evaluation of the potential benefit of a vaccine for vulnerable children, adolescents and adult populations at risk of *K. pneumoniae* disease are needed, including healthcare burden and societal costs, and accounting for specific costs related to AMR infections, and reducing outbreaks in hospitals.

Importantly, the discussion with regulators about vaccine licensure based on vaccine efficacy against a laboratory endpoint of culture-confirmed *K. pneumoniae* bacteraemia or on established sero-correlates of protection is warranted. Transplacental and breast milk transfer of *K. pneumoniae* antigen-specific antibody from pregnant women to the fetus and newborn needs to be evaluated.

Equitable access to the vaccine is also imperative given that the burden of invasive *K. pneumoniae* disease is high in both LMICs and HICs. The development and deployment of a vaccine against *K. pneumoniae* presents critical policy considerations and financing challenges, particularly in LMICs. Furthermore, to secure funding from Gavi, the vaccine must meet the rigorous prequalification standards set by the WHO, and a policy decision made by the WHO SAGE is essential.

Funding: This work was supported by the funding from Bill & Melinda Gates Foundation (INV-00518) to the World Health Organization.

CRediT authorship contribution statement

Ziyaad Dangor: Writing – review & editing, Writing – original draft, Project administration. **Nicole Benson:** Writing – review & editing, Writing – original draft. **James A. Berkley:** Writing – review & editing, Writing – original draft. **Julia Bielicki:** Writing – review & editing, Writing – original draft. **Merijn W. Bijsma:** Writing – review & editing, Writing – original draft. **Jonathan Broad:** Writing – review & editing,

Table 7
Overview of modelling studies that measure health impact on disease burden and transmission.

Policy question	Assessment method/ measure	Assumptions	Outcomes/interpretation
What is the impact of a *K. pneumoniae* vaccine given to pregnant mothers on health outcomes in neonates and infants? [4]	A Bayesian mixture-modelling framework was developed to estimate the effects of a hypothetical *K. pneumoniae* maternal vaccine with 70 % efficacy on neonatal sepsis and mortality. The model was parameterized using data from 3 global studies of neonatal sepsis and/or mortality, involving 2,330 neonates who died with sepsis, from 2016 to 2020, undertaken in 18 mainly LMICs across all WHO regions (Ethiopia, Kenya, Mali, Mozambique, Nigeria, Rwanda, Sierra Leone, South Africa, Uganda, Brazil, Italy, Greece, Pakistan, Bangladesh, India, Thailand, China, and Vietnam). Within these studies, 26.95 % of fatal neonatal sepsis cases were culture-positive for *K. pneumoniae*. To predict the future number of drug-resistant cases and deaths that could be averted by vaccination, 9,070 *K. pneumoniae* genomes from human isolates gathered globally from 2001 to 2020 were analyzed to quantify the temporal rate of acquisition of AMR genes in *K. pneumoniae* isolates.	**Incidence rate:** The model assumes a probability, ps,l, that *K. pneumoniae* was the cause of death for a neonate who died from neonatal sepsis in each location (l) and for each study (s). **Case Fatality Risk (CFR):** The model estimates the CFR for *K. pneumoniae* sepsis using data from the BARNARDS study. **Direct vaccine efficacy rate:** The model assumes a 70 % efficacy rate for the maternal *K. pneumoniae* vaccine, based on a conjugate vaccine candidate targeting the 15 most common *K. pneumoniae* capsular serotypes that cause invasive infections in neonates. **Herd effects:** The model does not explicitly mention herd effects. **Coverage rate:** The model assumes an effective coverage level equal to that of the maternal tetanus vaccine (median: 90 %; range: 38.5 % to 100 % of pregnant women immunized) for the maternal *K. pneumoniae* vaccine. **Vaccine duration and frequency:** The model does not explicitly mention vaccine duration or frequency; it assumes a one-time administration of the maternal *K. pneumoniae* vaccine. **Target populations:** The model focuses on neonates who died with sepsis in 18 mainly LMICs across all WHO regions. The target population includes pregnant women for vaccine coverage estimates. **Time period:** The model uses data from studies conducted between 2016 and 2020 for neonatal sepsis surveillance. For *K. pneumoniae* genome analysis, data from 2001 to 2020 are used to estimate future benefits. **Granularity (country/region):** The model analyzes data from 18 mainly LMICs across all WHO regions and includes 68 countries for *K. pneumoniae* genome analysis. The results are extrapolated to estimate global figures.	Resistance rates to carbapenems are observed to be increasing most rapidly, and meropenem-resistant *K. pneumoniae* is responsible for 22.43 % of neonatal sepsis deaths (95th percentile CI: 5.24—41.42).Globally, it is estimated that maternal vaccination could avert 80,258 neonatal deaths (CI: 18,084—189,040) and 399,015 neonatal sepsis cases yearly worldwide (CI: 334,523—485,442), which accounts for more than 3.40 % of all neonatal deaths (CI: 0.75—8.01).The largest relative benefits are observed in Africa (Sierra Leone, Mali, Niger) and South-East Asia (Bangladesh) , where vaccination could avert over 6 % of all neonatal deaths. However, it should be noted that the modelling only considers country-level trends in *K. pneumoniae* neonatal sepsis deaths and is unable to account for within-country variability in incidence, which may influence the projected burden of sepsis. It also does not consider any potential benefit that vaccination may have beyond the vaccinee, in reducing hospital and community transmission, and hence may underestimate vaccine benefit.
What is the impact of a *K. pneumoniae* vaccine given to pregnant mothers for prevention of blood stream infections in neonates and infants? [93]	The model is a static proportional impact model to estimate the vaccination impact on 15 bacterial pathogens in terms of reduction in age- specific AMR burden estimates for 2019 from the Global Research on Antimicrobial Resistance project in direct proportion to efficacy, coverage, target population for protection, and duration of protection of existing and future vaccines.	**Incidence rate:** The model uses bacterial AMR burden estimates from the GRAM project, which provides data for age-specific deaths and DALYs associated with and attributable to AMR by pathogen, infectious syndrome, and region for 2019. **CFR**: The model does not use CFR in the estimation process. **Direct vaccine efficacy rate**: 70 % Herd effects: not included in the modelling. **Coverage rate:** 70 % **Vaccine duration**: 6 months. **Target populations**: immunization of mothers to protect children between 0 and 6 months old **Granularity (country/region):** The model estimates vaccine-avertable deaths and DALYs attributable to and associated with AMR by region, infectious syndrome, and pathogen for two scenarios - baseline scenario and high-potential scenario.	27,333 (95th UI: 22,045—34,905) deaths associated with AMR could be averted by such a vaccine
What is the impact of a *K. pneumoniae* vaccine in preventing all disease outcomes given to children and the elderly? [4]	As above	Same as above except for: • Vaccine duration: 5 years. • Target populations: immunization of 6-week infants and 70 years elderly	64,484 (95 % UI: 58,747—72,028) of deaths associated with AMR could be averted by such vaccine

(*continued on next page*)

Table 7 (*continued*)

Policy question	Assessment method/ measure	Assumptions	Outcomes/interpretation
What is the impact of a *K. pneumoniae* vaccine in preventing all disease outcomes given to all who are at risk of acquiring infection? [4]	As above	Same as above except for: • Target populations: all age groups	321,242 (95 % UI: 308,878—335,698) of deaths associated with AMR could be averted by such vaccine

Table 8
Overview of expectations of evidence that are likely to be required to support a global / regional / national policy recommendation, or financing.

Parameter for policy/ financing consideration	Assumptions	Guidance/ reports available
Product efficacy and safety	Vaccines would need to demonstrate safety and efficacy in clinical trials.	
Evidence for vaccine efficacy in LMICs is available	Clinical trials must provide evidence of efficacy and safety in the LMICs.	This may be required by SAGE for a policy recommendation (has been required for some other vaccines), and licensure in some countries
WHO policy recommendationthrough SAGE	SAGE recommends the wide use of a maternal vaccine.	https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/about
Prequalification (PQ) of maternal vaccines by WHO	Manufacturers choose to submit package to WHO for PQ. Vaccines receive PQ.	https://www.who.int/publications/i/item/WHO-IVB-14.10
National (or at least regional) *Klebsiella*disease burden data	National policy for *Klebsiella* vaccines will be based on evidence of disease burden (including health care utilization).	https://www.who.int/publications/i/item/9789241506892
Favorable cost-effectiveness	Countries will more likely take up products if cost effectiveness analyses show favorable value for money.	https://www.who.int/publications/i/item/9789241506892
Product price acceptable to Gavi investment case for use in Gavi eligiblecountries	LICs that are Gavi eligible will likely apply for use of *Klebsiella* vaccines only if Gavi support is available.	https://www.gavi.org/our-alliance/strategy/vaccine-investment-strategy-2024
Feasibility of integration intoexisting delivery platforms (i.e., antenatal care, postnatal check-ups, routine EPI visits)	Integration into existing platforms will favor uptake of products.	
Impact of the vaccine on antibioticuse and AMR	The impact of *Klebsiella* vaccine on AMR has been modelled but data collected during clinical trials, post-licensure and surveillance studies must confirm the modelling findings [4,93].	

Writing – original draft. **Ed T. Buurman:** . **Alan Cross:** Writing – review & editing, Writing – original draft. **Erin M. Duffy:** Writing – review & editing, Writing – original draft. **Kathryn E. Holt:** Writing – review & editing, Writing – original draft. **Pui-Ying Iroh Tam:** Writing – review & editing, Writing – original draft. **Mark Jit:** Writing – review & editing, Writing – original draft. **Konstantinos Karampatsas:** Writing – review & editing, Writing – original draft. **Michael Katwere:** Writing – review & editing, Writing – original draft. **Gaurav Kwatra:** Writing – review & editing, Writing – original draft. **Ramanan Laxminarayan:** Writing – review & editing, Writing – original draft. **Kirsty Le Doare:** Writing – review & editing, Writing – original draft. **Robert Mboizi:** Writing – review & editing, Writing – original draft. **Francesca Micoli:** Writing – review & editing, Writing – original draft. **Catrin E. Moore:** Writing – review & editing, Writing – original draft. **Eve Nakabembe:** Writing – review & editing, Writing – original draft. **Nichola R. Naylor:** Writing – review & editing, Writing – original draft. **Seamus O'Brien:** Writing – review & editing, Writing – original draft. **Courtney Olwagen:** Writing – review & editing, Writing – original draft. **Denasha Reddy:** Writing – review & editing, Writing – original draft. **Charlene Rodrigues:** Writing – review & editing, Writing – original draft. **David A. Rosen:** Writing – review & editing, Writing – original draft. **Manish Sadarangani:** Writing – review & editing, Writing – original draft. **Padmini Srikantiah:** Writing – review & editing, Writing – original draft. **Sharon M. Tennant:** Writing – review & editing, Writing – original draft. **Mateusz Hasso-Agopsowicz:** Writing – review & editing, Writing – original draft, Conceptualization. **Shabir A. Madhi:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ziyaad Dangor reports financial support was provided by Bill & Melinda Gates Foundation. Ziyaad Dangor reports financial support was provided by World Health Organization. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Table 9
Overview of considerations that are likely to be required to approve, recommend, and deliver a vaccine where needed.

Indicator	Maternal vaccine to prevent against neonatal and infant sepsis	Vaccine given to those at high risk to prevent various disease presentations
Possibility of implementation within existing delivery systems	MODERATE Considering the feasibility of delivering a vaccine against *K. pneumoniae* to pregnant women in LMICs, the outlook appears moderate. This is due to the potential to leverage existing platforms used for delivering the tetanus vaccine to pregnant women. Moreover, the inclusion of GBS and RSV vaccines could further enhance the maternal vaccination platform, making it a viable option for implementing the *K. pneumoniae* vaccine and improving maternal and neonatal health. A key consideration, however, is the high burden of hospital acquired *K. pneumoniae* in preterm neonates. Therefore, vaccination would be required early in the second trimester and dependent on efficient transplacental antibody to protect the preterm neonate.	LOW Delivering a vaccine to those who are at high risk of infection is challenging. Such an immunization program would require establishing appropriate point of contacts with adolescents and adults. This would be particularly challenging in LMICs. In MICs and HICs markets, several patient populations may be identified and targeted within existing practice structures: those in long-term acute care facilities and nursing homes; since patients discharged from hospitals are likely to return within the year, one can immunize patients upon discharge from the hospital; patients undergoing elective surgery; and patients who will become immunocompromised (e.g. oncology or transplant patients) would merit immunization before undergoing treatment.
Commercial attractiveness	MODERATE There is a promising target population in all markets. However, defining the target population appropriately would necessitate surveillance efforts. Furthermore, the vaccine holds potential for Gavi support if it proves to be cost-effective and effectively averts a significant burden of disease in LICs. This support from Gavi could significantly enhance the commercial prospects and accessibility of the vaccine in these regions.	HIGH There is a potentially significant market in HICs. With the increase in AMR and the likelihood that any newly developed antibiotic will have a relatively short half-life, immunization may be an attractive complement to current approaches.
Clarity of licensure and policy decision pathway	MEDIUM Should maternal immunization be shown to be safe and able to decrease the incidence of neonatal sepsis and to reduce neonatal mortality, decisions on licensure and policy should be relatively straightforward. Based on the high incidence of invasive *K. pneumoniae* disease in most LMICs, a phase 3 efficacy trial with a clinical endpoint of disease prevention would need to be undertaken in various settings, including power to address the burden in preterm neonates	LOW Given the difficulty of performing a phase 3 trial for any vaccine targeting healthcare-associated infections, alternative strategies for assessing the efficacy of these vaccines will need to be developed in conjunction with licensing agencies. There might be a need for considering correlates of protection as a proxy for efficacy in phase 3 trials, while effectiveness will be evaluated post-vaccine licensure. Sero-epidemiological studies to establish an immune surrogate or correlate for protection against invasive *K. pneumoniae* disease will need to address the potential confounders in the control group.
Expected financing mechanism	MODERATE Potential interest from global funders, depending on public health impact data. There is interest from national procurement agencies.	HIGH As the vaccine market would predominantly be concentrated in HICs, the decision to introduce and finance a vaccine will depend on the standardized processes to evaluate and introduce vaccines, often supported by National Immunization Technical Advisory Groups (NITAGs) .
Ease of uptake	MODERATE Well-defined target population with likelihood of high acceptability, but possible difficulties in infrastructure for vaccination such as timely identification and immunization of pregnant women during early second trimester.	HIGH An effective *K. pneumoniae* vaccine could be incorporated into multiple clinical guidelines and implemented within the existing healthcare delivery systems. The increasing prevalence of AMR could further increase the ease of vaccine uptake.

Acknowledgement

This supplement was sponsored by the World Health Organization's Immunization, Vaccines, and Biologicals unit. The authors alone are responsible for the views expressed in each article and they do not necessarily represent the views, decisions, or policies of the institutions with which they are affiliated.

References

[1] Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet (London, England). 2022;400(10369):2221-48.
[2] Antimicrobial RC. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022;399(10325):629–55.
[3] Sands K, Carvalho MJ, Portal E, Thomson K, Dyer C, Akpulu C, et al. Characterization of antimicrobial-resistant gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries. Nat Microbiol 2021;6(4):512–23.
[4] Kumar CK, Sands K, Walsh TR, O'Brien S, Sharland M, Lewnard JA, et al. Global, regional, and national estimates of the impact of a maternal Klebsiella pneumoniae vaccine: a Bayesian modeling analysis. PLoS Med 2023;20(5):e1004239.
[5] Sharrow D, Hug L, You D, Alkema L, Black R, Cousens S, et al. Global, regional, and national trends in under-5 mortality between 1990 and 2019 with scenario-based projections until 2030: a systematic analysis by the UN inter-agency Group for Child Mortality Estimation. Lancet Glob Health 2022;10(2):e195–206.
[6] Zhu J, Wang T, Chen L, Du H. Virulence factors in hypervirulent Klebsiella pneumoniae. Front Microbiol 2021;12:642484.
[7] Podschun R, Ullmann U. Klebsiella spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. Clin Microbiol Rev 1998;11(4):589–603.
[8] Gorrie CL, Mirceta M, Wick RR, Edwards DJ, Thomson NR, Strugnell RA, et al. Gastrointestinal carriage is a major reservoir of Klebsiella pneumoniae infection in intensive care patients. Clin Infect Dis 2017;65(2):208–15.
[9] Osei MM, Dayie N, Azaglo GSK, Tettey EY, Nartey ET, Fenny AP, et al. Alarming levels of multidrug resistance in aerobic gram-negative bacilli isolated from the nasopharynx of healthy under-five children in Accra, Ghana. Int J Environ Res Public Health 2022;19(17).
[10] Farida H, Severin JA, Gasem MH, Keuter M, van den Broek P, Hermans PW, et al. Nasopharyngeal carriage of Klebsiella pneumoniae and other gram-negative bacilli in pneumonia-prone age groups in Semarang. Indonesia J Clin Microbiol 2013;51(5):1614–6.
[11] Rao K, Patel A, Sun Y, Vornhagen J, Motyka J, Collingwood A, et al. Risk factors for klebsiella infections among hospitalized patients with preexisting colonization. mSphere. 2021;6(3):e0013221.
[12] Asensio A, Oliver A, González-Diego P, Baquero F, Pérez-Díaz JC, Ros P, et al. Outbreak of a multiresistant Klebsiella pneumoniae strain in an intensive care unit: antibiotic use as risk factor for colonization and infection. Clin Infect Dis 2000;30(1):55–60.
[13] Lin YT, Siu LK, Lin JC, Chen TL, Tseng CP, Yeh KM, et al. Seroepidemiology of Klebsiella pneumoniae colonizing the intestinal tract of healthy Chinese and overseas Chinese adults in Asian countries. BMC Microbiol 2012;12:13.

[14] Wyres KL, Holt KE. Klebsiella pneumoniae as a key trafficker of drug resistance genes from environmental to clinically important bacteria. Curr Opin Microbiol 2018;45:131–9.
[15] Hu Y, Anes J, Devineau S, Fanning S. Klebsiella pneumoniae: prevalence, reservoirs, antimicrobial resistance, pathogenicity, and infection: a hitherto unrecognized zoonotic bacterium. Foodborne Pathog Dis 2021;18(2):63–84.
[16] Rodrigues C, Hauser K, Cahill N, Ligowska-Marzęta M, Centorotola G, Cornacchia A, et al. High prevalence of Klebsiella pneumoniae in european food products: a multicentric study comparing culture and molecular detection methods. Microbiol Spectr 2022;10(1):e0237621.
[17] Sands K, Carvalho MJ, Portal E, Thomson K, Dyer C, Akpulu C, et al. Characterization of antimicrobial-resistant Gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries. Nature microbiology. 2021;6(4):512-23.
[18] Fleischmann C, Reichert F, Cassini A, Horner R, Harder T, Markwart R, et al. Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Arch Dis Child 2021;106(8):745–52.
[19] Russell NJ, Stohr W, Plakkal N, Cook A, Berkley JA, Adhisivam B, et al. Patterns of antibiotic use, pathogens, and prediction of mortality in hospitalized neonates and young infants with sepsis: a global neonatal sepsis observational cohort study (NeoOBS). PLoS Med 2023;20(6):e1004179.
[20] Williams PCM, Isaacs D, Berkley JA. Antimicrobial resistance among children in sub-saharan Africa. Lancet Infect Dis 2018;18(2):e33–44.
[21] Mahtab S, Madhi SA, Baillie VL, Els T, Thwala BN, Onyango D, et al. Causes of death identified in neonates enrolled through child health and mortality prevention surveillance (CHAMPS), December 2016 -December 2021. PLOS Glob Public Health 2023;3(3):e0001612.
[22] Bassat Q, Blau DM, Ogbuanu IU, Samura S, Kaluma E, Bassey IA, et al. Causes of death among infants and children in the child health and mortality prevention surveillance (CHAMPS) network. JAMA Netw Open 2023;6(7):e2322494.
[23] Cai S, Thompson DK, Anderson PJ, Yang JY. Short- and long-term neurodevelopmental outcomes of very preterm infants with neonatal sepsis. A Systematic Review and Meta-Analysis Children (Basel) 2019;6(12).
[24] Mukhopadhyay S, Puopolo KM, Hansen NI, Lorch SA, DeMauro SB, Greenberg RG, et al. Neurodevelopmental outcomes following neonatal late-onset sepsis and blood culture-negative conditions. Arch Dis Child Fetal Neonatal Ed 2021;106(5):467–73.
[25] Shim SY, Cho SJ, Park EA. Neurodevelopmental outcomes at 18–24 months of corrected age in very low birth weight infants with late-onset sepsis. J Korean Med Sci 2021;36(35):e205.
[26] Ortgies T, Rullmann M, Ziegelhöfer D, Bläser A, Thome UH. The role of early-onset-sepsis in the neurodevelopment of very low birth weight infants. BMC Pediatr 2021;21(1):289.
[27] Hentges CR, Silveira RC, Procianoy RS, Carvalho CG, Filipouski GR, Fuentefria RN, et al. Association of late-onset neonatal sepsis with late neurodevelopment in the first two years of life of preterm infants with very low birth weight. J Pediatr (Rio J) 2014;90(1):50–7.
[28] Ferreira RC, Mello RR, Silva KS. Neonatal sepsis as a risk factor for neurodevelopmental changes in preterm infants with very low birth weight. J Pediatr (Rio J) 2014;90(3):293–9.
[29] Gonçalves BP, Procter SR, Paul P, Chandna J, Lewin A, Seedat F, et al. Group B streptococcus infection during pregnancy and infancy: estimates of regional and global burden. Lancet Glob Health 2022;10(6):e807–19.
[30] Horváth-Puhó E, van Kassel MN, Gonçalves BP, de Gier B, Procter SR, Paul P, et al. Mortality, neurodevelopmental impairments, and economic outcomes after invasive group B streptococcal disease in early infancy in Denmark and the Netherlands: a national matched cohort study. Lancet Child Adolesc Health 2021;5(6):398–407.
[31] Paul P, Chandna J, Procter SR, Dangor Z, Leahy S, Santhanam S, et al. Neurodevelopmental and growth outcomes after invasive group B streptococcus in early infancy: a multi-country matched cohort study in South Africa, Mozambique, India, Kenya, and Argentina. EClinicalMedicine 2022;47:101358.
[32] Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 2010;304(16):1787–94.
[33] Anderson DJ, Richet H, Chen LF, Spelman DW, Hung YJ, Huang AT, et al. Seasonal variation in Klebsiella pneumoniae bloodstream infection on 4 continents. J Infect Dis 2008;197(5):752–6.
[34] Choe YJ, Smit MA, Mermel LA. Seasonality of respiratory viruses and bacterial pathogens. Antimicrob Resist Infect Control 2019;8:125.
[35] Shah PS, Yoon W, Kalapesi Z, Bassil K, Dunn M, Lee SK. Seasonal variations in healthcare-associated infection in neonates in Canada. Arch Dis Child Fetal Neonatal Ed 2013;98(1):F65–9.
[36] Saleem AF, Qamar FN, Shahzad H, Qadir M, Zaidi AK. Trends in antibiotic susceptibility and incidence of late-onset Klebsiella pneumoniae neonatal sepsis over a six-year period in a neonatal intensive care unit in Karachi. Pakistan Int J Infect Dis 2013;17(11):e961–5.
[37] Opoku-Temeng C, Malachowa N, Kobayashi SD, DeLeo FR. Innate host defense against Klebsiella pneumoniae and the outlook for development of immunotherapies. J Innate Immun 2022;14(3):167–81.
[38] Gonzalez-Ferrer S, Peñaloza HF, Budnick JA, Bain WG, Nordstrom HR, Lee JS, et al. Finding order in the chaos: outstanding questions in Klebsiella pneumoniae pathogenesis. Infect Immun 2021;89(4).
[39] Wantuch PL, Rosen DA. Klebsiella pneumoniae: adaptive immune landscapes and vaccine horizons. Trends Immunol 2023;44(10):826–44.
[40] Wagstaffe HR, Johnson M, Osman G, Martin P, Carranza P, Goldblatt D. The development of immunological assays to evaluate the level and function of antibodies induced by Klebsiella pneumoniae O-antigen vaccines. mSphere. 2023;8(2):e0068022.
[41] Hall GS. Bailey & Scott's Diagnostic Microbiology, 13th Edn. Laboratory Medicine. 2013;44(4):e138-e9.
[42] MIndex. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition). Philadelphia: W.B. Saunders; 2015. p. I1-I120.
[43] Wyres KL, Wick RR, Gorrie C, Jenney A, Follador R, Thomson NR, et al. Identification of klebsiella capsule synthesis loci from whole genome data. Microb Genom 2016;2(12):e000102.
[44] Lam MMC, Wick RR, Judd LM, Holt KE, Wyres KL. Kaptive 2.0: updated capsule and lipopolysaccharide locus typing for the Klebsiella pneumoniae species complex. Microb Genom 2022;8(3).
[45] Lewis JM, Mphasa M, Banda R, Beale MA, Mallewa J, Heinz E, et al. Genomic and antigenic diversity of colonizing Klebsiella pneumoniae isolates mirrors that of invasive isolates in Blantyre, Malawi. Microb Genom 2022;8(3).
[46] Wyres KL, Nguyen TNT, Lam MMC, Judd LM, van Vinh CaN, Dance DAB, et al. Genomic surveillance for hypervirulence and multi-drug resistance in invasive Klebsiella pneumoniae from south and Southeast Asia. Genome Med 2020;12(1):11.
[47] Choi M, Hegerle N, Nkeze J, Sen S, Jamindar S, Nasrin S, et al. The diversity of lipopolysaccharide (O) and capsular polysaccharide (K) antigens of invasive Klebsiella pneumoniae in a multi-country collection. Front Microbiol 2020;11:1249.
[48] Ejaz H, Wang N, Wilksch JJ, Page AJ, Cao H, Gujaran S, et al. Phylogenetic analysis of Klebsiella pneumoniae from hospitalized children. Pakistan Emerg Infect Dis 2017;23(11):1872–5.
[49] Okomo U, Senghore M, Darboe S, Bojang E, Zaman SMA, Hossain MJ, et al. Investigation of sequential outbreaks of burkholderia cepacia and multidrug-resistant extended spectrum β-lactamase producing Klebsiella species in a west african tertiary hospital neonatal unit: a retrospective genomic analysis. Lancet Microbe 2020;1(3):e119–29.
[50] Hennart M, Guglielmini J, Bridel S, Maiden MCJ, Jolley KA, Criscuolo A, et al. A dual barcoding approach to bacterial strain nomenclature: genomic taxonomy of Klebsiella pneumoniae strains. Mol Biol Evol 2022;39(7).
[51] Wyres KL, Wick RR, Judd LM, Froumine R, Tokolyi A, Gorrie CL, et al. Distinct evolutionary dynamics of horizontal gene transfer in drug resistant and virulent clones of Klebsiella pneumoniae. PLoS Genet 2019;15(4):e1008114.
[52] World Health Organization. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. . 2017.
[53] Silvester R, Madhavan A, Kokkat A, Parolla A, B MA, M H, et al. Global surveillance of antimicrobial resistance and hypervirulence in Klebsiella pneumoniae from LMICs: An in-silico approach. Sci Total Environ. 2022;802:149859.
[54] Zhang Y, Zeng J, Liu W, Zhao F, Hu Z, Zhao C, et al. Emergence of a hypervirulent carbapenem-resistant Klebsiella pneumoniae isolate from clinical infections in China. J Infect 2015;71(5):553–60.
[55] Okomo UA, Darboe S, Bah SY, Ayorinde A, Jarju S, Sesay AK, et al. Maternal colonization and early-onset neonatal bacterial sepsis in the Gambia, West Africa: a genomic analysis of vertical transmission. Clin Microbiol Infect 2023. 29(3):386.e1-.e9.
[56] Robinson ML, Johnson J, Naik S, Patil S, Kulkarni R, Kinikar A, et al. Maternal colonization versus nosocomial transmission as the source of drug-resistant bloodstream infection in an indian neonatal intensive care unit: a prospective cohort study. Clin Infect Dis 2023;77(Suppl 1):S38–45.
[57] Roberts LW, Hoi LT, Khokhar FA, Hoa NT, Giang TV, Bui C, et al. Genomic characterisation of multidrug-resistant Escherichia coli, Klebsiella pneumoniae, and Acinetobacter baumannii in two intensive care units in Hanoi, Viet Nam: a prospective observational cohort study. Lancet Microbe 2022;3(11):e857–66.
[58] Davis GS, Waits K, Nordstrom L, Weaver B, Aziz M, Gauld L, et al. Intermingled Klebsiella pneumoniae populations between retail meats and human urinary tract infections. Clin Infect Dis 2015;61(6):892–9.
[59] Runcharoen C, Moradigaravand D, Blane B, Paksanont S, Thammachote J, Anun S, et al. Whole genome sequencing reveals high-resolution epidemiological links between clinical and environmental Klebsiella pneumoniae. Genome Med 2017;9(1):6.
[60] Klaper K, Hammerl JA, Rau J, Pfeifer Y, Werner G. Genome-based analysis of Klebsiella spp. isolates from animals and food products in Germany, 2013-2017. Pathogens. 2021;10(5).
[61] Marques C, Belas A, Aboim C, Cavaco-Silva P, Trigueiro G, Gama LT, et al. Evidence of sharing of Klebsiella pneumoniae strains between healthy companion animals and cohabiting humans. J Clin Microbiol 2019;57(6).
[62] Zhong XS, Li YZ, Ge J, Xiao G, Mo Y, Wen YQ, et al. Comparisons of microbiological characteristics and antibiotic resistance of Klebsiella pneumoniae isolates from urban rodents, shrews, and healthy people. BMC Microbiol 2020;20(1):12.
[63] Thorpe HA, Booton R, Kallonen T, Gibbon MJ, Couto N, Passet V, et al. A large-scale genomic snapshot of Klebsiella spp. isolates in Northern Italy reveals limited transmission between clinical and non-clinical settings. Nat Microbiol 2022;7(12):2054–67.
[64] Dereeper A, Gruel G, Pot M, Couvin D, Barbier E, Bastian S, et al. Limited transmission of Klebsiella pneumoniae among humans, animals, and the

environment in a Caribbean Island, Guadeloupe (French West Indies). Microbiol Spectr 2022;10(5):e0124222.
[65] Rocha J, Henriques I, Gomila M, Manaia CM. Common and distinctive genomic features of Klebsiella pneumoniae thriving in the natural environment or in clinical settings. Sci Rep 2022;12(1):10441.
[66] Gonçalves Barbosa LC, Silva ESJA, Bordoni GP, Barbosa GO, Carneiro LC. Elevated mortality risk from CRKp associated with comorbidities. Systematic Review and Meta-Analysis Antibiotics (Basel) 2022;11(7).
[67] Strakova N, Korena K, Karpiskova R. Klebsiella pneumoniae producing bacterial toxin colibactin as a risk of colorectal cancer development - a systematic review. Toxicon 2021;197:126–35.
[68] Ranjeva SL, Warf BC, Schiff SJ. Economic burden of neonatal sepsis in sub-saharan Africa. BMJ Glob Health 2018;3(1):e000347.
[69] Aerts C, Leahy S, Mucasse H, Lala S, Bramugy J, Tann CJ, et al. Quantifying the acute care costs of neonatal bacterial sepsis and meningitis in Mozambique and South Africa. Clin Infect Dis 2022. 74(Suppl_1):S64–s9.
[70] Huang W, Qiao F, Zhang Y, Huang J, Deng Y, Li J, et al. In-hospital medical costs of infections caused by carbapenem-resistant Klebsiella pneumoniae. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2018. 67(suppl_2):S225–s30.
[71] World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS) report 2022; 2022.
[72] van Duin D, Perez F, Rudin SD, Cober E, Hanrahan J, Ziegler J, et al. Surveillance of carbapenem-resistant Klebsiella pneumoniae: tracking molecular epidemiology and outcomes through a regional network. Antimicrob Agents Chemother 2014; 58(7):4035–41.
[73] Rodrigues C, Passet V, Rakotondrasoa A, Brisse S. Identification of Klebsiella pneumoniae, klebsiella quasipneumoniae, klebsiella variicola and related phylogroups by MALDI-TOF mass spectrometry. Front Microbiol 2018;9:3000.
[74] Barbier E, Rodrigues C, Depret G, Passet V, Gal L, Piveteau P, et al. The ZKIR assay, a real-time PCR method for the detection of Klebsiella pneumoniae and closely related species in environmental samples. Appl Environ Microbiol 2020; 86(7).
[75] Lindstedt K, Buczek D, Pedersen T, Hjerde E, Raffelsberger N, Suzuki Y, et al. Detection of Klebsiella pneumoniae human gut carriage: a comparison of culture, qPCR, and whole metagenomic sequencing methods. Gut Microbes 2022;14(1): 2118500.
[76] Conlan S, Kong HH, Segre JA. Species-level analysis of DNA sequence data from the NIH human microbiome project. PLoS One 2012;7(10):e47075.
[77] Harris PNA, Tambyah PA, Lye DC, Mo Y, Lee TH, Yilmaz M, et al. Effect of piperacillin-tazobactam vs meropenem on 30-day mortality for patients with E coli or Klebsiella pneumoniae bloodstream infection and ceftriaxone resistance: a randomized clinical trial. JAMA 2018;320(10):984–94.
[78] Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-lactam-β-lactamase inhibitor combinations. Clin Microbiol Rev 2020;34(1).
[79] Madhi SA, Anderson AS, Absalon J, Radley D, Simon R, Jongihlati B, et al. Potential for maternally administered vaccine for infant group B streptococcus. N Engl J Med 2023;389(3):215–27.
[80] Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis 2008;197(8):1079–81.
[81] Peters NK, Dixon DM, Holland SM, Fauci AS. The research agenda of the National Institute of Allergy and Infectious Diseases for antimicrobial resistance. J Infect Dis 2008;197(8):1087–93.
[82] Zea-Vera A, Ochoa TJ. Challenges in the diagnosis and management of neonatal sepsis. J Trop Pediatr 2015;61(1):1–13.
[83] Argimón S, David S, Underwood A, Abrudan M, Wheeler NE, Kekre M, et al. Rapid genomic characterization and global surveillance of klebsiella using pathogenwatch. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2021. 73(Suppl_4):S325–s35.
[84] Arato V, Raso MM, Gasperini G, Berlanda Scorza F, Micoli F. Prophylaxis and Treatment against Klebsiella pneumoniae: Current Insights on This Emerging Anti-Microbial Resistant Global Threat. Int J Mol Sci. 2021;22(8).
[85] Choi M, Tennant SM, Simon R, Cross AS. Progress towards the development of klebsiella vaccines. Expert Rev Vaccines 2019;18(7):681–91.
[86] Cross AS, Greenberg N, Billington M, Zhang L, DeFilippi C, May RC, et al. Phase 1 testing of detoxified LPS/GROUP B meningococcal outer membrane protein vaccine with and without synthetic CPG 7909 adjuvant for the prevention and treatment of sepsis. Vaccine 2015;33(48):6719–26.
[87] Prattley S, Geraghty R, Moore M, Somani BK. Role of vaccines for recurrent urinary tract infections: a systematic review. Eur Urol Focus 2020;6(3):593–604.
[88] Kochiashvili D, Khuskivadze A, Kochiashvili G, Koberidze G, Kvakhajelidze V. Role of the bacterial vaccine solco-urovac® in treatment and prevention of recurrent urinary tract infections of bacterial origin. Georgian Med News 2014; 231:11–6.
[89] Edelman R, Taylor DN, Wasserman SS, McClain JB, Cross AS, Sadoff JC, et al. Phase 1 trial of a 24-valent klebsiella capsular polysaccharide vaccine and an eight-valent pseudomonas O-polysaccharide conjugate vaccine administered simultaneously. Vaccine 1994;12(14):1288–94.
[90] Campbell WN, Hendrix E, Cryz Jr S, Cross AS. Immunogenicity of a 24-valent klebsiella capsular polysaccharide vaccine and an eight-valent pseudomonas O-polysaccharide conjugate vaccine administered to victims of acute trauma. Clin Infect Dis 1996;23(1):179–81.
[91] Donta ST, Peduzzi P, Cross AS, Sadoff J, Haakenson C, Cryz Jr SJ, et al. Immunoprophylaxis against klebsiella and pseudomonas aeruginosa infections. the Federal Hyperimmune Immunoglobulin Trial Study Group. J Infect Dis 1996; 174(3):537–43.
[92] Cryz Jr SJ, Mortimer P, Cross AS, Fürer E, Germanier R. Safety and immunogenicity of a polyvalent klebsiella capsular polysaccharide vaccine in humans. Vaccine 1986;4(1):15–20.
[93] Kim C, Holm M, Frost I, Hasso-Agopsowicz M, Abbas K. Global and regional burden of attributable and associated bacterial antimicrobial resistance avertable by vaccination: modelling study. BMJ Glob Health 2023;8(7).
[94] Debby BD, Ganor O, Yasmin M, David L, Nathan K, Ilana T, et al. Epidemiology of carbapenem resistant Klebsiella pneumoniae colonization in an intensive care unit. Eur J Clin Microbiol Infect Dis 2012;31(8):1811–7.
[95] Hayakawa K, Gattu S, Marchaim D, Bhargava A, Palla M, Alshabani K, et al. Epidemiology and risk factors for isolation of Escherichia coli producing CTX-M-type extended-spectrum β-lactamase in a large U.S. medical center. Antimicrob Agents Chemother 2013;57(8):4010–8.
[96] Lübbert C, Becker-Rux D, Rodloff AC, Laudi S, Busch T, Bartels M, et al. Colonization of liver transplant recipients with KPC-producing Klebsiella pneumoniae is associated with high infection rates and excess mortality: a case-control analysis. Infection 2014;42(2):309–16.
[97] Nouvenne A, Ticinesi A, Lauretani F, Maggio M, Lippi G, Guida L, et al. Comorbidities and disease severity as risk factors for carbapenem-resistant Klebsiella pneumoniae colonization: report of an experience in an internal medicine unit. PLoS One 2014;9(10):e110001.
[98] Pereira MR, Scully BF, Pouch SM, Uhlemann AC, Goudie S, Emond JE, et al. Risk factors and outcomes of carbapenem-resistant Klebsiella pneumoniae infections in liver transplant recipients. Liver Transpl 2015;21(12):1511–9.
[99] The cost of antibiotic resistance: effect of resistance among Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa on length of hospital stay. Infect Control Hosp Epidemiol. 2002;23(2): 106-8.
[100] Candevir Ulu A, Kurtaran B, Inal AS, Kömür S, Kibar F, Yapıcı Çiçekdemir H, et al. Risk factors of carbapenem-resistant Klebsiella pneumoniae infection: a serious threat in ICUs. Medical Sci Monitor : Int Med J Exp Clin Res 2015;21:219–24.
[101] Gürntke S, Kohler C, Steinmetz I, Pfeifer Y, Eller C, Gastmeier P, et al. Molecular epidemiology of extended-spectrum beta-lactamase (ESBL)-positive Klebsiella pneumoniae from bloodstream infections and risk factors for mortality. J Infect Chemother 2014;20(12):817–9.
[102] Kim BN, Woo JH, Kim MN, Ryu J, Kim YS. Clinical implications of extended-spectrum beta-lactamase-producing Klebsiella pneumoniae bacteraemia. J Hosp Infect 2002;52(2):99–106.
[103] Mosqueda-Gómez JL, Montaño-Loza A, Rolón AL, Cervantes C, Bobadilla-del-Valle JM, Silva-Sánchez J, et al. Molecular epidemiology and risk factors of bloodstream infections caused by extended-spectrum beta-lactamase-producing Klebsiella pneumoniae a case-control study. Int J Infect Dis 2008;12(6):653–9.
[104] Neidell MJ, Cohen B, Furuya Y, Hill J, Jeon CY, Glied S, et al. Costs of healthcare- and community-associated infections with antimicrobial-resistant versus antimicrobial-susceptible organisms. Clin Infect Dis 2012;55(6):807–15.
[105] Pau CK, Ma FF, Ip M, You JH. Characteristics and outcomes of Klebsiella pneumoniae bacteraemia in Hong Kong. Infect Dis (Lond) 2015;47(5):283–8.
[106] Stone PW, Gupta A, Loughrey M, Della-Latta P, Cimiotti J, Larson E, et al. Attributable costs and length of stay of an extended-spectrum beta-lactamase-producing Klebsiella pneumoniae outbreak in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2003;24(8):601–6.
[107] Otter JA, Burgess P, Davies F, Mookerjee S, Singleton J, Gilchrist M, et al. Counting the cost of an outbreak of carbapenemase-producing enterobacteriaceae: an economic evaluation from a hospital perspective. Clin Microbiol Infect 2017;23(3):188–96.
[108] Mollers M, Lutgens SP, Schoffelen AF, Schneeberger PM, Suijkerbuijk AWM. Cost of nosocomial outbreak caused by NDM-1-containing Klebsiella pneumoniae in the Netherlands, october 2015-january 2016. Emerg Infect Dis 2017;23(9): 1574–6.
[109] Santos WMD, Secoli SR. Economic burden of inpatients infected with Klebsiella pneumoniae carbapenemase. Einstein (Sao Paulo) 2019. 17(4):eGS4444.
[110] Zhu Y, Xiao T, Wang Y, Yang K, Zhou Y, Luo Q, et al. Socioeconomic burden of bloodstream infections caused by carbapenem-resistant enterobacteriaceae. Infection and drug resistance 2021;14:5385–93.
[111] Smith R, Coast J. The true cost of antimicrobial resistance. BMJ (Clinical research ed) 2013;346:f1493.
[112] Mora-Guzmán I, Rubio-Perez I, Maqueda González R, Domingo Garcia D, Martín-Pérez E. Surgical site infection by carbapenemase-producing enterobacteriaceae. a challenge for today's surgeons. Cir Esp (Engl Ed) 2020;98(6):342–9.
[113] Shrestha P, Cooper BS, Coast J, Oppong R, Do Thi Thuy N, Phodha T, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. antimicrob resist. Infect Control 2018. 7:98.