Bacterial vaccines in clinical and preclinical development 2021
An overview and analysis
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<td>Ag</td>
<td>antigen</td>
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<td>AMR</td>
<td>antimicrobial resistance</td>
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<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin</td>
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<td>BMGF</td>
<td>Bill &amp; Melinda Gates Foundation</td>
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<tr>
<td>CF</td>
<td>colonization factor</td>
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<td>CFA</td>
<td>colonization factor antigen</td>
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<tr>
<td>CgoX</td>
<td>coproporphyrinogen oxidase</td>
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<tr>
<td>CHIM</td>
<td>Controlled Human Infection Model</td>
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<tr>
<td>CJCV</td>
<td>capsule conjugate <em>Campylobacter</em> vaccine</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>COPS</td>
<td>Group D core + O-polysaccharide</td>
</tr>
<tr>
<td>COVID-19</td>
<td>coronavirus disease</td>
</tr>
<tr>
<td>CP, CPS</td>
<td>capsular polysaccharide</td>
</tr>
<tr>
<td>CS</td>
<td>coli surface</td>
</tr>
<tr>
<td>dmLT</td>
<td>double-mutant <em>Escherichia coli</em> heat-labile toxin</td>
</tr>
<tr>
<td>dPNAG</td>
<td>deacylated poly-N-β-(1-6)-acetyl-glucosamine</td>
</tr>
<tr>
<td>DT</td>
<td>diphtheria toxoid</td>
</tr>
<tr>
<td>EPA</td>
<td>ExoProtein A; a detoxified form of <em>Pseudomonas aeruginosa</em> Exotoxin A</td>
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<tr>
<td>ETEC</td>
<td>enterotoxigenic <em>Escherichia coli</em></td>
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<tr>
<td>ExPEC</td>
<td>extraintestinal pathogenic <em>Escherichia coli</em></td>
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<tr>
<td>FTA</td>
<td>fimbrial tip adhesin</td>
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<tr>
<td>GAPDH</td>
<td>glyceraldehyde 3-phosphate dehydrogenase</td>
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<td>Gates MRI</td>
<td>Bill &amp; Melinda Gates Medical Research Institute</td>
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<td>Gavi</td>
<td>Gavi, the Vaccine Alliance</td>
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<td>GGT</td>
<td>gamma-glutamyl transpeptidase</td>
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<td>GHIT</td>
<td>Global Health Innovative Technology Fund</td>
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<tr>
<td>GMMA</td>
<td>generalized modules for membrane antigens</td>
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<tr>
<td>GVGH</td>
<td>GSK Vaccine Institute for Global Health</td>
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<tr>
<td>Hib</td>
<td><em>Haemophilus influenzae</em> type B</td>
</tr>
<tr>
<td>HICs</td>
<td>high-income countries</td>
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<tr>
<td>HKMS</td>
<td>heat-killed multi-serotype <em>Shigella</em> immunogens</td>
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<tr>
<td>HLA</td>
<td>human leucocyte antigen</td>
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<tr>
<td>HtrA</td>
<td>protease high temperature requirement A</td>
</tr>
<tr>
<td>IATS</td>
<td>International Antigenic Typing Schema</td>
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<td>IAVI</td>
<td>International AIDS Vaccine Initiative</td>
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<td>ICMR</td>
<td>Indian Council of Medical Research</td>
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<tr>
<td>ICU</td>
<td>intensive care unit</td>
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<td>IDRI</td>
<td>Infectious Disease Research Institute</td>
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<tr>
<td>INTS</td>
<td>invasive non-typhoidal <em>Salmonella</em></td>
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<td>IPD</td>
<td>invasive pneumococcal disease</td>
</tr>
<tr>
<td>IVI</td>
<td>International Vaccine Institute</td>
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<tr>
<td>LMICs</td>
<td>low- and middle-income countries</td>
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<tr>
<td>LPS</td>
<td>lipopolysaccharide</td>
</tr>
<tr>
<td>LT</td>
<td><em>Escherichia coli</em> heat-labile toxin</td>
</tr>
<tr>
<td>MAPS</td>
<td>multiple antigen presenting system</td>
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<tr>
<td>MDR</td>
<td>multirdrug-resistant</td>
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<tr>
<td>MEFA</td>
<td>multiepitope fusion antigen</td>
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<tr>
<td>MIP</td>
<td><em>Mycobacterium indicus pranii</em></td>
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<tr>
<td>MSM</td>
<td>men who have sex with men</td>
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<tr>
<td>Mtb</td>
<td><em>Mycobacterium tuberculosis</em></td>
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<tr>
<td>MVA</td>
<td>modified Vaccinia virus Ankara</td>
</tr>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
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<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Disease</td>
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<td>NICED</td>
<td>National Institute of Cholera and Enteric Diseases</td>
</tr>
<tr>
<td>NICHD</td>
<td>National Institute of Child Health and Human Development</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>NIHCC</td>
<td>NIH Clinical Center</td>
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<td>NMRC</td>
<td>Naval Medical Research Center</td>
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<tr>
<td>NOMVs</td>
<td>native outer membrane vesicles</td>
</tr>
<tr>
<td>NRA</td>
<td>national regulatory authority</td>
</tr>
<tr>
<td>NTS</td>
<td>non-typhoidal <em>Salmonella</em></td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>OMP</td>
<td>outer membrane protein</td>
</tr>
<tr>
<td>OMV</td>
<td>outer membrane vesicle</td>
</tr>
<tr>
<td>PBPV</td>
<td>protein-based pneumococcal vaccine</td>
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<tr>
<td>PCV</td>
<td>pneumococcal conjugate vaccine</td>
</tr>
<tr>
<td>PDVAC</td>
<td>Product Development for Vaccines Advisory Committee</td>
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<tr>
<td>Pephyd</td>
<td>peptidoglycan hydrolase</td>
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<tr>
<td>PPrV</td>
<td>pneumococcal protein vaccine</td>
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<tr>
<td>PSSP-1</td>
<td>pan-<em>Shigella</em> surface protein 1</td>
</tr>
<tr>
<td>PPSV</td>
<td>pneumococcal polysaccharide vaccine</td>
</tr>
<tr>
<td>R&amp;D</td>
<td>research and development</td>
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<tr>
<td>rBCG</td>
<td>recombinant BCG</td>
</tr>
<tr>
<td>rTSST-1v</td>
<td>recombinant toxic shock syndrome toxin-1 variant</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome coronavirus 2</td>
</tr>
<tr>
<td>SEB</td>
<td>staphylococcal enterotoxin B</td>
</tr>
<tr>
<td>ser.</td>
<td>serovar</td>
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<td>spp.</td>
<td>species</td>
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<tr>
<td>SSI</td>
<td>Staten Serum Institute</td>
</tr>
<tr>
<td>SsIE</td>
<td>secreted and surface-associated lipoprotein from <em>Escherichia coli</em></td>
</tr>
<tr>
<td>ST</td>
<td><em>Escherichia coli</em> heat-stable toxin</td>
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<tr>
<td>TB</td>
<td>tuberculosis</td>
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<tr>
<td>TBVI</td>
<td>TuBerculosis Vaccine Initiative</td>
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<tr>
<td>TCV</td>
<td>typhoid conjugate vaccine</td>
</tr>
<tr>
<td>TLR</td>
<td>toll-like receptor</td>
</tr>
<tr>
<td>TPI</td>
<td>triose-phosphate isomerase</td>
</tr>
<tr>
<td>TPP</td>
<td>target product profile</td>
</tr>
<tr>
<td>TPV</td>
<td>typhoid polysaccharide vaccine</td>
</tr>
<tr>
<td>TT</td>
<td>tetanus toxoid</td>
</tr>
<tr>
<td>UPEC</td>
<td>uropathogenic <em>Escherichia coli</em></td>
</tr>
<tr>
<td>US FDA</td>
<td>US Food and Drug Administration</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>Vi</td>
<td>capsular virulence antigen</td>
</tr>
<tr>
<td>ViPS</td>
<td>Vi polysaccharide</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WHO SAGE</td>
<td>WHO Strategic Advisory Group of Experts on Immunization</td>
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<tr>
<td>WHO BPPL</td>
<td>WHO Bacterial Priority Pathogens List</td>
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<tr>
<td>WRAIR</td>
<td>Walter Reed Army Institute of Research</td>
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Executive summary

Vaccines can be highly effective tools in combating antimicrobial resistance (AMR). They reduce the incidence of both resistant and susceptible infections, thereby also decreasing antibiotic consumption. Advances in vaccine technology in recent decades have made developing vaccines against previously challenging targets possible. There is a need to understand what vaccines are currently in development and those which may be available as tools to contribute to controlling AMR in the future. This analysis considers vaccine candidates in preclinical and clinical development against pathogens on the 2017 WHO Bacterial Priority Pathogens List (WHO BPPL), in addition to *Clostridioides difficile* and *Mycobacterium tuberculosis*. Sixty-one vaccine candidates in active clinical development and 94 candidates in confirmed active preclinical development were identified.

The report identified four groups of pathogens with vaccine candidates in various stages of clinical development, and with varying degrees of feasibility for vaccine development.

The first group (Group A) contains pathogens with vaccines already licensed. These exist against four priority pathogens for AMR: *Salmonella enterica* ser. Typhi, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Mycobacterium tuberculosis*. The effectiveness of the vaccine against *S. pneumoniae* dramatically reduced mortality in the United States of America (USA) and Europe in comparison to other regions where the vaccine is not widely available and used. The coverage of authorized vaccines should be increased to maximise their impact on AMR. Current Bacillus Calmette-Guérin (BCG) vaccines against tuberculosis (TB) do not adequately protect against TB and the development of more effective vaccines against TB should be accelerated.

The second group (Group B) includes pathogens with vaccines that are in late-stage clinical trials with high development feasibility: extraintestinal pathogenic *Escherichia coli* (ExPEC), *Salmonella enterica* ser. Paratyphi A, *Neisseria gonorrhoeae*, and *Clostridioides difficile*. Hence, for two out of the six leading pathogens for deaths associated with AMR (1), a vaccine either already exists, as for *S. pneumoniae*, or maybe feasible, as for *E. coli*. R&D efforts and development of vaccines in late-stage clinical trials should be continued and where possible accelerated.

The third group (Group C) contains pathogens with vaccine candidates either in early clinical trials or with moderate to high feasibility of vaccine development: enterotoxigenic *E. coli* (ETEC), *Klebsiella pneumoniae*, non-typhoidal *Salmonella* (NTS), *Campylobacter* spp., and *Shigella* spp. Vaccines against these pathogens might be available in the long term, however, short term solutions to prevent resistance should focus on other interventions to reduce AMR.

The fourth group (Group D) contains pathogens with a small number or no vaccine candidates in the pipeline and low vaccine development feasibility: *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., *Enterococcus faecium*, *Staphylococcus aureus*, and *Helicobacter pylori*. Vaccines against these pathogens are unlikely to be available in the short term, and alternative interventions to prevent AMR caused by these pathogens should be considered. It is even more worrying that the drug development pipeline for *A. baumannii* and *P. aeruginosa* also is insufficient to counter this threat.

All data contained in this report can be downloaded from the WHO Global Observatory on Health R&D.
1. Introduction

Antimicrobial resistance (AMR) refers to the growing threat of bacteria, viruses, fungi or parasites becoming unresponsive to antimicrobial medicines (2–4). Most recent estimates suggest that 4.95 million deaths were associated with AMR in 2019 (1) meaning that if all resistant infections were prevented, this many lives would be saved (5). Models also estimate AMR could result in 2.4 million deaths across Europe, North America and Australia between 2015 and 2050, with even more in low- and middle-income countries (LMICs) (4).

The challenge of AMR is not limited to the threat that we are running out of effective treatments for infectious diseases. AMR also compromises other modern medical procedures that rely on effective control of secondary infections, including surgery, organ transplants and treatment for HIV, liver and kidney disease, physical trauma and cancer (6).

The potential of vaccines as effective tools to slow the emergence and spread of AMR is well established. However, a broad overview of the vaccine development landscape to inform funders, researchers and policymakers is lacking. This pipeline analysis of bacterial vaccines in preclinical and clinical development is part of the broader World Health Organization (WHO) strategy to optimize the development and use of vaccines in reducing the spread of AMR. This analysis maps out the preclinical and clinical development landscape for vaccines. The report focuses on products that target bacterial pathogens outlined in the first WHO bacterial priority pathogens list (WHO BPPL), including \( M. \) tuberculosis (7). In addition, this analysis also includes the pipeline of vaccines for \( C. \) difficile. It is important to note that the criteria for establishing priorities for antibiotic development differ from those for prioritizing vaccine development (8). AMR pathogens that have low incidence may be better controlled by different methods than prophylactic vaccines.

There are a number of published reports evaluating research and development (R&D) opportunities to tackle drug-resistant infections with vaccines. These previous evaluations include the WHO preclinical antibacterial pipeline (9); the Pew Charitable Trust analysis of non-traditional antibacterial products in development (10); the Access to Medicine Foundation benchmark report (11); and the Wellcome Trust report evaluating research and development (R&D) opportunities for tackling drug-resistant infections with vaccines (12). However, none of these earlier reports analyse the complete vaccine pipeline for pathogens on the WHO BPPL nor goes into the depth of this analysis which considers both preclinical and clinical stages of development and lessons learned from vaccines no longer under development.

This analysis of the vaccine pipeline should be read in conjunction with the WHO antibacterial pipeline reviews (9). These reviews have been published annually since 2017 and provide detailed analyses of the preclinical and clinical development pipelines for antibacterial treatments. This analysis of the vaccine pipeline aims to fill the data gap in the vaccine research landscape. All data used in this report are also made available in an interactive format on the WHO Global Health R&D Observatory.
Tuberculosis (TB) is caused by both resistant and non-resistant pathogens. Vaccines prevent infections, decrease antibiotic use, protect individuals, prevent complications, decrease individual risk, suppress resistance evolution, safeguard communities, and decrease infections. Vaccines can decrease exposure of pathogens residing in and on the body to antibiotics that select for resistance. Current antibiotics can be used for a lot longer; less need to develop new antibiotics.
Role of vaccines in addressing AMR

While it is important to invest in developing new antibacterial treatments, vaccines can be an important additional tool in addressing AMR (12-17) and they operate through multiple mechanisms (18) (Fig. 1). First, vaccination against a bacterial infection can reduce transmission of drug-resistant and susceptible strains directly in vaccinated populations and indirectly, in unvaccinated populations, through herd immunity. For example, the introduction of pneumococcal conjugate vaccine (PCV-7) in children in the USA resulted in an 84% reduction in invasive disease caused by the forms of drug-resistant Streptococcus pneumoniae specifically targeted by the vaccine, in children under 2 years of age. The same vaccination campaign also reduced invasive pneumococcal disease (IPD) in over-65-year-olds by 49%, despite vaccines not being given to this group (19). Second, by reducing the overall burden of infectious diseases, bacterial and viral vaccines reduce antibiotic use, a key driver of resistance (18). Vaccination against viruses, though beyond the scope of this report, reduces the number of people who are susceptible to secondary bacterial infections and require antibiotic treatment, as well as the number of antibiotics inappropriately prescribed to treat viral infections (20). Rotavirus vaccination is estimated to prevent 13.6 million antibiotic prescriptions every year for children under the age of 5 in LMICs (21).

The 2021 WHO AMR Vaccine Action Framework (8, 22) outlines actions for understanding, characterizing and communicating the role of vaccines in preventing AMR. The document emphasises the need to expand the use of licensed vaccines, accelerate research into new vaccines and expand global understanding and awareness of the impact of these vaccines.

While resistance has emerged to every antibiotic that has been introduced, resistance to bacterial vaccines is less an issue of concern. Consequently, they are highly attractive as tools for combatting AMR. Vaccines form part of a sustainable response to AMR, as they prevent infections without selecting for antibiotic resistance. Although vaccine-evading strains can evolve in rare cases (e.g. PCVs) and there are concerns regarding novel variants and coronavirus (COVID-19) vaccines, the processes involved tend to be comparatively slow and often do not obliterate the vaccine’s efficacy entirely. Therefore, an effective vaccine can continue to be viable for a long time (23). Vaccines can also be utilised to rapidly respond to disease outbreaks in conjunction with improvements to water, sanitation and hygiene, and appropriate use of public infection prevention measures, such as mask wearing and social distancing. The use of typhoid conjugate vaccine to address drug-resistant typhoid in Pakistan provides one example (24).

Vaccines may be able to act in a way that is synergistic with antibiotics. For example, although the primary selection criteria for serotypes of S. pneumoniae included in PCV was disease burden, the majority of strains selected carried genetic elements conferring drug resistance. Some current PCVs include 10-20 strains and cover 90% of drug-resistant strains causing disease in children (25). By directly reducing the burden of circulating drug-resistant strains, vaccines may make antibiotics that would otherwise have become ineffective useful again. Some limitations to multivalent PCVs remain, including serotype coverage, serotype replacement, not all age groups making antibodies and duration of immunity. However, research to improve these vaccines is ongoing. PCVs targeting even more strains have been licensed, and additional ones are under development.
2. Results

This report identifies and describes vaccines in preclinical and clinical development as well as failed vaccine candidates. For each pathogen, assessments of the feasibility of generating a vaccine based on analyses of biological, product development, and access and implementation feasibility are also incorporated (Table 1; see (26) for full methodology).

Summary of main findings

In the analysis, pathogens in the WHO BPPL have been broadly categorized in terms of feasibility (based on the progression of vaccine candidates in clinical and preclinical development and assessments of the feasibility of generating a vaccine based on analyses of biological, product development and access and implementation feasibility (Table 1; see (26) for full methodology)) into the four groups outlined below. The report is structured by pathogen and ordered by Pipeline Feasibility Group.

- Pipeline Feasibility Group A (very high): Constitutes AMR priority pathogens for which licensed vaccines already exist. This includes *Salmonella enterica* ser. Typhi, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib) and *Mycobacterium tuberculosis*. **Recommendation for Group A:** Increase the coverage of authorized vaccines in line with WHO immunization targets to maximise impact on AMR. Also, the development of more effective vaccines against *M. tuberculosis* should be accelerated.

- Pipeline Feasibility Group B (high): Constitutes AMR priority pathogens for which a vaccine candidate is in late-stage development Phase 3) and vaccines would be suitable to target AMR infections caused by these priority pathogens in the coming years. This includes: Extraintestinal pathogenic *E. coli* (ExPEC), *S. enterica* ser. Paratyphi A, *Neisseria gonorrhoeae*, and *Clostridioides difficile*. **Recommendation for Group B:** Accelerate the development of a vaccine for these pathogens.

- Pipeline Feasibility Group C (moderate): Constitutes AMR priority pathogens for which a vaccine candidate has either been identified in early clinical trials or been identified as a feasible vaccine target during expert review. For these pathogens, vaccines may be feasible solutions to target AMR infections. These pathogens are associated with moderate feasibility of vaccine development and include enterotoxigenic *E. coli* (ETEC), *Klebsiella pneumoniae*, non-typhoidal *Salmonella* (NTS), *Campylobacter* spp. and *Shigella* spp. Given the early stages of development, no vaccine for these pathogens will be available on the market soon. **Recommendation for Group C:** Continue the development of a vaccine for these pathogens and expand knowledge of potential for vaccine use and impact and other tools to combat the AMR threat.

- Pipeline Feasibility Group D (low): Constitutes AMR priority pathogens for which no vaccine candidate has been identified in clinical development and therefore vaccines are not a feasible solution to target AMR infections in the foreseeable future. These pathogens are associated with low feasibility of vaccine development and include the priority pathogens *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter* spp., *Enterococcus faecium*, *Staphylococcus aureus* and *Helicobacter pylori*. Research and investment should explore alternative methods of control, including treatments and effective infection prevention and should ensure access to clean water and adequate sanitation and hygiene facilities. This is even more urgent as the drug development pipeline for *A. baumannii* and *P. aeruginosa* is currently also insufficient to adequately address the burden posed by these critical pathogens. **Recommendation for Group D:** Focus on other prevention and control tools to combat AMR threat linked to these priority pathogens.

Preclinical vaccine pipeline

The analysis identified a total of 94 confirmed active preclinical candidates. Of the critical priority pathogens, ETEC has the most candidates in preclinical development (10), followed by *A. baumannii* (5), ExPEC (4), *K. pneumoniae* (5) and *P. aeruginosa* (4) (Fig. 2). In terms of the high priority pathogens, *S. aureus* has the most candidates in preclinical development (14), followed by *Salmonella enterica* ser. Typhi (8), *H. pylori* (6), NTS (6), *C. jejuni* (4), *S. enterica* ser. Paratyphi A (3) and *N. gonorrhoeae* (2). Of the medium priority pathogens, *S. pneumoniae* (17) has the highest number of vaccine candidates, followed by *Shigella* spp. (10) and Hib (3). In general, critical priority pathogens have fewer preclinical candidates in development. *M. tuberculosis* has the highest number of vaccine candidates (20) in preclinical development. *C. difficile* has 5 candidates.
Table 1. Definition of feasibility based on biological, product development, and access and implementation feasibility. Indicators and thresholds were developed for each of these categories, and pathogens were rated from very low to very high feasibility (26).

- **Biological Feasibility**
  - Considers progression of clinical development
  - Existence of immunity from natural exposure
  - Current understanding of mechanisms of immunity
  - Likelihood of a vaccine protecting against the majority of pathogenic strains

- **Product Development Feasibility**
  - Considers the existence of established animal and in vitro models to facilitate vaccine development
  - Ease of clinical development and setting a late-stage clinical trial
  - Availability of human challenge models if these are likely to be required

- **Access and Implementation Feasibility**
  - Considers the possibility of implementation within existing delivery systems, in particular childhood immunization programmes
  - Commercial attractiveness and whether there are likely to be high-income markets to support tiered pricing
  - Clarity of the licensure and policy decision pathway
  - Ease of uptake and acceptability in target populations

**Fig. 2.** Total number of candidates in preclinical development by pathogen. Note that some vaccine candidates are double counted here, as they target more than one pathogen. Pathogen type refers to status as defined by the WHO priority pathogens list (7). ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; Hib: *Haemophilus influenzae* type b; NTS: non-typhoidal *Salmonella*; BPPL: bacterial priority pathogen list; spp.: species; TB: tuberculosis.
Fig. 3. (a) Total number of candidates in active clinical development by pathogen.

Fig. 3. (b) Total number of candidates both in active clinical development and that have become inactive or discontinued over the last 10 years, by pathogen. Note that some vaccine candidates are double counted here as they target more than one pathogen. Pathogen type refers to status as defined by the WHO priority pathogens list (7). ETEC: enterotoxigenic Escherichia coli; ExPEC: extraintestinal pathogenic E. coli; Hib: Haemophilus influenzae type b; NTS: non-typhoidal Salmonella; BPPL: bacterial priority pathogen list; spp.: species; TB: tuberculosis.
Clinical pipeline

This report has identified a total of 61 vaccine candidates in active clinical development. *S. pneumoniae* has the greatest number of vaccine candidates in clinical development (16), closely followed by *M. tuberculosis* (13) (Fig. 3a). There are no vaccine candidates in clinical development against *A. baumannii*, *Enterobacter* spp., *Enterococcus faecium*, *H. pylori* or *P. aeruginosa*. For the remaining pathogens rated as a critical priority in the 2017 WHO BPPL, *Klebsiella pneumoniae* has one vaccine candidate that recently entered the clinical pipeline, and *Escherichia coli*, which includes ETEC and ExPEC, has six and four vaccine candidates in development respectively.

For the remaining pathogens rated as high priority, there are two vaccine candidates in the pipeline against *Staphylococcus aureus*, six against *Helicobacter pylori*, four against *C. jejuni*, nine candidates against all serovars of *Salmonella*, and only one vaccine candidate against *Neisseria gonorrhoeae*. All medium priority pathogens have vaccine candidates in clinical development. Overall, pathogens rated as a critical or high priority in the 2017 WHO priority pathogens list tend to have fewer candidates in clinical development than the pathogens categorized as medium priority.

Fig. 4. Number of candidates in different phases of clinical development. Bars are stacked by those candidates that are currently in active development and those that are no longer under development, stratified by pathogen. Note that some vaccine candidates are double counted here as they target more than one pathogen. Phase 2 includes candidates in Phases 1/2, 2a, and 2b; Phase 3 includes candidates in Phases 2/3 and Phase 3. Data as of October 2021. ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; Hib: *Haemophilus influenzae* type b; NTS: non-typhoidal *Salmonella*; TB: tuberculosis.
Fig. 5. (a) Total number of candidates in active clinical development, by pathogen and route of administration.

Fig. 5. (b) Total number of candidates in active clinical development, by pathogen and approach. The approach is split into two levels; the first level describes whether the vaccine candidate approach is subunit, viral vector or whole pathogen and the following description describes more specifically the approach within this categorization. ‘Combination’ denotes that a combination of approaches was used and ‘NA’ denotes that there was no appropriate sub-category of approach. Note that some vaccine candidates are double counted here as they target more than one pathogen. ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; GMMA: generalized modules for membrane antigens; Hib: *Haemophilus influenzae* type b; NTS: non-typhoidal *Salmonella*; OMV: outer membrane vesicle; TB: tuberculosis.
The broader picture of investment is shown in Fig. 3b, which shows both active and inactive or discontinued candidates. As previously mentioned, currently there are no candidates in clinical development against *Shigella dysenteriae*, *H. pylori*, and the critical priority pathogen, *P. aeruginosa*. In the past there have been vaccine candidates for these pathogens in different stages of clinical development but all were discontinued (Fig. 3b). This is not uncommon given the scientific, logistical and economic challenges associated with vaccine development. Similarly, there were nine vaccine candidates against *S. aureus* that failed or were discontinued, including three candidates in late-stage clinical trials.

The pathogen which has the greatest number of vaccine candidates in Phase 2 or Phase 3 of clinical development is *S. pneumoniae*, closely followed by TB (Fig. 4). The pathogens with the highest number of candidates in Phase 1 are ETEC, *S. pneumoniae* and *Shigella flexneri* (Fig. 4). The analysis indicates that most candidates fail in early-phase clinical trials. Some exceptions are candidates discontinued in late-stages against *S. aureus*, *C. difficile*, *S. pneumoniae*, Hib and ETEC (Fig. 4). This is challenging for developers as when vaccine candidates fail in late clinical stages high levels of investment have already occurred.

**Route of administration**

The majority of active vaccine candidates are parenteral, in particular for *S. pneumoniae* (Fig. 5a). Most vaccine candidates against enteric pathogens (ETEC, *Shigella sonnei* and *Salmonella enterica* ser. Paratyphi A) are orally administered. The route of administration may reflect the location of infection and, hence, primary immune response. Oral vaccines tend to broaden accessibility, especially in settings with limited access to cold-chain facilities.

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**Fig. 6.** Total number of candidates in active clinical development, by pathogen and main developer type. Note that some vaccine candidates are double counted here as they target more than one pathogen. ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; Hib: *Haemophilus influenzae* type b; NTS: non-typhoidal *Salmonella*; TB: tuberculosis.
Fig. 7. Total number of candidates in active clinical development, by pathogen and whether they are prophylactic or therapeutic. Note that some vaccine candidates are double counted here as they target more than one pathogen. ETEC: enterotoxigenic \textit{Escherichia coli}; ExPEC: extraintestinal pathogenic \textit{E. coli}; Hib: \textit{Haemophilus influenzae} type b; NTS: non-typhoidal \textit{Salmonella}; TB: tuberculosis.

**Scientific approaches**

Many different scientific approaches are being explored to develop and manufacture vaccines (Fig. 5b). Some pathogen targets show less diversity in approaches than others, perhaps as a consequence of past success in clinical development. Where less is known, research may be more diverse. For example, the vast majority of research on \textit{S. pneumoniae}, for which there are already licensed pneumococcal conjugate vaccines, focuses on conjugate vaccines and advancing the success of this technology. On the other hand, vaccine candidates against ETEC are not yet licensed and include a variety of approaches, such as inactive whole cell, live attenuated and recombinant technologies.

**Developers**

Unsurprisingly, given the scale and resources required for vaccine clinical trials, the vast majority of developers are in the private sector (Fig. 6). However, the presence of academic developers of vaccines for \textit{M. tuberculosis}, ETEC, \textit{S. enterica} ser. Paratyphi A, NTS, \textit{S. flexneri} and others may reflect the limited commercial attractiveness of diseases where potential markets are predominantly in low-income countries.

**Prophylactic vs therapeutic vaccines**

The majority of vaccine candidates identified are prophylactic (Fig. 7). Only a few therapeutic vaccines target tuberculosis (TB) and ExPEC. Therapeutic vaccines have the potential to reduce reinfections, for example urinary tract infections (UTI) caused by ExPEC, and reduce associated antibiotic use. Therapeutic vaccines have the advantage that they could be administered to at-risk populations that are already colonized or infected with the pathogen.
Vaccines being developed against WHO bacterial priority pathogens

*Group A: Pathogens with licensed vaccines*

*Salmonella enterica* ser. *Typhi*

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 8; Phase 1: 1; Phase 2: 1; Phase 3: 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>9-15-month-old infants (routine immunization) and children up to 15 years of age (catch-up campaigns) in <em>Salmonella enterica</em> ser. Typhi endemic settings</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>High</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>High</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>High</td>
</tr>
</tbody>
</table>

Eight vaccines are in late-stage preclinical development against *S. enterica* ser. *Typhi* (Table 2). Three of these candidates are trivalent: modified recombinant Ty21a, which targets *S. enterica* ser. *Typhi*, *Shigella flexneri* and *S. sonnei*; the combined iNTS-GMMA (invasive NTS-generalized modules for membrane antigens) and iNTS-TCV (typhoid conjugate vaccine) vaccine candidates, both of which target non-typhoidal *Salmonella (NTS) enterica* serotypes Typhimurium and Enteritidis, in addition to *S. enterica* ser. *Typhi*. The combined iNTS-GMMA and TCV vaccine is scheduled to begin Phase 1a in 2022 and Phase 2 in 2023. There are also three bivalent candidates which target *S. enterica* ser. *Typhi* and *S. enterica* ser. *Paratyphi A*.

Five vaccine candidates are currently in clinical trials (Table 3). The Vi-DT conjugate vaccine is currently in Phase 3 trials in the Philippines and Indonesia (NCT04051268, NCT04204096) (27, 28). WHO prequalification will be sought after Indonesian national regulatory authority (NRA) approval. In addition, CVD1000 is a trivalent candidate under development for non-typhoidal *S. enterica* ser. *Typhimurium* and Enteritidis, and typhoid. The Phase 1 trial is scheduled for completion in September 2022 (NCT03981952). In addition to conjugate vaccines, another approach includes a live attenuated whole cell vaccine which targets both *S. enterica* ser. *Paratyphi A* and *Typhi*. This candidate was scheduled to finish Phase 2b clinical trials in August 2021 (NCT01405521) (29).

Two projects that reached clinical trials are no longer under active development or have been discontinued. TyphETEC-ZH9 typhoid-LT/ST (heat-labile/heat-stable) toxoid vaccine passed the Phase 1 clinical trial but has returned to preclinical development for expansion to include *Shigella* antigens in addition to ETEC and *S. enterica* ser. *Typhi*. Typhvax vaccine candidate, which used a novel approach to vaccine development by noncovalently entrapping the Vi polysaccharide capsule in a matrix, was found to be safe and immunogenic in Phase 1 trials. But there has been no further work since February 2017 (30) (NCT03926455).

Over 20 vaccines have been authorized and brought to market for *S. enterica* ser. *Typhi*, which causes typhoid fever (12). These vaccines fall into three categories: unconjugated Vi polysaccharide (ViPS), live attenuated Ty21a vaccine and TCV (31). The WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommends existing approved TCV over ViPS and Ty21a due to improved immune response, expected longer duration of protection and suitability for use in those under 2 years of age (31). Increased uptake and roll-out of TCV will be effective in reducing the incidence of typhoid fever caused by *S. enterica* ser. *Typhi*, including AMR strains. However, research to explore the impact of the vaccine on long-term carriers of *S. enterica* ser. *Typhi* is ongoing. Current research emphasizes creating a vaccine that incorporates multiple pathogenic targets, which would make the value proposition for vaccination even more favourable.
<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>iNTS-TCV</td>
<td><em>Salmonella enterica</em> ser. Typhi and Typhimurium</td>
<td>Subunit; conjugate</td>
<td>GVGH</td>
<td>Private sector</td>
<td>Italy</td>
<td>Active</td>
</tr>
<tr>
<td>Trivalent conjugate vaccine</td>
<td><em>S. enterica</em> ser. Typhi, Typhimurium and Enteritidis</td>
<td>Subunit; conjugate, Trivalent conjugate vaccine building on SK Bioscience Vi-DT vaccine.</td>
<td>SK Bioscience</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>Active</td>
</tr>
<tr>
<td>iNTS-GMMA</td>
<td><em>S. enterica</em> ser. Typhi, Typhimurium and Enteritidis</td>
<td>Subunit; conjugate; GMMA. Three-component vaccine based on iNTS-GMMA and TCV.</td>
<td>GVGH</td>
<td>Private sector</td>
<td>Italy</td>
<td>Active</td>
</tr>
<tr>
<td>Vi-PsaA-PdT</td>
<td><em>S. enterica</em> ser. Typhi</td>
<td>Subunit; conjugate</td>
<td>Harvard Medical School</td>
<td>Academic</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>O:2,12-DT + Vi-DT</td>
<td><em>S. enterica</em> ser. Typhi and Paratyphi A</td>
<td>Subunit; conjugate. O:2 of <em>S. enterica</em> ser. Paratyphi A conjugated to diphtheria toxoid (O:2-DT), with an adipic acid dihydrazide linker.</td>
<td>International Vaccine Institute</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>Active</td>
</tr>
<tr>
<td>O:2,12-CRM197 + Vi-CRM197</td>
<td><em>S. enterica</em> ser. Typhi and Paratyphi A</td>
<td>Subunit; conjugate. Two surface polysaccharide antigens, Vi and O:2, targeting <em>S. enterica</em> ser. Typhi and Paratyphi A, respectively, each conjugated individually to CRM197, the mutant diphtheria toxin protein.</td>
<td>Biological E.; GVGH</td>
<td>Private sector</td>
<td>India; Italy</td>
<td>Active</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
<th>NCT number(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EuTCV</td>
<td><em>Salmonella enterica</em> ser. Typhi</td>
<td>Subunit; conjugate Vi-TT</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>EuBiologics</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>3</td>
<td>NCT04830371</td>
</tr>
<tr>
<td>Vi-DT (27, 28)</td>
<td><em>S. enterica</em> ser. Typhi</td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>PT Bio Farm; Indonesia University; SK Bioscience; BMGF/IVI</td>
<td>Private sector</td>
<td>Indonesia; Philippines; USA; Republic of Korea</td>
<td>3</td>
<td>NCT04051268; NCT04204096</td>
</tr>
<tr>
<td>Typhoid Vi conjugate vaccine</td>
<td><em>S. enterica</em> ser. Typhi</td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td></td>
<td>CNBG; Sinopharm</td>
<td>Private sector</td>
<td>China</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Entervax (previously M01ZH09) (29)</td>
<td><em>S. enterica</em> ser. Typhi and Paratyphi A</td>
<td>Whole pathogen; live attenuated. Bacterial combination vaccine comprising live attenuated Typhi ZH9 plus an engineered derivative providing an immune response to the key antigens (LPS O:2 and H:a flagellin from <em>S. enterica</em> ser. Paratyphi A (ZH9 PA)).</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>Prokarium</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>2b</td>
<td>NCT01405521</td>
</tr>
<tr>
<td>CVD 1000</td>
<td><em>S. enterica</em> ser. Typhi, Typhimurium and Enteritidis</td>
<td>Subunit; conjugate. Trivalent conjugate vaccine <em>S. enterica</em> ser. Enteritidis conjugate – Group D core + O-polysaccharide (COPS) linked to Enteritidis Phase 1 flagellin. <em>S. enterica</em> ser. Typhimurium conjugate – Group B COPS linked to Typhimurium Phase 1 flagellin. <em>S. enterica</em> ser. Typhi Vi-TT conjugate – ViPS linked to tetanus toxoid (Typbar TCV).</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Bharat Biotech; CVD; University of Maryland</td>
<td>Private sector</td>
<td>India; USA</td>
<td>1</td>
<td>NCT03981952A</td>
</tr>
</tbody>
</table>

Table 4. Clinical development pipeline for vaccine candidates no longer under active development against *Salmonella enterica* ser. Typhi.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TyphETEC-ZH9 typhoid-LT/ST toxoid</td>
<td><em>S. enterica</em> ser. Typhi and <em>ETEC</em></td>
<td>Subunit; toxoid. ZH9 typhoid vectoring LT/ST toxoid and CF/C'S antigens.</td>
<td>Prophylactic</td>
<td>Prokariom</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typhvax (30)</td>
<td><em>S. enterica</em> ser. Typhi</td>
<td>Subunit; protein capsular matrix</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Matrivax</td>
<td>Private sector</td>
<td>USA</td>
<td>1</td>
<td>NCT03926455</td>
</tr>
</tbody>
</table>

Three vaccines against Hib are in active preclinical development and forty-six vaccines are already licensed against Hib. Indeed, vaccines against Hib have been available since the 1990s and have almost eliminated invasive Hib in children under 5 in developed countries (12). Vaccines have been shown to reduce the prevalence of certain drug-resistant strains of Hib (32). Although current Hib vaccines are approximately 70% effective, four vaccines are in active clinical trials, three of which were in or recently completed Phase 3 clinical trials (Table 5). For example, the paediatric hexavalent vaccine Shan 6 (NCT04429295), which was scheduled to complete its Phase 3 trial in November 2021 and has already filed an New Drug Application (NDA). In addition, LBVD, a combined DTP-HepB-IPV-Hib (diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Hib) vaccine completed Phase 1 trials in August 2019 (NCT04429295). Four clinical candidates ceased or stalled development in the last 10 years (Table 7).

Despite the availability of a safe and effective vaccine for Hib, greater uptake and global coverage are needed to combat the increasing incidence of drug-resistant Hib (22, 33).

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 3, Phase 1: 1; Phase 2: 0; Phase 3: 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>1-12 months</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Very high</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>Very high</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Very high</td>
</tr>
</tbody>
</table>

**Haemophilus influenzae type b**

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 3, Phase 1: 1; Phase 2: 0; Phase 3: 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>1-12 months</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Very high</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>Very high</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Very high</td>
</tr>
</tbody>
</table>
### Table 5. Preclinical development pipeline for *Haemophilus influenzae* type b.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTcP-Hib (type b)</td>
<td>Subunit; conjugate</td>
<td>CanSino</td>
<td>Private sector</td>
<td>China</td>
<td>Active</td>
</tr>
<tr>
<td>Hib vaccine</td>
<td>Unknown</td>
<td>Wellstat Therapeutics</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>Hib vaccine</td>
<td>Unknown</td>
<td>HanaVax</td>
<td>Private sector</td>
<td>Japan</td>
<td>Active</td>
</tr>
</tbody>
</table>

**DTcP:** diphtheria, tetanus, pertussis; **MCV2:** measles-containing vaccine second dose.

### Table 6. Clinical development pipeline for vaccine candidates actively undergoing clinical trials against *Haemophilus influenzae* type b.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shan 6</td>
<td>Hib</td>
<td>Paediatric hexavalent vaccine</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>Sanofi Pasteur</td>
<td>Private sector</td>
<td>France</td>
<td>3 NCT04429295</td>
</tr>
<tr>
<td>Freeze-dried <em>Haemophilus influenzae</em> type b. (Hib) combined vaccine</td>
<td>Hib</td>
<td>Unknown</td>
<td>Prophylactic</td>
<td>Beijing Zhifei Lzhu Biopharmaceutical</td>
<td>Private sector</td>
<td>China</td>
<td>3 Chi-CTR20-00032281</td>
<td></td>
</tr>
<tr>
<td>MT-2355 (BK1310)</td>
<td>Hib</td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Mitsubishi Tanabe Pharma</td>
<td>Private sector</td>
<td>Japan</td>
<td>3 NCT03891758</td>
</tr>
<tr>
<td>LBVD</td>
<td>Hib</td>
<td>DTP-HepB-IPV-Hib vaccine</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>LG Chem</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>1 NCT04429295</td>
</tr>
</tbody>
</table>

**DTP:** diphtheria-tetanus-pertussis; **HepB:** hepatitis B; **IPV:** inactivated polio vaccine.
Table 7. **Clinical development pipeline** for vaccine candidates no longer under active development against *Haemophilus influenzae* type b.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
<th>NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em> type b (Hib) conjugate vaccine</td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Jiangsu Province Center for Disease Control and Prevention; Chengdu Olymvax Biopharmaceuticals</td>
<td>Private sector</td>
<td>China</td>
<td>3</td>
<td>01732198</td>
</tr>
<tr>
<td>VN-0105</td>
<td>Paediatric pentavalent vaccine</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>Sanoft; Kitasato; Daiichi Sankyo</td>
<td>Private sector</td>
<td>Japan</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Hib vaccine (Bio Farma), single shot</td>
<td>Immunostimulants</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>PT Bio Farma</td>
<td>Private sector</td>
<td>Indonesia</td>
<td>3</td>
<td>01986335</td>
</tr>
<tr>
<td>Investigational Hib vaccine (NU300)</td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>Nuron Biotech</td>
<td>Private sector</td>
<td>USA</td>
<td>2</td>
<td>01732198</td>
</tr>
</tbody>
</table>
Seventeen vaccines in preclinical development specifically target *S. pneumoniae*, all of which are being developed in the private sector. Five of the candidates are conjugate vaccines, while other approaches include multiple antigen presenting system (MAPS), recombinant vaccine, pathogen-agnostic mechanisms, and outer membrane vesicles (OMV) (Table 8). There is also work on preclinical models to demonstrate that mucosal maternal vaccination with novel pneumococcal vaccines can protect offspring from the establishment of pathogenic pneumococcal infections (34).

Currently, 16 vaccine candidates are in active clinical trials (Table 9), including multiple pneumococcal conjugate vaccines (PCV), that follow the approach of some licensed pneumococcal vaccines, which mix purified capsular polysaccharide of pneumococcal serotypes conjugated to a carrier protein. Four vaccines are in Phase 1 clinical trials, including two 13-valent vaccines, a 15-valent euPCV vaccine, and a protein-based pneumococcal vaccine (PBPV). The last covers 70% of all pneumococcal serotypes and is scheduled for completion in April 2022 (NCT04087460).

Eight vaccines are in Phase 2 clinical trials, including multiple PCVs with valencies from 11 to 23. A pneumococcal protein vaccine (PPrV) using a recombinant protein method which proved to increase protection over current polysaccharide and conjugate vaccines is also in Phase 2 clinical trials (NCT01446926) (35). A MAPS vaccine, which showed proof of concept in Phase 1 trials (NCT03803202), has now moved to Phase 2. Four vaccines are in Phase 3 clinical trials, all of which range from being 13- to 23-valent vaccines.

Clinical development of 12 vaccine candidates has become inactive or been discontinued in the last 10 years (Table 10). Research on several vaccine candidates became inactive after Phase 1 trials. For example, PnuBioVax, a toxoid vaccine which aimed to provide protection against all *S. pneumoniae* serotypes and a >95% reduction in production costs compared to PCV13; however, there has been no further research since Phase 1 trials in 2016 (NCT02572635). GSK2189242A conjugate vaccine was discontinued during Phase 2 trials (NCT00307528) to move towards the 10-valent (PCV10) and 13-valent (PCV13) vaccines.
The PCV10 and PCV13 vaccines are safe, effective pneumococcal polysaccharide-protein conjugate vaccines that have been available since 2009 (36). Another 10-valent PCV vaccine, (with overlapping serotypes with PCV10 and PCV13) was prequalified by WHO in December 2019 (37), and a 23-valent pneumococcal polysaccharide vaccine (PPV23) is licensed for use in adults (38, 39). These vaccines are highly effective against invasive pneumococcal disease (IPD) and provide some protection against pneumonia. Current vaccines against *S. pneumoniae* have been highly effective in reducing the prevalence of drug-resistant infections. Five years after the first PCV was used in the USA, IPD caused by multidrug-resistant (MDR) strains in children under age 2 decreased by 84% and penicillin-resistant IPD in adults over 65 fell by 49% (19). In South Africa, the use of PCV was related to an 82% reduction in the rate of penicillin-resistant pneumococcal disease in children, and a 47% reduction in disease caused by penicillin-susceptible strains (40).

The high cost of vaccines against *S. pneumoniae* is a significant barrier to uptake and worldwide coverage is approximately 40% of the target population (1-12 months of age) (41). Although there are more than 100 *S. pneumoniae* serotypes, most strains responsible for disease are covered by currently available PCVs. Research is now aimed at reducing the cost of manufacture and increasing serotype coverage (12).
### Table 8. Preclinical development pipeline for *Streptococcus pneumoniae*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal vaccine</td>
<td>Subunit; BERA platform where OMVs are decorated with novel and highly conserved antigens</td>
<td>Abera Bioscience</td>
<td>Private sector</td>
<td>Sweden</td>
<td>Active</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> research project (next-generation)</td>
<td>Subunit; MAPS platform</td>
<td>Affinivax</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> research project (next-generation)</td>
<td>Unknown</td>
<td>Astrogenetix</td>
<td>Private sector</td>
<td>USA</td>
<td>Unknown</td>
</tr>
<tr>
<td>13-Valent pneumococcal conjugate vaccine (PCV)</td>
<td>Subunit; conjugate</td>
<td>ZFSW</td>
<td>Private sector</td>
<td>China</td>
<td>Active</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Subunit; recombinant</td>
<td>Eurocine Vaccines</td>
<td>Private sector</td>
<td>Sweden</td>
<td>Active</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Unknown</td>
<td>Gamma Vaccines</td>
<td>Private sector</td>
<td>Australia</td>
<td>Active</td>
</tr>
<tr>
<td>13-Valent PCV (CRM197, TT, PCV 13)</td>
<td>Subunit; conjugate</td>
<td>Sinovac Biotech</td>
<td>Private sector</td>
<td>China</td>
<td>Unknown</td>
</tr>
<tr>
<td>VA X-24</td>
<td>Subunit; conjugate; 24-valent</td>
<td>Vaxcyte</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>VA X-XP</td>
<td>Subunit; conjugate; next-generation &gt;30 valent</td>
<td>Vaxcyte</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Unknown</td>
<td>Virometix</td>
<td>Private sector</td>
<td>Switzerland</td>
<td>Inactive</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Subunit; conjugate</td>
<td>Wellstat Therapeutics</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Unknown</td>
<td>Abcombi Biosciences</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Unknown</td>
<td>Synovac</td>
<td>Private sector</td>
<td>China</td>
<td>Active</td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>Unknown</td>
<td>HanaVax</td>
<td>Private sector</td>
<td>Japan</td>
<td>Active</td>
</tr>
<tr>
<td>MVX01</td>
<td>Unknown</td>
<td>Matrixvax</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>PnuVax</td>
<td>Unknown</td>
<td>PnuVax</td>
<td>Private sector</td>
<td>Canada</td>
<td>Unknown</td>
</tr>
<tr>
<td>CMTX-301</td>
<td>Pathogen-agnostic vaccine against bacterial biofilm-mediated infections such as otitis media, pulmonary infections and prosthetic joint infections</td>
<td>Clarametyx Biosciences</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>Active</td>
</tr>
</tbody>
</table>

MAPS: multiple antigen presenting system; OMVs: outer membrane vesicles; ZFSW: Chongqing Zhifei Biological Products.
Table 9. Clinical development pipeline for vaccine candidates actively undergoing clinical trials against *Streptococcus pneumoniae*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Route of administration</th>
<th>Prophylactic/therapeutic</th>
<th>Target pathogens</th>
<th>Phase</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Country of sponsor</th>
<th>Sponsor</th>
<th>Country of sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>23-Valent pneumococcal polysaccharide vaccine (PPSV23)</td>
<td>Subunit</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>3</td>
<td>Private sector</td>
<td>China</td>
<td>Beijing Zhifei Loo Bio-pharmaceutical</td>
<td>China</td>
<td>NCT04275068</td>
</tr>
<tr>
<td>15-Valent pneumococcal conjugate vaccine</td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>3</td>
<td>Private sector</td>
<td>China</td>
<td>Beijing Zhifei Loo Bio-pharmaceutical</td>
<td>China</td>
<td>NCT04357522</td>
</tr>
<tr>
<td>14-Valent PCV (adsorbed)</td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>Private sector</td>
<td>India</td>
<td>Biological E</td>
<td>India</td>
<td>NCT03469784</td>
</tr>
<tr>
<td>13-Valent PCV</td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>3</td>
<td>Private sector</td>
<td>China</td>
<td>Beijing Minhai Biotechnology</td>
<td>China</td>
<td>NCT03803202</td>
</tr>
<tr>
<td>ASP3772</td>
<td>Subunit; pneumococcal MAPS vaccine</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>Private sector</td>
<td>USA; Japan</td>
<td>Affinivax; Astellas Pharma</td>
<td>USA; Japan</td>
<td>NCT02494999</td>
</tr>
<tr>
<td>PCV (LBVE)</td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>LG Chem</td>
<td>Republic of Korea</td>
<td>Republic of Korea</td>
</tr>
<tr>
<td>Polyvalent PCV V116</td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>Private sector</td>
<td>USA</td>
<td>Merck Sharp &amp; Dohme</td>
<td>USA</td>
<td>NCT04138190</td>
</tr>
<tr>
<td>Nucovac</td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>Private sector</td>
<td>India</td>
<td>Panacea Biotec</td>
<td>India</td>
<td>CTRI/2013/05/003711</td>
</tr>
<tr>
<td>Pneumococcal recombinant protein vaccine (PPrV)</td>
<td>Protein-based pneumococcal vaccine; trivalent protein vaccine carrying combined recombinant proteins FpsA, PhtD and PlyD1</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>Private sector</td>
<td>France; Republic of Korea</td>
<td>Sanofi Pasteur; SK Bioscience; SK Chemical</td>
<td>France; Republic of Korea</td>
<td>NCT04583618</td>
</tr>
<tr>
<td>SP0202, SKVPAC</td>
<td>Subunit; next generation conjugate vaccine</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>Private sector</td>
<td>India; Korea</td>
<td>Sanofi Pasteur; SK Bioscience</td>
<td>India; Korea</td>
<td>NCT0439706</td>
</tr>
<tr>
<td>15-Valent PCV</td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>Private sector</td>
<td>India</td>
<td>Tergene Biotech; Aurobindo Pharma</td>
<td>India</td>
<td>CTRI2019-02-07527</td>
</tr>
</tbody>
</table>

2. Results
### Table 9. (continued) Clinical development pipeline for vaccine candidates actively undergoing clinical trials against *Streptococcus pneumoniae*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/ therapeautic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
<th>EudraCT (or NCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-06842433</td>
<td><em>S. pneumoniae</em></td>
<td>Unknown</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>Pfizer</td>
<td>Private sector</td>
<td>USA</td>
<td>2</td>
<td>EudraCT 2020-005039-59</td>
</tr>
<tr>
<td>13-Valent PCV</td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>CanSino</td>
<td>Private sector</td>
<td>China</td>
<td>1</td>
<td>NCT04100772</td>
</tr>
<tr>
<td>Protein-based pneumococcal vaccine (PBPV)</td>
<td><em>S. pneumoniae</em></td>
<td>PBPV</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>CanSino; Henan Center for Disease Control and Prevention</td>
<td>Private sector</td>
<td>China</td>
<td>1</td>
<td>NCT04087460</td>
</tr>
<tr>
<td>13-Valent PCV</td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; conjugate</td>
<td>Unknown</td>
<td>Unknown</td>
<td>China National Biotech Group (CNBG)</td>
<td>Private sector</td>
<td>China</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>euPCV15</td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; conjugate</td>
<td>Unknown</td>
<td>Unknown</td>
<td>EuBioscience</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>1</td>
<td>NCT04830358</td>
</tr>
</tbody>
</table>

CNBG: China National Biotech Group; MAPS: multiple antigen presenting system.

### Table 10. Clinical development pipeline for vaccine candidates no longer under active development against *Streptococcus pneumoniae*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/ therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
<th>NCT (or EudraCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEN-004, SP0148, 1912, 2108</td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; recombinant, A PPSV containing three pneumococcal Th17-stimulating antigens. Two of the proteins, SP_2180 and SP_0148, are lipoproteins, and lipid moieties enhance the immunogenicity and protective efficacy through activation of TLR2.</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Genocea Biosciences</td>
<td>Private sector</td>
<td>USA</td>
<td>3</td>
<td>NCT01995617</td>
</tr>
<tr>
<td>PCV7 (VCN7-T)</td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Intramuscular</td>
<td>Biomolecular Chemistry Center (CQB)</td>
<td>Academic</td>
<td>Cuba</td>
<td>2/3</td>
<td>RPCEC000000-182</td>
</tr>
</tbody>
</table>
Table 10. (continued) **Clinical development pipeline** for vaccine candidates no longer under active development against *Streptococcus pneumoniae*.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Organism</th>
<th>Vaccine Type</th>
<th>Route</th>
<th>Manufacturer</th>
<th>Region</th>
<th>Phase</th>
<th>ID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCV13a</strong></td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; conjugate, PHID-CV: 10-valent PCV (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F)</td>
<td>Intramuscular</td>
<td>GSK</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>2</td>
</tr>
<tr>
<td>Pneumo Nexgen multivalent pneumococcal conjugate vaccine (PCV20)</td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Pfizer</td>
<td>Private sector</td>
<td>USA</td>
<td>2</td>
</tr>
<tr>
<td>IC47</td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; recombinant/purified protein vaccine (PcsB, StkP, PsaA)</td>
<td>Intramuscular</td>
<td>Valneva Austria; PATH</td>
<td>Private sector</td>
<td>Austria; USA</td>
<td>1</td>
</tr>
<tr>
<td>RASV (recombinant avirulent <em>S. enterica</em> ser. Typhi)</td>
<td><em>S. pneumoniae</em></td>
<td>Whole cell; recombinant attenuated <em>Salmonella enterica</em> ser. Typhi vaccine vectors producing <em>Streptococcus pneumoniae</em> PspA</td>
<td>Oral</td>
<td>Arizona State University</td>
<td>Academic</td>
<td>USA</td>
<td>1</td>
</tr>
<tr>
<td>PCV13a</td>
<td><em>S. pneumoniae</em></td>
<td>Subunit; conjugate</td>
<td>Parenteral</td>
<td>Beijing Chaoyang District Centre for Disease Control and Prevention</td>
<td>Other</td>
<td>China</td>
<td>1</td>
</tr>
<tr>
<td>AV0328</td>
<td><em>S. aureus, S. pneumoniae</em></td>
<td>dPNAG conjugated to TT</td>
<td>Parenteral</td>
<td>Alopexx Vaccine</td>
<td>Private sector</td>
<td>USA</td>
<td>1/2</td>
</tr>
<tr>
<td><em>S. pneumoniae</em> whole cell vaccine + Alum (SPWCV)</td>
<td><em>S. pneumoniae</em></td>
<td>Whole pathogen; inactivated</td>
<td>Parenteral</td>
<td>PATH; Intercell; Novartis</td>
<td>Private sector</td>
<td>USA; United Kingdom; Austria</td>
<td>1/2</td>
</tr>
<tr>
<td>PnuBiovax</td>
<td><em>S. pneumoniae</em></td>
<td>Vaccine containing multiple protein antigens. Mutated the pneumococcal toxin, pneumolysin, of <em>S. pneumoniae</em> serotype 4 TIGR4 strain into a nontoxic form.</td>
<td>Parenteral</td>
<td>ImmunoBiology; Simbec Research; Oxford Therapeutics Consulting; ORION Clinical Services</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>1</td>
</tr>
<tr>
<td>Pneumococcal vaccine programme</td>
<td><em>S. pneumoniae</em></td>
<td>Unknown</td>
<td>Unknown</td>
<td>Instituto Butantan</td>
<td>Academic</td>
<td>Brazil</td>
<td>1</td>
</tr>
<tr>
<td>Bioconjugate pneumococcal vaccine</td>
<td><em>S. pneumoniae</em></td>
<td>Multivalent polysaccharide</td>
<td>Parenteral</td>
<td>LimmaTech Biologics</td>
<td>Private sector</td>
<td>Switzerland</td>
<td>1</td>
</tr>
</tbody>
</table>

PPSV: pneumococcal polysaccharide vaccine; TLR: toll-like receptor; TT: tetanus toxoid
Mycobacterium tuberculosis

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 20; Phase 1: 2; Phase 2: 7; Phase 3: 4</th>
</tr>
</thead>
</table>
| Potential target population | 1. A vaccine against progression to active pulmonary TB would target children of 10 years and above and adults with TB infection.  
2. A vaccine against active TB disease and its recurrence would target people of all ages. |
| Biological feasibility | Against pulmonary TB: medium  
Against active TB: medium |
| Product development feasibility | Against pulmonary TB: low  
Against active TB: low |
| Access and implementation feasibility | Against pulmonary TB: medium  
Against active TB: high |

The first vaccine against *M. tuberculosis*, the Bacillus Calmette–Guérin (BCG) vaccine, was developed 100 years ago. It is the most widely administered vaccine in the world. BCG provides moderate to good protection against severe forms of TB in infants and young children (averting thousands of paediatric deaths annually). However, the efficacy of BCG is variable in preventing adult forms of disease and wanes over time. Moreover, BCG does not reduce transmission of *M. tuberculosis*. Hence, the use of BCG in preventing TB in most upper-income countries has been revised and is limited to at-risk populations. Safe and effective vaccines that prevent TB infection or disease across all age groups are urgently needed to achieve the goals and targets of the WHO End TB Strategy (42). Drug-resistant TB threatens TB control globally, with 500 000 out of 10 million total cases resistant to first-line treatment in 2018 alone. Second-line treatment entails high costs, longer duration, a lower success rate and is toxic. Model estimates suggest a vaccine could avert 499 000 deaths due to rifampicin-resistant TB between 2020 and 2035 (43). There are 13 novel vaccine candidates against TB in active clinical trials; two candidates are in Phase 1, 7 are in Phase 2, and four are in Phase 3, with at least 20 in preclinical development (Table 11). The vaccines are prophylactic, therapeutic or both (Table 12).

There are seven prophylactic vaccines in clinical trials. VPM 1002 (rBCG) is a recombinant vaccine, scheduled to complete Phase 3 trials in June 2025 (NCT04351685). This candidate has shown immunogenicity in both endemic and non-endemic settings. A Phase 2/3 trial for preventing TB recurrence in treated patients is underway in India. In addition, there are three whole cell vaccine candidates under development. MTBVAC is the only live attenuated candidate using *M. tuberculosis* and is predicted to complete Phase 2a trial by March 2022 (NCT02933281), Phase 3 development is also underway (NCT04975178). DAR-901 booster is a heat-inactivated non-TB mycobacterial vaccine which has completed Phase 2b clinical trials (NCT02712424). MIP/Immuvac consists of heat-killed *Mycobacterium indicus pranii* and is in Phase 3 trials in India (CTRI/2019/01/017026).

Moreover, M72/AS01E is a prophylactic subunit candidate consisting of an immunogenic fusion protein (M72) derived from two *M. tuberculosis* antigens (MTB32A and MTB39A), and adjuvant AS01E (44). M72/AS01E completed Phase 2b clinical trials in November 2018 and has reported an efficacy of 50% in preventing active TB over 3 years in adults who were already infected (NCT01755598). Data on safety and efficacy in HIV-positive patients are expected in 2023. Phase 3 trials are not anticipated to be completed until 2028.
One vaccine candidate is both prophylactic and therapeutic; ID93 + GLA-SE. It is a recombinant subunit vaccine candidate that completed Phase 2 clinical trials in June 2020 (NCT02465216). ID93 + GLA-SE is composed of four *M. tuberculosis* antigens associated with either virulence (Rv2608, Rv3619 and Rv3620) or latency (Rv1813), alongside the adjuvant GLA-SE. A Phase 2a trial is currently underway in BCG-vaccinated healthy adult care workers (NCT03806686) in addition to a Phase 1 age de-escalation trial in BCG-vaccinated adolescents (NCT03806699).

Three exclusively therapeutic vaccine candidates are in active development (Table 12). TB/Flu-04L is an attenuated influenza virus mucosal vector vaccine, which expresses the antigens Ag85A and ESAT-6 of *M. tuberculosis* (NCT02501421). The RUTI therapeutic vaccine is composed of purified and liposomal cellular fragments of *M. tuberculosis* and was scheduled to complete Phase 2b trials in September 2021 (NCT02711735). H56:IC31 is an adjuvanted subunit vaccine that combines three *M. tuberculosis* antigens (Ag85B, ESAT-6 and Rv2660c) with the IC31 adjuvant. Early clinical trials of this preventative vaccine have been completed, showing acceptable safety and immunogenicity (PACTR201403000464306; DoH-27-0612-3947). Phase 2b trials are projected for completion in or after December 2024 (NCT03512249).

Eight vaccines that were in clinical trials have been discontinued in the last 10 years (Table 13). These include the AERAS-422 recombinant vaccine, which experienced safety problems in Phase 1 trials in 2012 (NCT01340820). GX-70 DNA vaccine was withdrawn from trials due to “unconfirmed research expenses” in 2018 (NCT03159975). The H4:iC31 vaccine showed low efficacy in Phase 2. Nevertheless, this trial was the first to show that a subunit vaccine could provide some protection against TB (48). The KCMC-001 DNA therapeutic vaccine began Phase 1 clinical trials in June 2019 but is not currently under active development. Tubivac (V7) heat-inactivated whole *Mycobacterium vaccae* cell therapeutic vaccine completed Phase 3 trials in December 2018; however, follow-up studies are required to confirm findings of reduced TB-associated weight loss and inflammation (NCT01977768) (49).

Licensed vaccines were outside the search criteria for this analysis, even where the potential for repurposing against TB is being explored. For example, the BMGF is funding studies of the effectiveness of revaccination with BCG in preventing pulmonary TB. *Mycobacterium indicus pranii* (MIP) or Immuvac vaccine is already licensed for use against leprosy (50). Immuvac uses *M. indicus pranii*, a live attenuated non-pathogenic species which is related to *M. tuberculosis* and which was initially trialled as a candidate for therapeutic use against TB. Phase 3 trials showed increased side effects despite in vitro efficacy. Current Phase 3 trials are testing preventive efficacy for exposed contacts (CTR/2019/01/017026).

One of the multiple challenges is that the vaccine would need to be administered to adults and adolescents, who are outside the established childhood immunization schedule (37). Scientific challenges include the lack of validated, predictive animal models of TB infection and disease, few biomarkers that can act as prospective signatures of the risk of developing TB or as correlates of protection, and an incomplete understanding of the nature of protective immunity to TB (51). From a developer perspective, vaccine R&D is an expensive process with long timelines. Industry engagement in TB vaccine development is low, owing to the lack of market incentives to invest in a disease that is concentrated in LMICs, and which disproportionately affects the poor (52). However, a therapeutic vaccine against pulmonary TB is considered biologically feasible (53). Research is focused on novel adjuvants to improve immunogenicity, decrease the required dose of antigen, ensure targeted delivery and optimize the interaction of the antigen with the immune system (54).

The fight against TB will likely require more than one type of vaccine, working in multiple ways, to prevent the establishment of an initial infection (pre-exposure) or to prevent progression to disease (post-exposure). A vaccine might also serve as an immunotherapeutic agent by shortening TB treatment or reducing the risk of recurrence after treatment completion. The current pipeline of new vaccine candidates has limited antigenic and immunological diversity to deliver on this need.
<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (TB) vaccine</td>
<td>Unknown</td>
<td>EpiVax</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>GI-19000 TB vaccine</td>
<td>Unknown</td>
<td>GlobeImmune</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>T-BioVax</td>
<td>Unknown</td>
<td>ImmBio</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>Active</td>
</tr>
<tr>
<td>Lipovax-Fg115-TB</td>
<td>Unknown</td>
<td>Lipotek</td>
<td>Private sector</td>
<td>Australia</td>
<td>Active</td>
</tr>
<tr>
<td>Lipovax-FiC-TB</td>
<td>Unknown</td>
<td>Lipotek</td>
<td>Private sector</td>
<td>Australia</td>
<td>Active</td>
</tr>
<tr>
<td>TB research programme</td>
<td>Unknown</td>
<td>Longhorn Vaccines and Diagnostics</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>Therapeutic MDR TB programme</td>
<td>Unknown</td>
<td>TheraVectys</td>
<td>Private sector</td>
<td>France</td>
<td>Active</td>
</tr>
<tr>
<td>TVI-Tuberculosis-1</td>
<td>Unknown</td>
<td>TVAX Biomedical</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>MT-buVax</td>
<td>Unknown</td>
<td>Vaxil Bio</td>
<td>Private sector</td>
<td>Israel</td>
<td>Active</td>
</tr>
<tr>
<td>TB vaccine</td>
<td>Unknown</td>
<td>Greffex</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>TB vaccine</td>
<td>RNA-based therapeutics</td>
<td>Janssen; Synthetic Genomics</td>
<td>Private sector</td>
<td>Belgium</td>
<td>Active</td>
</tr>
<tr>
<td>TB vaccine</td>
<td>Unknown</td>
<td>HanaVax</td>
<td>Private sector</td>
<td>Japan</td>
<td>Active</td>
</tr>
<tr>
<td>H107</td>
<td>Unknown</td>
<td>SSL; TBVI</td>
<td>Other</td>
<td>Denmark</td>
<td>Active</td>
</tr>
<tr>
<td>CysVac2/Ad</td>
<td>Unknown</td>
<td>University of Sydney; TBVI</td>
<td>Academic</td>
<td>Australia</td>
<td>Active</td>
</tr>
<tr>
<td>MVA Multivacc</td>
<td>Unknown</td>
<td>Transgene; TBVI</td>
<td>Private sector</td>
<td>France</td>
<td>Active</td>
</tr>
<tr>
<td>BCG-ZMP1</td>
<td>Unknown</td>
<td>University of Zurich; TBVI</td>
<td>Academic</td>
<td>Switzerland</td>
<td>Active</td>
</tr>
<tr>
<td>BCG, ChAdOx/MVA PPE15-85A</td>
<td>Unknown</td>
<td>University of Oxford; TBVI</td>
<td>Academic</td>
<td>United Kingdom</td>
<td>Active</td>
</tr>
<tr>
<td>TB vaccine</td>
<td>mRNA-based vaccine</td>
<td>BioNTech</td>
<td>Private sector</td>
<td>Germany</td>
<td>Active</td>
</tr>
<tr>
<td>PDS0201</td>
<td>Versamune platform with bacillus M. tuberculosis antigens</td>
<td>PDS Biotechnology</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>CMV-TB</td>
<td>Unknown</td>
<td>Vir Biotechnology</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
</tbody>
</table>

**Table 11. Preclinical development pipeline for Mycobacterium tuberculosis.**

BCG: Bacillus Calmette-Guérin; CMV: cytomegalovirus; MDR: multidrug-resistant; MVA: modified Vaccinia virus Ankara; SSL: Staten Serum Institute; TB: tuberculosis; TBVI: TuBerculosis Vaccine Initiative.
Table 12. Clinical development pipeline for vaccine candidates actively undergoing clinical trials against *Mycobacterium tuberculosis*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPM 1002 (rBCG)</td>
<td>Recombinant BCG (BCGureC::hly): a listeriolysin gene has been added to the BCG genome and a urease gene has been deleted, permitting the rBCG to escape the macrophage lysosome.</td>
<td>Prophylactic</td>
<td>Intradermal</td>
<td>Serum Institute of India; VPM; IAVI; Biofabri; Universidad de Zaragoza</td>
<td>Private sector</td>
<td>India; Germany</td>
<td>3 NCT04351685</td>
</tr>
<tr>
<td>Immuvac (MIP)</td>
<td>Heat-killed <em>Mycobacterium indicus pranii</em> vaccine</td>
<td>Prophylactic</td>
<td>Intradermal</td>
<td>ICMR; Cadila Pharmaceuticals</td>
<td>Public-private</td>
<td>India</td>
<td>3 CTRI/2019/01/017026</td>
</tr>
<tr>
<td>RUTI</td>
<td>Inactivated partial target organism, i.e. cell wall fragments of <em>M. tuberculosis</em> (Mtbo) formulated in a liposome suspension.</td>
<td>Therapeutic</td>
<td>Intramuscular</td>
<td>University Medical Center Groningen</td>
<td>Academic</td>
<td>Netherlands</td>
<td>2b NCT02711735</td>
</tr>
<tr>
<td>H56:IC31 (47)</td>
<td>Recombinant subunit; adjuvanted fusion protein consisting of three highly immunogenic Mtbo antigens – Ag85B, ESAT-6 and Rv2660c – and adjuvanted with Valneva IC31 consisting of ODN1a, a TLR9 ligand and a stabilizing molecule that helps establish depot formation.</td>
<td>Therapeutic</td>
<td>Parenteral</td>
<td>SS; IAVI</td>
<td>Private sector</td>
<td>Global</td>
<td>2b NCT03512249</td>
</tr>
<tr>
<td>M72/AS01E (originally GSK TB vaccine 692342 [later M72])</td>
<td>Recombinant subunit; fusion protein expressing two immunogenic Mtbo antigens: Mtb39A, a membrane-associated protein expressed early in the Mtb life cycle, putatively identified as an immune evasion factor; and Mtb32A, a constitutively expressed secreted protein and a putative serine protease, combined with the adjuvant AS01E containing monophosphoryl lipid A and QS21 in a liposomal suspension.</td>
<td>Prophylactic</td>
<td>Intramuscular</td>
<td>GSK; IAVI; Gates MRI</td>
<td>Private sector</td>
<td>USA; United Kingdom</td>
<td>2b NCT01755598</td>
</tr>
<tr>
<td>DAR-901 booster</td>
<td>Heat inactivated non-Mtb, killed whole cell</td>
<td>Prophylactic</td>
<td>Intradermal</td>
<td>University of Dartmouth Hitchcock Medical Center; IAVI; GHIT</td>
<td>Academic</td>
<td>USA</td>
<td>2b NCT02712424</td>
</tr>
<tr>
<td>ChadOx1.85A MVA 85A (AERAS 485, MVA 85A-IMX-313)</td>
<td>Viral vectored vaccine</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>University of Oxford</td>
<td>Academic</td>
<td>United Kingdom; Uganda</td>
<td>2a NCT03681860</td>
</tr>
</tbody>
</table>

2. Results
| ID93 + GLA-SE | Prophylactic/therapeutic | Parenteral | Quratis, IDRI | USA | 2a | NCT04975737 |
| GamTBac | Prophylactic | Subcutaneous | Ministry of Health, Russia | Russia | 2 | NCT02.0514-20 |
| TB(Flu-O4L) | Prophylactic | Intranasal | Research Institute for Biological Safety Problems; Research Institute of Influenza | Kazakhstan | 1 | NCT02.3327-20 |
| AEC/BC02 | Prophylactic | Intradermal | AnHui Zhifei Longcom Biologic Pharmacy | China,Private sector | 1b | NCT04.2935-13 |

**Table 12.** (continued) Clinical development pipeline for vaccine candidates actively undergoing clinical trials against *Mycobacterium tuberculosis*.

28 Bacterial vaccines in clinical and preclinical development 2021: an overview and analysis
Table 13. **Clinical development pipeline** for vaccine candidates no longer under active development against *Mycobacterium tuberculosis*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERAS-422</td>
<td>Recombinant BCG; rBCG over-expressing TB antigens, Ag85A, Ag85B and Rv3407, and expressing mutant perfringolysin.</td>
<td>Prophylactic</td>
<td>Intradermal</td>
<td>Aeras Global TB Vaccine Foundation</td>
<td>Other</td>
<td>USA</td>
<td>1 NCT01340820</td>
</tr>
<tr>
<td>GX-70</td>
<td>DNA vaccine</td>
<td>Therapeutic</td>
<td>Intramuscular</td>
<td>Yonsei University</td>
<td>Academic</td>
<td>Republic of Korea</td>
<td>1 NCT03159975</td>
</tr>
<tr>
<td>Ag85B-ESAT-6 + IC31</td>
<td>Adjuvanted TB subunit vaccine</td>
<td>Prophylactic</td>
<td>Intramuscular</td>
<td>SSI</td>
<td>Academic</td>
<td>Denmark</td>
<td>1 NCT01049282</td>
</tr>
<tr>
<td>H4:IC31 (AERAS-404)</td>
<td>Recombinant subunit; fusion protein (Ag85B [mycolyl transferase; necessary for maintaining cell wall integrity] and TB 10.4 [virulence factor; member of ESAT-6 protein family]). IC31 adjuvant (Valneva) is a T-cell stimulator (TLR9 agonist).</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Aeras; SSI; Sanofi-Pasteur; Intercell</td>
<td>Private sector</td>
<td>USA</td>
<td>2 NCT02378207 NCT01861730</td>
</tr>
<tr>
<td>MVA85A + BCG</td>
<td>Recombinant viral vector</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Aeras; University of Oxford</td>
<td>Academic</td>
<td>United Kingdom; USA</td>
<td>2 NCT01650389</td>
</tr>
<tr>
<td>Tubivac (V7) (49)</td>
<td>Heat-inactivated Mycobacterium vaccae</td>
<td>Therapeutic</td>
<td>Oral</td>
<td>Immunitor</td>
<td>Private sector</td>
<td>Canada</td>
<td>3 NCT01977768</td>
</tr>
<tr>
<td>H1-IC31 (ESAT-6, Ag85B) (47)</td>
<td>Protein subunit</td>
<td>Prophylactic/therapeutic</td>
<td>Parenteral</td>
<td>SSI</td>
<td>Academic</td>
<td>USA</td>
<td>2 PACTR20140-3000444306 DoH-27-0612-3947</td>
</tr>
<tr>
<td>KCMC-001 (HVJ-E/HSP65 DNA + IL-12 DNA vaccine)</td>
<td>DNA vaccine</td>
<td>Therapeutic</td>
<td>Parenteral</td>
<td>National Hospital Organization, Ibaraki Higashi Hospital</td>
<td>Academic</td>
<td>Japan</td>
<td>1 JPRN-jRCT20-53190023</td>
</tr>
</tbody>
</table>

BCG: Bacillus Calmette–Guérin; IL-12: interleukin 12; TB: tuberculosis; SSI: Staten Serum Institute; TLR: toll-like receptor.
**Group B: Pathogens with feasible vaccine candidates in late-stage clinical development**

**Extraintestinal pathogenic *Escherichia coli* (ExPEC)**

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 4; Phase 1: 1; Phase 2: 2; Phase 3: 1</th>
</tr>
</thead>
</table>
| **Potential target population** | 1. A vaccine with 5 or more years of efficacy against invasive sepsis might target infants and older adults.  
2. A vaccine with 2 or more years of efficacy in preventing UTI could be given to high-risk populations (those with recurrent, complicated or catheter-associated UTI). |
| **Biological feasibility** | Against UTI: low  
Against sepsis: medium |
| **Product development feasibility** | Against UTI: medium  
Against sepsis: high |
| **Access and implementation feasibility** | Against UTI: medium  
Against sepsis: medium |

Four vaccine candidates against ExPEC were identified in preclinical development (Table 14). Of these, only one targets both uro-pathogenic *E. coli* (UPEC, a form of ExPEC) and ETEC, and another *E. coli* and *K. pneumoniae*.

Four active vaccine candidates against ExPEC are in clinical trials (Table 15). ExPEC9V is a nine-valent O-polysaccharide conjugate vaccine for which a Phase 3 clinical trial (NCT04899336) began in June 2021 and is estimated to finish in May 2027. ExPEC10V is also a polysaccharide conjugate vaccine in Phase 1/2 clinical trials (NCT03819049, NCT04306302). The vaccine consists of the ExPEC serotypes O1A, O2, O4, O6A, O8, O15, O16, O18A, O25B and O75 separately bioconjugated to the carrier protein, a genetically detoxified form of exotoxin A (EPA) derived from *P. aeruginosa*. Research on ExPEC4V has been discontinued to pursue these higher-valent vaccines. The FimH vaccine candidate is moving into Phase 2 clinical trials. This vaccine uses FimH, a bacterial adhesin protein as an antigen alongside a TLR4 (toll-like receptor 4) agonist adjuvant (55). OM-89 is a vaccine directly derived from bacterial cells consisting of heat-inactivated *E. coli* membrane proteins derived from 18 different *E. coli* strains. The vaccine is currently in a Phase 2 clinical trial (NCT02591901) as immune prophylaxis for recurrent UTI (56). However, the composition is not yet well characterized (57), and whole cell vaccines such as Urovaxom and Solco-Urovac are considered to have suboptimal properties.

The relatively low incidence of ExPEC in hospitals makes recruiting for clinical trials for sepsis challenging. High-risk populations, including women with recurrent UTI, older males undergoing transurethral prostatic biopsy and adults with urinary catheterization, do not overlap. The target population for a vaccine needs to be clearly defined but would likely include those at high risk of UTI in clinical settings, including recurrent UTI, catheter-associated UTI and complicated UTI. Prevention of UTI caused by *E. coli* could avoid a considerable amount of antibiotic consumption. In addition, a greater understanding of the impact of a vaccine targeting *E. coli*, an integral component of the human microbiome, is needed.
Table 14. **Preclinical development pipeline** for Extraintestinal pathogenic *Escherichia coli* (ExPEC).

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Lead developer</th>
<th>Sponsor type</th>
<th>Country of lead developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paragon Novel Vaccine</td>
<td><em>Staphylococcus aureus</em>, ETEC, ExPEC</td>
<td>Subunit; recombinant, peptide-based candidate vaccine, elicits bacterial GAPDH-specific blocking antibodies to protect the host from infection.</td>
<td>Immunethep</td>
<td>Private sector</td>
<td>Portugal</td>
</tr>
<tr>
<td>ExPEC vaccine</td>
<td>ExPEC</td>
<td>Unknown</td>
<td>Pfizer</td>
<td>Private sector</td>
<td>USA</td>
</tr>
<tr>
<td>Glycoprotein-based candidate</td>
<td>ETEC, ExPEC</td>
<td>Subunit; conjugate. Conserved YghJ (SslE) shared by UPEC and ETEC.</td>
<td>GlyProVac</td>
<td>Private sector</td>
<td>Denmark</td>
</tr>
<tr>
<td><em>E. coli</em> and <em>Klebsiella</em> vaccine</td>
<td>ExPEC and <em>K. pneumoniae</em></td>
<td>Subunit; alloy platform</td>
<td>Syntiron</td>
<td>Private sector</td>
<td>USA</td>
</tr>
</tbody>
</table>

ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; SslE: secreted and surface-associated lipoprotein from *E. coli*; UPEC: uropathogenic *E. coli*.
Table 15. **Clinical development pipeline** for vaccine candidates actively undergoing clinical trials against Extraintestinal pathogenic *Escherichia coli* (ExPEC).

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ExPEC9V</td>
<td>ExPEC</td>
<td>Subunit; conjugate. Nine-valent O-polysaccharide conjugate vaccine.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Johnson &amp; Johnson</td>
<td>3 NCT04899336</td>
</tr>
<tr>
<td>UTI Vx, FimH vaccine (FimCH155)</td>
<td>ExPEC</td>
<td>Subunit; recombinant. FimH, a bacterial adhesin protein, and TLR4 agonist as adjuvant.</td>
<td>Therapeutic</td>
<td>Parenteral</td>
<td>Sequoia Sciences</td>
<td>2</td>
</tr>
<tr>
<td>Uro-Vaxom (OM-89)</td>
<td>ExPEC</td>
<td>Subunit; OMV. Bacterial vaccine containing 6 mg heat-inactivated <em>E. coli</em> membrane glycoproteins derived from 18 different strains.</td>
<td>Prophylactic/therapeutic</td>
<td>Oral</td>
<td>Vifor Pharma; OM Pharma; Buckinghamshire Healthcare NHS Trust</td>
<td>2 NCT02591901</td>
</tr>
<tr>
<td>ExPEC10V (VAC52416, JNJ-69968054)</td>
<td>ExPEC</td>
<td>Subunit; conjugate. ExPEC10V is an O-polysaccharide conjugate vaccine and consists of O-antigen polysaccharides of the ExPEC serotypes O1A, O2, O4, O6A, O8, O15, O16, O18A, O25B and O75 separately bioconjugated to the carrier protein, a genetically detoxified form of exotoxin A (EPA) derived from <em>P. aeruginosa</em>.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Johnson &amp; Johnson</td>
<td>1/2 NCT03819049 NCT04306302</td>
</tr>
</tbody>
</table>

ExPEC: extraintestinal pathogenic *Escherichia coli*; TLR: toll-like receptor; OMV: outer membrane vesicle; UTI: urinary tract infection.

Table 16. **Clinical development pipeline** for vaccine candidates no longer under active development against Extraintestinal pathogenic *Escherichia coli* (ExPEC).

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ExPEC4V (JNJ-63871860)</td>
<td>ExPEC</td>
<td>Subunit; conjugate. Four-valent O-polysaccharide conjugate vaccine</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Johnson &amp; Johnson</td>
<td>2 NCT02546960</td>
</tr>
</tbody>
</table>

ExPEC: extraintestinal pathogenic *Escherichia coli*.
**Salmonella enterica ser. Paratyphi A**

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 4; Phase 1: 1; Phase 2: 1; Phase 3: 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>1–59 months in endemic settings</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Medium</td>
</tr>
</tbody>
</table>

There are multiple serotypes of *S. enterica* ser. Paratyphi, with *S. enterica* ser. Paratyphi A being the most common. There are no licensed vaccines against *S. enterica* ser. Paratyphi A.

Four vaccine candidates are in late-stage preclinical development. All candidates are bivalent and target both *S. enterica* ser. Paratyphi A and Typhi (Table 17).

Three candidates are in clinical trials. Of these two target only *S. enterica* ser. Paratyphi A; first, O:2, 12-TT conjugate vaccine, which was shown to be safe and immunogenic in Phase 1/2 clinical trials but failed to elicit a booster immune response after the second dose (58) and is now in Phase 3 trials. Second, CVD 1902, which is a live attenuated whole cell vaccine. This candidate completed Phase 1 trials in 2013 (NCT01129453) (59), showing a single dose to be safe and immunogenic. CVD 1902 is ultimately intended to become part of a bivalent vaccine when combined with CVD 909 to target *S. enterica* ser. Paratyphi A and Typhi (58). The bivalent Entervax live attenuated whole cell vaccine targets both *S. enterica* ser. Paratyphi A and Typhi, and was scheduled to complete Phase 2b clinical trials in August 2021 but no updates have been published yet (NCT01405521) (29).

A vaccine against *S. enterica* ser. Paratyphi A is likely to be developed and administered as a combination with a vaccine against *S. enterica* ser. Typhi. Such a bivalent vaccine would have a better value proposition than either monovalent vaccine. Structurally, *S. enterica* ser. Paratyphi A lacks the Vi (virulence) capsular polysaccharide, a widely used vaccine target. However, recent success in developing the typhoid conjugate vaccine is encouraging, and suggests a vaccine against *S. enterica* ser. Paratyphi A is also possible (37). There are multiple challenges to vaccine development against Paratyphoid. The burden of *S. enterica* ser. Paratyphi A and its relationship to the ecology of Typhoid remains poorly defined. Relatively low incidence would require large clinical trials and/or a human infection model, which exists but has yet to be used for vaccine evaluation (37, 60). At present, correlates of protection have not been defined, and small-animal infection models are lacking.
<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>O:2, 12-CRM197 + Vi-CRM197</td>
<td><em>S. enterica</em> ser. Paratyphi A and Typhi</td>
<td>Subunit; conjugate. Two surface polysaccharide antigens, Vi and O:2, targeting <em>S. enterica</em> ser. Typhi and <em>S. enterica</em> ser. Paratyphi A, respectively, each conjugated individually to CRM197, the mutant DT protein.</td>
<td>Biological E., GVGH</td>
<td>Private sector</td>
<td>India; Italy</td>
<td>Active</td>
</tr>
<tr>
<td><em>Salmonella enterica</em> ser. Typhi and Paratyphi vaccine</td>
<td><em>S. enterica</em> ser. Paratyphi A and Typhi</td>
<td>Bivalent vaccine</td>
<td>University of Oxford</td>
<td>Academic</td>
<td>United Kingdom</td>
<td>Active</td>
</tr>
<tr>
<td><em>S. enterica</em> ser. Paratyphi A</td>
<td><em>S. enterica</em> ser. Paratyphi A</td>
<td>Subunit; Conjugate. OPS-Nanoparticle conjugate</td>
<td>KJ Biosciences</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
</tbody>
</table>

GVGH: GSK Vaccine Institute for Global Health; Vi: virulence factor.
Table 18. **Clinical development pipeline** for vaccine candidates actively undergoing clinical trials against *Salmonella enterica* ser. Paratyphi A.

### Candidates actively undergoing clinical trials

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>O:2,12-TT</td>
<td><em>S. enterica</em> ser. Paratyphi A</td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>Lanzhou Institutes of Biological Products</td>
<td>Private sector</td>
<td>China</td>
<td>3</td>
</tr>
<tr>
<td>Entervax (previously M01ZH09) (29)</td>
<td><em>S. enterica</em> ser. Paratyphi A and Typhi</td>
<td>Whole pathogen; live attenuated. Typhi ZH9 plus an engineered derivative providing an immune response to the key antigens (LPS O:2 and H:a flagella) from <em>S. enterica</em> ser. Paratyphi A (ZH9PA).</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>Prokarium</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>2bNCT01405521</td>
</tr>
<tr>
<td>CVD 1902 (VASP; Vaccine against <em>S. enterica</em> ser. Paratyphi A) (59)</td>
<td><em>S. enterica</em> ser. Paratyphi A</td>
<td>Whole pathogen; live attenuated strain with two independently attenuating mutations in guaBA and clpX.</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>University of Oxford; University of Maryland; Bharat Biotech</td>
<td>Academic</td>
<td>United Kingdom; USA; India</td>
<td>1NCT01129453</td>
</tr>
</tbody>
</table>

LPS: lipopolysaccharide; TT: typhoid toxin.

**Candidates no longer under active development or discontinued:** None
### Neisseria gonorrhoeae

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 2; Phase 1: 0; Phase 2: 0; Phase 3: 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>10–24 years old; populations at risk (men who have sex with men, sexual workers, transgender) and vulnerable populations</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Low</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>High</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Medium</td>
</tr>
</tbody>
</table>

No vaccines are currently licensed against *N. gonorrhoeae*; however, one candidate is in Phase 3 of clinical development. A moderate amount of very early-stage preclinical research in this area was identified, including two vaccine candidates in late stages of preclinical development.

Evidence suggests that the 4CMenB vaccine, licensed against group B meningococcal infections, also provides protection from gonorrhoea. The 4CMenB Phase 3 trial (NCT04415424) dates in 2020 were delayed due to the SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2) (61). The last update in summer 2021 showed it as recruiting. There is a moderate amount of very early-stage preclinical research in this area and two vaccine candidates in late stages of preclinical development were identified. Both NGoXIM and dmGC_0817560 NOMV vaccine candidates use outer membrane vesicles as an approach.

Biological challenges to vaccine development include the lack of known correlates of protection, lack of immunity from natural exposure, poor understanding of immunity and the existence of multiple pathogenic strains, though conserved antigenic targets have been identified (37). A vaccine would ideally prevent both reproductive health morbidity and AMR associated with gonorrhoea. The disease burden is high across high- and low-income countries. However, the cultural acceptability of a vaccine against a sexually transmitted infection may make uptake challenging. A combined *N. gonorrhoeae* and *N. meningitidis* vaccine would improve the value proposition and may address some of the cultural barriers (12).
Table 19. **Preclinical development pipeline** for *Neisseria gonorrhoeae*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of Sponsor</th>
<th>Activity Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGoXIM</td>
<td>Combination of a sustained-release formulation of interleukin 12 (GneX12TM) and bacterial OMVs formulated for mucosal delivery</td>
<td>Intravacc; TherapyX</td>
<td>Private sector</td>
<td>USA; Netherlands</td>
<td>Active</td>
</tr>
<tr>
<td>dmGC_0817560 NOMV</td>
<td>Biebs (NOMVs) from the outer surface of gonococcus</td>
<td>Jenner Institute; Oxford Vaccine Group</td>
<td>Academic</td>
<td>United Kingdom</td>
<td>Active</td>
</tr>
</tbody>
</table>

NOMVs: native outer membrane vesicles; OMVs: outer membrane vesicles.

Table 20. **Clinical development pipeline** for vaccine candidates actively undergoing clinical trials against *Neisseria gonorrhoeae*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>4CMenB (Bexsero)</td>
<td><em>N. gonorrhoeae</em></td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Kirby Institute</td>
<td>Academic</td>
<td>China Australia</td>
<td>3 NCT04415424</td>
</tr>
</tbody>
</table>

Candidates no longer under active development or discontinued: None
There are five vaccine candidates against *C. difficile* in preclinical trials, representing a combination of different approaches that include the MAPS platform, the exome-like bacterial vesicles and the use of *Bacillus subtilis* spores as a delivery agent. These are all private sector vaccines (Table 21).

No vaccines are currently available against *C. difficile*. However, two candidates are in active clinical trials, both of recombinant vaccines (Table 22). The GSK2904545A recombinant protein vaccine will complete phase 1 in April 2022 (NCT04026009). The PF-06425090 vaccine candidate was fast-tracked by the US FDA in 2014. However, the Phase 3 trial, which recruited 17 500 patients, failed to meet the primary endpoint of preventing *C. difficile* infections, though it did reduce duration and severity of disease based on secondary endpoints (NCT03090191) (62–64).

Research on multiple vaccine candidates against *C. difficile* has become inactive or discontinued in the last 10 years. The Phase 3 trial of ACAM-CDIFF toxoid vaccine candidate, which enrolled 9302 participants, was terminated in 2018 after interim data showed that it was unlikely to demonstrate prevention of primary *C. difficile* infection (NCT01887912) (65), despite having shown good immunogenicity and safety. This was the first global Phase 3 study to evaluate a vaccine against *C. difficile* infection, and the results of the trial highlighted the difficulties associated with vaccine development for bacterial nosocomial infections. Participants were over 65 and many had comorbidities, which may have affected their immune response. Participants were also *C. difficile* naïve and at high risk for *C. difficile*. However, the vaccination of a large cohort was required given the unpredictable epidemiology. Another candidate, VLA84 recombinant vaccine, completed Phase 2 trials (NCT02316470) in 2015 (66). This vaccine lacks several neutralizing epitopes, does not target host receptor-binding regions and is unlikely to cover all variants of TcdB. However, it could progress to Phase 3 with a suitable partner, but there has been no activity since 2018.

*C. difficile* infection is hard to treat effectively with antibiotics and therefore alternative management strategies are much needed. However, designing clinical trials is complicated as the end point, diarrhoea, is hard to assess, especially in elderly patients, and those who are ill. This is because, in these populations, the incidence of diarrhoea might be high and due to multiple causes, which makes attributing episodes to *C. difficile* infection difficult. The role of the microbiome in modulating the immune response to vaccines is not well understood. In addition, faecal microbiome transplants and biotherapeutic agents have shown recent success against *C. difficile* and may reduce the need for a vaccine. However, access to these interventions is still largely limited to high income settings. Vaccines may target prevention of recurrence of *C. difficile* or prevention of first infection, which are very different. Current data from vaccine candidates in clinical development suggest that it may be possible to reduce symptomatic disease, but *C. difficile* may still persist in the host and be shed (67). An antibody to *C. difficile* toxin has been successfully developed, suggesting that if a vaccine could deliver local antibodies in the gut, it may be successful.
Table 21. Preclinical development pipeline for *Clostridioides difficile*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile vaccine</td>
<td>Subunit; MAPS platform</td>
<td>Astellas Pharma; Affinivax</td>
<td>Private sector</td>
<td>Japan; USA</td>
<td>Active</td>
</tr>
<tr>
<td>MVX02 C. difficile vaccine</td>
<td>Combination vaccine targeting toxins TcdA, TcdB and PSII, a conserved cell surface polysaccharide</td>
<td>Matrivax; Stellar Biotechnologies; University of Guelph</td>
<td>Private sector</td>
<td>USA; India; Canada</td>
<td>Active</td>
</tr>
<tr>
<td>C. difficile vaccine</td>
<td>Exosome-like bacterial vesicles</td>
<td>Versatope Therapeutics</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>SporeVax C. difficile oral vaccine</td>
<td><em>Bacillus subtilis</em> spores as a vaccine delivery agent</td>
<td>SporeGen</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

MAPS: multiple antigen presenting system.

Table 22. Clinical development pipeline for vaccine candidates actively undergoing clinical trials against *Clostridioides difficile*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF-06425090 (+/- adjuvant) (62–64, 68)</td>
<td>Subunit; recombinant toxin; genetically and chemically detoxified TcdA and TcdB toxins</td>
<td>Parenteral</td>
<td>Pfizer</td>
<td>Private sector</td>
<td>USA</td>
<td>3</td>
</tr>
<tr>
<td>GSK2904545A (+/- adjuvant A501B (CDIFF Ag ~ GSK)</td>
<td>Subunit; recombinant protein F2 antigen</td>
<td>Parenteral</td>
<td>GSK</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>1</td>
</tr>
</tbody>
</table>

Ag: antigen.
Table 23. **Clinical development pipeline** for vaccine candidates no longer under active development against *Clostridioides difficile*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACAM-CDIFF</td>
<td>Subunit; toxoid. Chemically detoxified TcdA and TcdB.</td>
<td>Therapeutic</td>
<td>Parenteral</td>
<td>Sanofi Pasteur</td>
<td>Private sector</td>
<td>France</td>
<td>3 NCT01887912</td>
</tr>
<tr>
<td>VLA84 (IC84)</td>
<td>Subunit; recombinant. Recombinant chimeric protein linking the binding domains of TcdA and TcdB.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Valneva Austria</td>
<td>Private sector</td>
<td>Austria</td>
<td>2 NCT02316470</td>
</tr>
<tr>
<td>CDVAX</td>
<td>Recombinant spores of the bacterium Bacillus subtilis that have been engineered to display an antigen which is part of TcdA</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>Royal Holloway University</td>
<td>Academic</td>
<td>United Kingdom</td>
<td>1 NCT02991417</td>
</tr>
</tbody>
</table>

*CDIFF: Clostridioides difficile; TcdA, TcdB: C. difficile toxins A and B.*
**Group C: Pathogens which are feasible, but challenging as targets for vaccine development**

**Enterotoxigenic Escherichia coli (ETEC)**

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 10; Phase 1: 4; Phase 2: 2; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>6–24 months old in endemic countries and international travellers</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>High</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Ten preclinical vaccine candidates were identified against ETEC. Six of these solely targeted ETEC. The other four target different pathogen combinations, including ExPEC, *S. aureus*, *C. jejuni* or *S. flexneri* (Table 24).

Six vaccine candidates against ETEC are currently in active in clinical trials (Table 25). Half of these also target *Shigella* spp. The most advanced vaccine candidate, ETVAX, is an inactivated whole cell vaccine composed of four *E. coli* strains administered with dmLT as both immunogen and adjuvant (69) (Phase 2b, PACTR202010819218562).

Four vaccine candidates against ETEC have reached clinical trials and been discontinued or become inactive over the last 10 years (Table 26). For example, TyphETEC-ZH9, which was being developed against typhoid and ETEC, passed Phase 1 but has returned to preclinical development to include *Shigella* as a target. VLA1701, an inactivated *Vibrio cholerae* bacteria and recombinant cholera toxin B subunit completed Phase 2 in 2018 (NCT03576183) but is no longer listed on the developer’s pipeline. In addition, ACE527-102 is a live attenuated vaccine combining three strains of *E. coli* that collectively express coli surface antigens CS1, CS2, CS3 and CS5, colonization factor antigen I (CFAI) and the heat labile toxin (LT) B subunit (70). Despite showing significant protection in combination with dmLT as an adjuvant and an antigen (70), ACE5327 did not meet the primary end point of protection against moderate/severe diarrhoea and development is currently inactive (71) (NCT01060748, NCT01739231).

The B-subunit/whole-cell cholera vaccine (BS-WC) has been shown to provide 3 months of partial protection against some strains of ETEC (72). Challenge with wild-type ETEC provides nearly complete protection from reinfection resulting in severe diarrhoea. However, precise correlates of protection have not been established, and these levels of protection have not been replicated by a vaccine (70). Despite the high diversity of ETEC strains, a vaccine targeting LT toxoid and CFAs could cover up to 80% of disease-causing strains (73). There are multiple different markets for an ETEC vaccine, including infants in LMICs, travellers and the military. The development of a vaccine covering ETEC in addition to other pathogens may further improve its value proposition.
<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paragon Novel Vaccine</td>
<td><em>S. aureus</em>, ETEC, ExPEC</td>
<td>Subunit. Peptide-based candidate vaccine, elicits bacterial GAPDH-specific blocking antibodies to protect the host from infection.</td>
<td>Immunethep; Merck</td>
<td>Private sector</td>
<td>Portugal; USA</td>
</tr>
<tr>
<td>ETEC vaccine</td>
<td>ETEC</td>
<td>Unknown</td>
<td>Hilleman Laboratories</td>
<td>Private sector</td>
<td>India</td>
</tr>
<tr>
<td>MecVax (Multi-Epitope Antigen (MEFA) vaccine)</td>
<td>ETEC</td>
<td>Subunit; toxoid. Tag-less toxoid fusion 3xSTaN125-mLT192G/L211A and CFA/II/IV MEFA induce neutralizing antibodies to seven adhesins (CFA/I, CS1-CS6) and both enterotoxins (LT, STa) of ETEC</td>
<td>University of Illinois; Johns Hopkins University</td>
<td>Academic</td>
<td>USA</td>
</tr>
<tr>
<td>LT/ST toxoids</td>
<td>ETEC</td>
<td>Subunit; conjugate</td>
<td>ENTVAC Consortium; GLOBVAC; STOPENTERICS; PATH</td>
<td>Academic</td>
<td>Global</td>
</tr>
<tr>
<td>Fimbrial tip adhesins</td>
<td>ETEC</td>
<td>Unknown</td>
<td>NMRC; PATH</td>
<td>Other</td>
<td>USA</td>
</tr>
<tr>
<td>ETEC vaccine</td>
<td>ETEC</td>
<td>Subunit; conjugate. ST/LT toxoid fusion, conjugate or vectored.</td>
<td>University of Bergen</td>
<td>Academic</td>
<td>Norway</td>
</tr>
<tr>
<td>ETEC vaccine</td>
<td>ETEC</td>
<td>Subunit; recombinant. Mix of conserved ETEC antigens: EtpA and EtaA.</td>
<td>Washington University School of Medicine</td>
<td>Academic</td>
<td>USA</td>
</tr>
<tr>
<td>Campylobacter/ETEC vaccines</td>
<td><em>C. jejuni</em>, ETEC</td>
<td>Unknown</td>
<td>Immuron; Naval Medical Research Centre</td>
<td>Private sector</td>
<td>Australia</td>
</tr>
<tr>
<td>Glycoconjugate vaccine</td>
<td><em>C. jejuni</em>, ETEC, <em>S. flexneri</em></td>
<td>Subunit; glycoconjugate</td>
<td>NMRC; WRAIR</td>
<td>Other</td>
<td>USA</td>
</tr>
<tr>
<td>Glycoprotein-based candidate</td>
<td>ETEC, ExPEC</td>
<td>Subunit; conjugate. Conserved YpsJ (SsIE) shared by UPEC and ETEC.</td>
<td>GlyProVac</td>
<td>Private sector</td>
<td>Denmark</td>
</tr>
</tbody>
</table>

CFA: colonization factor antigen; ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; LT: heat-labile toxin; NIAID: National Institute of Allergy and Infectious Diseases; NMRC: Naval Medical Research Center; SsIE: secreted and surface-associated lipoprotein from *E. coli*; ST, STa: heat-stable toxin; UPEC: uropathogenic *E. coli*; WRAIR: Walter Reed Army Institute of Research.
<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Route of administration</th>
<th>Prophylactic/therapeutic</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETVA X/dmLT; ETVAX (OEV-122); ETVAX (OEV-123); ETVAX (OEV-121); (OEV-124)</td>
<td>Enterotoxigenic Escherichia coli (ETEC)</td>
<td>Whole cell; inactivated four E. coli strains overexpressing the most prevalent colonization factors (CFA/I, CS3, CS5 and CS6) and a hybrid LT/CBT and targeted with the dmLT enterotoxin as both an immunogen and an adjuvant.</td>
<td>Oral</td>
<td>Prophylactic</td>
<td>Scandinavian Biopharma; Gothenburg University; United Medix Laboratories; Oy Medfiles; University of Helsinki; University of Virginia</td>
<td>Private sector</td>
<td>Sweden; Finland; USA</td>
<td>Phase 1: CfaE + mLT (ID); Phase 2: CfaE + mLT (74)</td>
<td>2</td>
<td>NCT0192856</td>
</tr>
<tr>
<td>ETEC Subunit; recombinant (fimbrial and non-fimbrial targeting CFA/I (dscCfaE) and CS6 (CssBA) using modified E. coli LT enterotoxin LTR192G or LTR2/L21A.</td>
<td></td>
<td></td>
<td>Parenteral</td>
<td>Prophylactic</td>
<td>NMRC; US Army Surgeon General</td>
<td>Private sector</td>
<td>USA</td>
<td>USA</td>
<td>1</td>
<td>NCT04534513</td>
</tr>
<tr>
<td>ShigETEC (75, 76)</td>
<td>ETEC, S. sonnei, S. flexneri</td>
<td>Whole pathogen; live attenuated Shigella vaccine expressing ETEC antigens.</td>
<td>Oral</td>
<td>Prophylactic</td>
<td>Emergent Biosolutions</td>
<td>Private sector</td>
<td>USA</td>
<td>USA</td>
<td>Phase 1</td>
<td>Not yet registered</td>
</tr>
<tr>
<td>CVD 31000 (CVD 1208S-122)</td>
<td>ETEC, S. flexneri</td>
<td>Whole pathogen; live attenuated S. Flexneri expressing ETEC antigens.</td>
<td>Oral</td>
<td>Prophylactic</td>
<td>University of Maryland Academic</td>
<td>Private sector</td>
<td>USA</td>
<td>USA</td>
<td>Phase 1</td>
<td>NCT04348054</td>
</tr>
<tr>
<td>dmLT (LTR192G/L211A)</td>
<td>ETEC</td>
<td>Subunit; recombinant dmLT enterotoxin (R192G/L211A).</td>
<td>Oral</td>
<td>Prophylactic</td>
<td>NIAID Other USA</td>
<td>Public sector</td>
<td>Other</td>
<td>USA</td>
<td>Phase 1</td>
<td>NCT04348054</td>
</tr>
</tbody>
</table>

**Citation:**

1. **ETEC:** cholera toxin B subunit; dmLT: double-mutant heat-labile, ETEC: enterotoxigenic Escherichia coli; ExETEC: extraintestinal pathogenic E. coli; LPS: lipopolysaccharide; LTB: heat-labile enterotoxin B subunit of ETEC; mL: mutant LT; NIAID: National Institute of Allergy and Infectious Diseases; NMRC: Naval Medical Research Center; O-Ag: O-antigen.
### Table 26. Clinical development pipeline for vaccine candidates no longer under active development against Enterotoxigenic *Escherichia coli* (ETEC).

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETEC vaccine</td>
<td>ETEC</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>EuBiologics</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>3</td>
</tr>
<tr>
<td>VLA1701</td>
<td>ETEC</td>
<td>Whole pathogen; inactivated. Inactivated <em>Vibrio cholerae</em> and recombinant cholera toxin B subunit.</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>Valneva Austria; Johns Hopkins University; NMRC.</td>
<td>Private sector</td>
<td>Austria</td>
<td>2</td>
</tr>
<tr>
<td>ACE527-102 (71)</td>
<td>ETEC</td>
<td>Whole pathogen; live attenuated. Combination of ETEC strains ACAM2025, ACAM2022 and ACAM2027 that collectively express CFA/I, CS1, CS2, CS3, CS5, CS6 and the B subunit of LT.</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>TD Vaccines; Pierrel Research USA; Johns Hopkins University</td>
<td>Private sector</td>
<td>USA</td>
<td>2</td>
</tr>
<tr>
<td>TyphETEC-ZH9</td>
<td>ETEC, <em>Salmonella enterica</em> ser. Typhi</td>
<td>Subunit; toxoid; ZH9 typhoid vectoring LT/ST toxoid and CF/CS antigens.</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>Prokarium</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>1</td>
</tr>
</tbody>
</table>

CTB: cholera toxin B subunit; dMLT: double-mutant heat-labile; ETEC: enterotoxigenic *Escherichia coli*; ExETEC: extraintestinal pathogenic *E. coli*; LPS: lipopolysaccharide; LT: heat-labile enterotoxin B subunit of ETEC; mLT: mutant LT; NIAID: National Institute of Allergy and Infectious Diseases; NMRC: Naval Medical Research Center; O-Ag: O-antigen.
### Klebsiella pneumoniae

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 5; Phase 1: 1; Phase 2: 0; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>Immunocompromised patients, patients requiring mechanical ventilation or urinary catheters, patients in long-term care facilities, presurgical patients, and other patients at high risk of infection or potentially neonates via maternal immunization</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Maternal immunization: low Patient immunization: medium</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>Maternal immunization: medium Patient immunization: medium</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Maternal immunization: medium Patient immunization: medium</td>
</tr>
</tbody>
</table>

One unlicensed vaccine candidate against *K. pneumoniae* is in clinical trials. Five preclinical *K. pneumoniae* vaccine candidates were identified using different technologies, including semi-synthetic conjugation, MAPS platform, Syntiron’s Alloy platform and the inactivated whole cells (Table 27).

Phase 1/2 trials were recently initiated (NCT04959344) (Table 28) to assess the tetravalent bioconjugated vaccine candidate, KlebV4, with and without the AS03 adjuvant. Another vaccine against *K. pneumoniae* – MV140 (Uromune), a poorly characterized vaccine comprising heat-killed bacteria – is in late-stage clinical trials (Phase 3: NCT02543827; Phase 2: NCT04096820). Uromune was excluded from this analysis as it has been licensed in Spain since 2010. Moreover, Uromune was recommended in the 2019 European Association of Urology guidelines as immunoactive prophylaxis to reduce recurrent UTI, and retrospective studies suggest it may reduce recurrent UTI by up to 90% compared with antibiotic prophylaxis (78).

*K. pneumoniae* has a high propensity to acquire resistance genes and spreads easily, in comparison with other Enterobacterales. This may be an argument for considering vaccination against certain strains. A capsular polysaccharide vaccine was developed three decades ago but failed in human trials (79). Four of the 12 O serotypes that exist for *K. pneumoniae* would encompass 80% of clinical strains (80–82). *K. pneumoniae* has been associated with a high burden of neonatal sepsis in low-income countries. Clinical trials involving neonates are challenging, and commercial attractiveness is limited (37). In HICs, *K. pneumoniae* infections are most often hospital acquired. The lack of a clearly defined target population makes recruitment for clinical trials and the cost-effectiveness case for a vaccine challenging (12).
### Table 27. Preclinical development pipeline for *Klebsiella pneumoniae*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogens</th>
<th>Approach</th>
<th>Developer</th>
<th>Developer type</th>
<th>Country of developer</th>
</tr>
</thead>
<tbody>
<tr>
<td>VXN-319</td>
<td><em>K. pneumoniae</em></td>
<td>Subunit; semi-synthetic conjugate</td>
<td>Idorsia Pharmaceuticals (previously Vaxxilon)</td>
<td>Private sector</td>
<td>Switzerland</td>
</tr>
<tr>
<td>ASP1004</td>
<td><em>K. pneumoniae</em></td>
<td>Subunit; MAPS platform</td>
<td>Affinivax; Astellas Pharma</td>
<td>Private sector</td>
<td>USA; Japan</td>
</tr>
<tr>
<td><em>Escherichia coli</em> and <em>Klebsiella vaccine</em>”</td>
<td><em>K. pneumoniae</em> and <em>E. coli</em></td>
<td>Subunit; alloy platform</td>
<td>Syntiron</td>
<td>Private sector</td>
<td>USA</td>
</tr>
<tr>
<td>KapαVax (VXD-005)</td>
<td><em>K. pneumoniae</em>, <em>Pseudomonas aeruginosa</em> and <em>Acinetobacter baumannii</em></td>
<td>Whole cell; inactivated. LPS-null (endotoxin free) whole-cell <em>A. baumannii</em> vaccine displaying at the cell surface multiple conserved antigens from <em>P. aeruginosa</em> and <em>K. pneumoniae</em>.</td>
<td>Vaxdyn</td>
<td>Private sector</td>
<td>Spain</td>
</tr>
<tr>
<td><em>K pneumoniae vaccine</em></td>
<td><em>K. pneumoniae</em></td>
<td></td>
<td>Tulane University</td>
<td>Academic</td>
<td>USA</td>
</tr>
</tbody>
</table>

LPS: lipopolysaccharide; MAPS: multiple antigen presenting system.

### Table 28. Clinical development pipeline for vaccine candidates actively undergoing clinical trials against *Klebsiella pneumoniae*.

<table>
<thead>
<tr>
<th>Candidates actively undergoing clinical trials</th>
<th>Candidate vaccine</th>
<th>Target pathogens</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Name of developer</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>KlebV4</td>
<td><em>Klebsiella pneumoniae</em></td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Intramuscular</td>
<td>LimmaTech Biologics AG (in collaboration with GSK)</td>
<td>1/2</td>
<td>NCT04959344</td>
</tr>
</tbody>
</table>

Candidates no longer under active development or discontinued
**Non-typhoidal Salmonella**

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 5; Phase 1: 1; Phase 2: 0; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>1–59 months in endemic settings</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>High</td>
</tr>
</tbody>
</table>

Five vaccine candidates are in preclinical development against non-typhoidal *Salmonella* (NTS) (Table 29). Two of these candidates are trivalent and target *S. enterica* ser. Typhimurium, Enteritidis and Typhi, including iNTS-GMMA and TCV vaccine candidate, which was planned to begin Phase 1a in 2021 in the United Kingdom and Phase 2 in Kenya in 2022, however no updates have been published. In addition, there are two bivalent vaccines under development.

Currently no vaccines are licensed against NTS, and only one vaccine is currently in clinical development. CVD1000 is a trivalent vaccine candidate that targets non-typhoidal *S. enterica* ser. Typhimurium, Enteritidis and Typhi. The Phase 1 trial is scheduled for completion in September 2022 (NCT03981952).

Despite a relatively high burden of both disease and associated mortality, and the biological feasibility of a vaccine, less investment has been made to date in vaccines to prevent NTS compared with typhoid fever (*S. enterica* ser. Typhi), (12). The majority of invasive NTS disease occurs in sub-Saharan Africa and is mostly caused by two serovars; *S. enterica* ser. Typhimurium and Enteritidis (83, 84). A vaccine active against these serovars would therefore cover the majority of pathogenic strains. The main market would be populations in endemic areas, which tend to be low-resourced, and have limited ability to pay for a vaccine without support from Gavi, the Vaccine Alliance. Transmission of NTS has a significant livestock and foodborne component, which may affect the impact of a human vaccine (85).
Table 29. **Preclinical development pipeline** for Non-typhoidal *Salmonella*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>iNTS-TCV vaccine</td>
<td><em>S. enterica</em> ser. Typhi and Typhimurium</td>
<td>Subunit; conjugate</td>
<td>GSK</td>
<td>Private sector</td>
<td>Italy</td>
<td>Active</td>
</tr>
<tr>
<td>Trivalent conjugate vaccine</td>
<td><em>S. enterica</em> ser. Typhi, Typhimurium and Enteritidis</td>
<td>Subunit; conjugate. Trivalent conjugate vaccine building on SK Bioscience Vi-DT vaccine.</td>
<td>SK Bioscience</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>Active</td>
</tr>
<tr>
<td>iNTS-GMMA and TCV</td>
<td><em>S. enterica</em> ser. Typhi, Typhimurium and Enteritidis</td>
<td>Subunit; conjugate. Three-component vaccine based on iNTS-GMMA and TCV.</td>
<td>GSK</td>
<td>Private sector</td>
<td>Italy</td>
<td>Active</td>
</tr>
<tr>
<td>CVD 1944 (derived from <em>S. enterica</em> ser. Enteritidis and CVD 1931 (derived from <em>S. enterica</em> ser. Typhimurium))</td>
<td><em>S. enterica</em> ser. Typhimurium and Enteritidis</td>
<td>Whole pathogen; live attenuated</td>
<td>University of Maryland</td>
<td>Academic</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>OmpD (87)</td>
<td><em>S. enterica</em> ser. Typhimurium</td>
<td>Subunit; recombinant</td>
<td>University of Birmingham</td>
<td>Academic</td>
<td>United Kingdom</td>
<td>Active</td>
</tr>
</tbody>
</table>

DT: diphtheria toxoid; GMMA: generalized modules for membrane antigens; GVGHI: GSK Vaccines Institute for Global Health; iNTS: invasive non-typhoidal *Salmonella*; TCV: typhoid conjugate vaccine; Vi: virulence factor.

Table 30. **Clinical development pipeline** for vaccine candidates actively undergoing clinical trials against Non-typhoidal *Salmonella*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
</table>

OPS: O-polysaccharide; TCV: typhoid conjugate vaccine; TT: tetanus toxoid; Vi, ViPS: virulence factor capsular polysaccharide.

Candidates no longer under active development or discontinued
**Campylobacter spp.**

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 4; Phase 1: 0; Phase 2: 0; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>Infants of 6–12 months and international travellers</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>High</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Four vaccine candidates against *Campylobacter* spp. were identified under preclinical development, all of which aim to protect against *C. jejuni* alone or with other bacteria such as ETEC or *S. flexneri* (Table 31).

No vaccines are licensed against *Campylobacter* spp., and no vaccines are in active clinical trials. One vaccine which was in clinical trials is no longer being actively researched; the Capsule conjugate *Campylobacter* vaccine (CJCV), was deemed safe after a Phase 1 clinical trial in January 2016 (NCT02067676). However, the same trial reported CJCV to be only weakly immunogenic, likely due to trial design that used only two dose regimens rather than the three used in previous studies.

Although, there are no licensed vaccines against *Campylobacter* spp., a conjugate vaccine developed for use in cows has shown it to be a viable vaccine target. Moreover, an ideal candidate would cover *Campylobacter coli* as well as *C. jejuni* as both show resistance to fluoroquinolones and macrolides (88). Though 35 serotypes of *C. jejuni* have been identified, the majority of human disease is caused by 8-10 of these, making an effective vaccine with broad protection possible. In addition, a conserved heptasaccharide shared by all strains of *C. coli* and *C. jejuni* has been identified (37).

A vaccine would have multiple markets, including travellers and military personnel, among others in HICs, in addition to those living in LMICs endemic for *Campylobacter*. Though the latter may be less able to afford a vaccine without external support, such as Gavi funding. *Campylobacter* is the second most common cause of foodborne illness in the USA, often in children under 5 (89), and is the leading cause of gastroenteritis and associated morbidity in HICs. A better understanding of the *Campylobacter* burden and transmission in LMICs, through animal, environmental and human pathways, is needed to inform the value of a vaccine in these settings (12).
Table 31. Preclinical development pipeline for *Campylobacter* spp.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter/ETEC vaccines</td>
<td>C. jejuni, ETEC</td>
<td>Unknown</td>
<td>Immuron; NMRC</td>
<td>Private sector</td>
<td>Australia</td>
<td>Active</td>
</tr>
<tr>
<td>Glycoconjugate vaccine</td>
<td>C. jejuni, ETEC, Shigella flexneri</td>
<td>Subunit; glycoconjugate</td>
<td>NMRC; WRAIR</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>PEB1 DNA prime/protein boost</td>
<td>C. jejuni</td>
<td>Nucleic acid; DNA</td>
<td>Shandong Medical College</td>
<td>Private sector</td>
<td>China</td>
<td>Unknown</td>
</tr>
<tr>
<td>CJCV2</td>
<td>C. jejuni</td>
<td>Subunit; conjugate</td>
<td>US Naval Medical Research Unit</td>
<td>Government</td>
<td>USA</td>
<td>Active</td>
</tr>
</tbody>
</table>

CJCV2: capsule conjugate *Campylobacter* vaccine 2; ETEC: enterotoxigenic *Escherichia coli*; NMRC: Naval Medical Research Center; WRAIR: Walter Reed Army Institute of Research.

Table 32. Clinical development pipeline for vaccine candidates no longer under active development against *Campylobacter* spp.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>CJCV</td>
<td>Subunit; conjugate, CPS conjugate vaccine using CRM197 as protein carrier. Completed Phase 1 with aluminium hydroxide adjuvant; a second Phase 1 was scheduled for late 2021 with ALF-Q as an adjuvant.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>NMRC; WRAIR</td>
<td>Government</td>
<td>USA</td>
<td>1 NCT02067676</td>
</tr>
</tbody>
</table>

CJCV: capsule conjugate *Campylobacter* vaccine; CPS: capsular polysaccharide; GVGH: GSK Vaccines Institute for Global Health; NMRC: Naval Medical Research Center; WRAIR: Walter Reed Army Institute of Research.

Candidates actively undergoing clinical trials: None
Shigella spp.

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 10; Phase 1: 3 against S. flexneri, 0 against S. sonnei, 3 against both; Phase 2: 1 against S. flexneri, 1 against S. sonnei; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>1–12-month-old infants in Shigella-endemic countries. Travellers and military personnel may also be targeted.</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>High</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Medium</td>
</tr>
</tbody>
</table>

Ten vaccines against *Shigella* spp. are in preclinical development. The majority of these are multivalent and incorporate other pathogenic targets alongside *Shigella* (Table 33).

Currently no licensed vaccines protect against *Shigella*; however, *Shigella* vaccines are an active area of research, with eight vaccine candidates in active clinical trials. ShigETEC, targets ETEC, *S. flexneri* and *S. sonnei* and was scheduled to start Phase 1 trials in 2021, however, these trials are on hold due to the COVID-19 pandemic (75). Results of the Phase 1a clinical trial will permit selecting the optimal dose and interval for administration in a Phase 1b trial in endemic populations in Bangladesh. In addition, CVD 31000 is a bivalent live attenuated vaccine using the *S. flexneri* 2a live vector expressing ETEC antigens which targets ETEC and *S. flexneri*. Phase 1 clinical trials were delayed due to the SARS-CoV-2 pandemic but began in June 2021 and are predicted to be completed in June 2023 (NCT04634513). Shigella4V is a monovalent vaccine candidate against *S. flexneri* (90), which was safe and immunogenic in a human challenge model (91). It is currently in Phase 1/2 clinical trials in Kenya in an age escalation study, scheduled for completion in July 2022 (NCT02388009).

Research on seven vaccine candidates against *Shigella* has become inactive or been discontinued over the past 10 years. Flexyn2a, a monovalent bioconjugate vaccine has been inactive since Phase 2b trials in 2017 to pursue the four-valent Shigella4V. Similarly, the GVXN SD133 conjugate vaccine was discontinued in 2010, after a Phase 1 trial (NCT01069471), to develop the Flexyn2a vaccine. CVD 1208S live attenuated vaccine was abandoned due to high levels of reactogenicity in the Phase 2 trial (92) (NCT00866242, NCT00866476). However, this experience has led to more recent candidates including CVD 31000. WRSS1 failed to achieve full immunogenicity in 2016 Phase 2 trials (NCT01813071). However, research has continued in the form of the WRSS2/WRSS3 live attenuated candidate (93) (NCT04242264). An Sf2aWC + dmLT inactivated whole cell vaccine was withdrawn during Phase 2 trials and discontinued due to lack of funding (NCT03038243) (94).

It is encouraging that *Shigella* vaccine candidates providing coverage against *S. flexneri* 1a, 2a, 3a, and 6, and *S. sonnei* are moving into clinical trials, and research suggests that a four-valent conjugate vaccine could cover more than 80% of strains causing disease (95). However, uncertainties remain as to whether conjugate vaccines will provide protection to the target age group of children under 3 and in pristine subjects, although the use of adjuvants is being explored in response to this issue (37). Most of the target population is in lower-resourced settings, which would require Gavi support to finance uptake. Travellers, men who have sex with men (MSM), and military personnel from HICs, however, may also present markets with financial resources to pay for a vaccine. The inclusion of multiple antigens, not only against *Shigella* but also ETEC, would improve the value proposition of a vaccine. With many candidates in clinical development, a marketed *Shigella* vaccine is likely but not earlier than in the next 7–10 years (12).
<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycoconjugate vaccine</td>
<td>Campylobacter jejuni, ETEC, S. flexneri</td>
<td>Subunit, glycoconjugates</td>
<td>NMRC; WRAIR</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>DB Fusion, Serotype-independent Shigella vaccine</td>
<td>S. sonnei, S. flexneri</td>
<td>Whole pathogen, inactivated</td>
<td>PATH; Oklahoma State University</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>Glycoconjugate vaccine</td>
<td>S. sonnei, S. flexneri</td>
<td>Subunit; glycoconjugates</td>
<td>NMRC; WRAIR</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>DB Fusion, Serotype-independent Shigella vaccine</td>
<td>S. sonnei, S. flexneri</td>
<td>Subunit; DB Fusion and adjuvant; fusion protein of two Type III secretion system antigens, invasion plasmid antigen B (Ipa B) and D (Ipa D).</td>
<td>PATH; Oklahoma State University</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>ShigOraVax</td>
<td>S. sonnei, S. flexneri</td>
<td>Whole pathogen; inactivated</td>
<td>European Vaccine Initiative; Leiden University Medical Center; Group de Recherche Action en Santé; Centre for Infectious Disease Research in Zambia; University of Gothenburg; Hillman Laboratories</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>34 kDa OMP</td>
<td>S. flexneri</td>
<td>Subunit; OMP</td>
<td>IVI</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>Truncated mutant</td>
<td>S. sonnei, S. flexneri, S. dysenteriae</td>
<td>Whole pathogen; truncated Shigella target; OMP for universal Shigella vaccine</td>
<td>University of Navarra</td>
<td>Academic</td>
<td>Germany; Netherlands; Burkina Faso; Brazil; Sweden; India</td>
<td>Active</td>
</tr>
<tr>
<td>OMV Sf12a</td>
<td>S. sonnei, S. flexneri, S. dysenteriae</td>
<td>Whole pathogen; inactivated</td>
<td>IVI</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>PSSP-1</td>
<td>S. sonnei, S. flexneri, S. dysenteriae</td>
<td>Whole pathogen; inactivated</td>
<td>IVI</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>HKMS</td>
<td>S. sonnei, S. flexneri, S. dysenteriae</td>
<td>Whole pathogen; inactivated</td>
<td>IVI</td>
<td>Other</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>Ty21a typhoid vaccine expressing Shigella LPS</td>
<td>Salmonella enterica ser. Typhi, S. flexneri, S. sonnei</td>
<td>Whole pathogen; live, attenuated; Chimeric vector</td>
<td>Protein Potential</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>S. flexneri 2a and S. sonnei conjugate</td>
<td>S. sonnei, S. flexneri</td>
<td>Subunit, conjugate</td>
<td>ZFSW</td>
<td>Private sector</td>
<td>China</td>
<td>Active</td>
</tr>
</tbody>
</table>

ETEC: enterotoxigenic Escherichia coli; IVI: International Vaccine Institute; LPS: lipopolysaccharide; NICED: National Institute of Cholera and Enteric Diseases; NMRC: Naval Medical Research Center; O-Ag: O-antigen; OMP: outer membrane protein; OMV: outer membrane vesicle; PSSP-1: pan-Shigella surface protein antigen 1; ser.: serovar; WRAIR: Walter Reed Army Institute of Research; ZFSW: Chongqing Zhifei Biological Products.
Table 34. Clinical development pipeline for vaccine candidates actively undergoing clinical trials against *Shigella* spp.

<table>
<thead>
<tr>
<th>Vaccine candidate</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlycoShig3 (SF2a-TT15)</td>
<td><em>Shigella flexneri</em></td>
<td>Subunit; glyco-conjugate recombinant. Functional oligosaccharide mimic of O-Ag, the bacterial OMP, coupled to TT.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Pasteur Institute</td>
<td>Academic</td>
<td>France</td>
<td>2 NCT04602975</td>
</tr>
<tr>
<td>WRSS2/WRSS3 (VirG series)</td>
<td><em>S. sonnei</em></td>
<td>Whole cell; live attenuated. WRSS2 and WRSS3; virG based.</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>WRAIR; NIAID</td>
<td>Other</td>
<td>USA</td>
<td>2 NCT04242264</td>
</tr>
<tr>
<td>Shigella-ETEC</td>
<td><em>ETEC</em>, <em>S. sonnei</em>, <em>S. flexneri</em></td>
<td>Whole pathogen; live attenuated <em>Shigella</em> vaccine expressing ETEC antigens.</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>Emergent Biosolutions</td>
<td>Private sector</td>
<td>USA</td>
<td>1 Not yet registered</td>
</tr>
<tr>
<td>ShigETEC (75, 76)</td>
<td><em>ETEC</em>, <em>S. sonnei</em>, <em>S. flexneri</em></td>
<td>Whole pathogen; live attenuated, mutation to the LPS antigen and invasion proteins.</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>EveliQure Biotechnologies</td>
<td>Private sector</td>
<td>Austria</td>
<td>1 EudraCT: 2020-000248-79</td>
</tr>
<tr>
<td>CVD 31000 (CVD 12085-122)</td>
<td><em>ETEC</em>, <em>S. flexneri</em></td>
<td>Whole pathogen; live attenuated, <em>S. flexneri</em> 2a expressing ETEC antigens.</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>University of Maryland</td>
<td>Academic</td>
<td>USA</td>
<td>1 NCT04634513</td>
</tr>
<tr>
<td>InvaplexAR; InvaplexAR-DETOX (98)</td>
<td><em>S. flexneri</em></td>
<td>Subunit; recombinant, <em>Shigella</em> LPS and the Type 3 secretion system proteins (Ipa B, Ipa C).</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>WRAIR; PATH</td>
<td>Other</td>
<td>USA</td>
<td>1 NCT03869333</td>
</tr>
<tr>
<td>Shigella4V (GSK4069327A) (94, 98)</td>
<td><em>S. flexneri</em></td>
<td>Subunit; bioconjugate vaccine alone or in combination with adjuvant (aluminium hydroxide). Covers O-Ag polysaccharides from <em>S. flexneri</em> 2a, 3a and 6.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>GlycoVaxyn; LimmaTech Biologics; GSK</td>
<td>Private sector</td>
<td>United Kingdom; Switzerland</td>
<td>1 NCT02388009</td>
</tr>
<tr>
<td>Multivalent Shigella GMMA</td>
<td><em>S. flexneri</em>, <em>S. sonnei</em></td>
<td>Subunit; GMMA</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>GVGH</td>
<td>Private sector</td>
<td>Italy</td>
<td>1 / 2 NCT05073003</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexyn2a</td>
<td>Bioconjugate vaccine alone or in combination with adjuvant (aluminium hydroxide). Covers O-Ag polysaccharides from <em>Shigella sonnei</em>, <em>S. flexneri</em> 2a, 3a and 6.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>GlycoVaxyn; LimmaTech Biologics; GSK</td>
<td>Private sector</td>
<td>United Kingdom; Switzerland</td>
<td>2b NCT02646371</td>
</tr>
<tr>
<td>WRSS1</td>
<td>Live, attenuated vaccine; virG-based</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>WRAIR; PATH</td>
<td>Other</td>
<td>USA</td>
<td>2 NCT01813071</td>
</tr>
<tr>
<td>CVD 1208S, CVD 1208 (92)</td>
<td>Whole pathogen; live attenuated, guaBA based.</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>University of Maryland</td>
<td>Academic</td>
<td>USA</td>
<td>2 NCT00866242 NCT00866476</td>
</tr>
<tr>
<td>Sf2aWC + dmLT (94)</td>
<td>Whole pathogen; inactivated <em>S. flexneri</em> 2a killed vaccine</td>
<td>Prophylactic</td>
<td>Oral</td>
<td>PATH</td>
<td>Other</td>
<td>USA</td>
<td>2 NCT03038243</td>
</tr>
<tr>
<td>1790GAHB, GSK3902986A/GSK3536852A (99)</td>
<td>Subunit; GMMA, <em>S. sonnei</em> O-Ag</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>GVGH</td>
<td>Private sector</td>
<td>Italy</td>
<td>2 NCT03527173 NCT02676895</td>
</tr>
<tr>
<td>O-SPC/BRU</td>
<td>Subunit; conjugate</td>
<td>Prophylactic</td>
<td>Intramuscular</td>
<td>Eunice Kennedy Shriver NICHD; NIHCC</td>
<td>Academic</td>
<td>USA</td>
<td>1 NCT01369927 NCT01399424</td>
</tr>
<tr>
<td>GVXN SD133</td>
<td>Subunit; conjugate, <em>S. dysenteriae</em> bioconjugate alone or in combination with aluminium hydroxide</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>GlycoVaxyn; LimmaTech Biologics</td>
<td>Private sector</td>
<td>Switzerland</td>
<td>1 NCT01069471</td>
</tr>
</tbody>
</table>

**Group D: Pathogens which currently have low feasibility for vaccine development**

**Acinetobacter baumannii**

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 5; Phase 1: 0; Phase 2: 0; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>Immunocompromised patients, patients requiring mechanical ventilation or urinary catheters, patients in long-term care facilities, presurgical patients in high-risk settings, other patients at high risk of infection</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Low</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Low</td>
</tr>
</tbody>
</table>

While no vaccines are in clinical development against *A. baumannii*, five vaccine candidates are in preclinical development. Of these, two are inactivated whole cell vaccine candidates, one of which additionally targets *P. aeruginosa* and *K. pneumoniae*, and one is a conjugate vaccine which additionally targets *Streptococcus agalactiae* (Table 36).

Multiple candidates have been characterized in preclinical studies based on recombinant proteins, inactivated/attenuated whole cells and surface polysaccharides that have not made it to the clinical stage (37, 100). The lack of vaccines against *A. baumannii* in clinical development might be explained by the biological complexities, which makes it scientifically challenging to arrive at a sound concept for an *A. baumannii* vaccine. In addition, there are number of challenges along the pathway to clinical development. Even if one of the candidates in preclinical development made it to the clinical stages of development, large efficacy trials would be required due to low disease prevalence in vulnerable populations (12). The target population includes critically ill patients with multiple comorbidities and/or a compromised immune response, and who are often in intensive care. All of this makes it hard to recruit subjects for such trials and complicates the establishment of appropriate efficacy end points (100, 101).

In addition, there is currently no precedent for the routine use of vaccines to prevent hospital-acquired infections in high-risk populations. It is unclear when such a vaccine would need to be administered to be effective if a patient were hospitalized.
### Table 36. Preclinical development pipeline for *A. baumannii*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogens</th>
<th>Approach</th>
<th>Developer</th>
<th>Developer type</th>
<th>Country of sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii and <em>Streptococcus agalactiae</em> conjugate vaccine</td>
<td>A. baumannii and <em>S. agalactiae</em></td>
<td>Conjugate vaccine</td>
<td>Bio-Manguinhos</td>
<td>Private sector</td>
<td>Brazil</td>
</tr>
<tr>
<td>Acinet Vax (VXD-001)</td>
<td>A. baumannii</td>
<td>Inactivated whole cell of LPS-null A. baumannii</td>
<td>Vaxdyn</td>
<td>Private sector</td>
<td>Spain</td>
</tr>
<tr>
<td>KapaVax (VXD-005)</td>
<td>A. baumannii, <em>Pseudomonas aeruginosa</em> and <em>Klebsiella pneumoniae</em></td>
<td>Inactivated LPS-null (endotoxin-free) whole-cell A. baumannii vaccine displaying at the cell surface multiple conserved antigens from <em>P. aeruginosa</em> and <em>K. pneumoniae</em>.</td>
<td>Vaxdyn</td>
<td>Private sector</td>
<td>Spain</td>
</tr>
<tr>
<td>A. baumannii vaccine</td>
<td>A. baumannii</td>
<td>Unknown</td>
<td>Oswaldo Cruz Foundation</td>
<td>Academic</td>
<td>Brazil</td>
</tr>
<tr>
<td>A. baumannii vaccine</td>
<td>A. baumannii</td>
<td>Unknown</td>
<td>University of Birmingham</td>
<td>Academic</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>

LPS: lipopolysaccharide.
**Pseudomonas aeruginosa**

| Vaccines in development | Preclinical: 4; Phase 1: 0; Phase 2: 0; Phase 3: 0 |
|--------------------------|-------------------------------------------------
| Potential target population | Patients with the following risk factors: burns, neurological conditions, chronic pulmonary disease, cystic fibrosis, invasive procedures, prior colonization and patients undergoing antibiotic treatment |
| Biological feasibility | Medium |
| Product development feasibility | Medium |
| Access and implementation feasibility | Low |

No active candidates are in clinical development against *P. aeruginosa*. The analysis identified four active *P. aeruginosa* vaccine candidates in the later stages of preclinical development. These use a range of technologies, including the MAPS platform (102), phage-based vaccine, a live attenuated *Salmonella* strain and inactivated whole cell vaccine. In addition, multiple promising vaccine candidates were identified in earlier stages of preclinical development.

Several vaccines have advanced to clinical trials and failed over the past 3 decades (79, 103–105). In the last ten years, VLA43 (IC43) completed a Phase 2/3 clinical trial (NCT01563263) and was discontinued as it failed to reduce all-cause mortality (105). A *P. aeruginosa* vaccine that incorporates 8 of the 16–20 different *P. aeruginosa* International Antigenic Typing Schema (IATS) subtypes could provide approximately 80% coverage of clinical strains (26).

However, similarly to Acinetobacter infections, the incidence of *P. aeruginosa* infections in hospitals, and the risk factors and co-morbidities associated with these infections make it hard to conduct a clinical trial without specifically targeting high-risk populations. These high-risk populations include those in intensive care units (ICUs), nursing homes or long-term acute care facilities, or patients who are immunosuppressed due to surgery or immunotherapy (37). This makes clinical development very challenging. For instance, one of the main difficulties facing the VLA43 trial was defining end points. Impact on mortality was hard to demonstrate in critically ill patients, many of whom were receiving antibiotics, particularly without selecting a group of patients at high risk of *P. aeruginosa* infection. The administration of a vaccine at ICU admission left limited time for a protective immunological response. A vaccine-based approach to *P. aeruginosa* prevention may be more effective if at-risk target populations can be identified prior to ICU admission (e.g. patients with cystic fibrosis are at risk of *P. aeruginosa* infection and may be a good target group) (105).
### Table 37. Preclinical development pipeline for *Pseudomonas aeruginosa*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogens</th>
<th>Approach</th>
<th>Name of developer</th>
<th>Developer type</th>
<th>Country of sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASP1004</td>
<td><em>Klebsiella pneumoniae</em>, <em>Pseudomonas aeruginosa</em></td>
<td>Subunit; MAPS platform</td>
<td>Affinivax; Astellas Pharma</td>
<td>Private sector</td>
<td>USA; Japan</td>
</tr>
<tr>
<td>INI-2002</td>
<td><em>P. aeruginosa</em></td>
<td>Phage-based vaccine to prevent Gram-negative bacterial infections</td>
<td>Inimmune</td>
<td>Private sector</td>
<td>USA</td>
</tr>
<tr>
<td>OprF and OprL</td>
<td><em>P. aeruginosa</em></td>
<td>Whole pathogen; live attenuated. Attenuated <em>Salmonella</em> (strains CVD908 and Ty21a), followed by a systemic booster vaccination. Vaccines based on recombinant fusion protein of the highly conserved <em>P. aeruginosa</em> OMPs OprF and OprI as antigen.</td>
<td>Unknown</td>
<td>Unknown</td>
<td>China</td>
</tr>
<tr>
<td>KapaVax (VXD-005)</td>
<td><em>Acinetobacter baumannii</em>, <em>P. aeruginosa</em>, <em>K. pneumoniae</em></td>
<td>Whole cell; inactivated. Inactivated LPS-null (endotoxin-free) whole cell <em>A. baumannii</em> vaccine displaying at the cell surface multiple conserved antigens from <em>P. aeruginosa</em> and <em>K. pneumoniae</em>.</td>
<td>Vaxdyn</td>
<td>Private sector</td>
<td>Spain</td>
</tr>
</tbody>
</table>

LPS: lipopolysaccharide; MAPS: multiple antigen presenting system; OMP: outer membrane protein.

### Table 38. Clinical development pipeline for vaccine candidates no longer under active development against *Pseudomonas aeruginosa*.

<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogens</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Name of developer</th>
<th>Phase Clinical trial registration number</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLA43 (IC43)</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Recombinant; subunit. Recombinant OMP-based vaccine consisting of OprF and OprI epitopes (Opr, outer membrane protein; OprF/I, OprF/OprI hybrid vaccine) with an N-terminal His 6 tag (Met-Ala-(His)_6-OprF_190–342-OprI_21–83).</td>
<td>Prophylactic</td>
<td>Oral or nasal</td>
<td>Valneva</td>
<td>2/3 NCT01563326</td>
<td>Discontinued</td>
</tr>
</tbody>
</table>

OMP: outer membrane protein.
Enterobacter spp.

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 0; Phase 1: 0; Phase 2: 0; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>NA*</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>NA*</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>NA*</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>NA*</td>
</tr>
</tbody>
</table>

*Not included in feasibility assessments cited for other pathogens.

Enterobacter spp. were identified by the Wellcome Trust as not well suited for vaccine development due to their relatively low incidence, morbidity and mortality (12). The global burden of bacterial AMR study however, estimates that Enterobacter spp. are responsible for between 100 000 and 250 000 deaths associated with AMR globally in 2019 (5), however, the challenge remains to identify the appropriate target population for a vaccine with high enough disease incidence.

**Preclinical pipeline:** None

**Clinical pipeline:** None

**Candidates actively undergoing clinical trials:** None

**Candidates no longer under active development or discontinued:** None
### Enterococcus faecium

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 0; Phase 1: 0; Phase 2: 0; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>Patients in intensive care, immunocompromised individuals, patients with comorbidities and patients with foreign bodies</td>
</tr>
<tr>
<td>Biological feasibility</td>
<td>Low</td>
</tr>
<tr>
<td>Product development feasibility</td>
<td>Medium</td>
</tr>
<tr>
<td>Access and implementation feasibility</td>
<td>Low</td>
</tr>
</tbody>
</table>

No vaccine candidates against *E. faecium* are currently in preclinical or clinical trials. Several capsular polysaccharides and surface-associated proteins have been described as potential antigens (106); however, these have not yet arrived at late stages of preclinical research. *E. faecium* was also identified by the Wellcome Trust as not well suited for vaccine development due to comparatively low incidence, morbidity and mortality (12). In addition, there are multiple factors that make vaccine development against *E. faecium* challenging. Natural immunity response to the switch from commensal to pathogen is not well understood (107), correlates of protection are lacking, and the target population for a vaccine is not clearly defined (12, 37). *E. faecium* infections have relatively low incidence and tend to affect highly immunocompromised patients with a range of co-morbidities, which would be challenging to target for vaccination (12). Recent estimates the burden of *E. faecium* deaths associated with AMR at 100 000-250 000 globally in 2019 (5).

**Preclinical pipeline:** None

**Clinical pipeline:** None

**Candidates actively undergoing clinical trials:** None

**Candidates no longer under active development or discontinued:** None
**Staphylococcus aureus**

<table>
<thead>
<tr>
<th>Vaccines in development</th>
<th>Preclinical: 14; Phase 1: 1; Phase 2: 1; Phase 3: 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential target population</td>
<td>Infants 6–59 months old, those over 60 years</td>
</tr>
<tr>
<td></td>
<td>of age, immunocompromised patients and/or</td>
</tr>
<tr>
<td></td>
<td>suffering from comorbidities, hospital</td>
</tr>
<tr>
<td></td>
<td>patients undergoing elective surgery or other</td>
</tr>
<tr>
<td></td>
<td>invasive procedures with high risk of <em>S.</em></td>
</tr>
<tr>
<td></td>
<td><em>aureus</em> infection. Those with recurrent skin</td>
</tr>
<tr>
<td></td>
<td>and soft tissue infections are also a possible</td>
</tr>
<tr>
<td></td>
<td>target population.</td>
</tr>
</tbody>
</table>

| Biological feasibility       | Very low                                       |
| Product development feasibility | Medium                                        |
| Access and implementation feasibility | Medium                                     |

*Not included in feasibility assessments cited for other pathogens.*

There are currently 12 active preclinical vaccine candidates against *S. aureus*, these include a peptide-based vaccine that targets ETEC and ExPEC and all the others (n = 11) that are specific to *S. aureus*. Research is being pursued both by academic and private sectors (Table 39). A seven-antigen (five-protein) toxin-based vaccine, IBT-V02, is planned for a Phase 1 clinical trial in 2022 (37) and is likely to target prevention of recurrent skin and soft tissue infections (SSTIs).

Currently no licensed vaccines prevent *S. aureus* infection exist however, two vaccine candidates which specifically target *S. aureus* are in clinical trials. The most recent is the GSK3878858A recombinant protein vaccine that targets recurrent skin infections. It is currently in a Phase 1/2 trial and enrolment is expected to be completed in December 2022 (NCT04420221).

Despite relatively high industry investment, many vaccine candidates against *S. aureus* have been developed and failed (Table 41). Over the last 10 years, nine vaccine candidates in clinical development have been discontinued or research has become inactive, mostly in Phase 1 clinical trials. For example, the recombinant toxin vaccine STEBVax (IBT-V01) (NCT00974935) was discontinued in order to work towards the IBT-V02 pentavalent toxoid vaccine, currently in preclinical stages. Also, AVO0328, a partially de-N-acetylated poly-N-acetyl glucosamine polymer that targeted a variety of bacterial species, including *S. pneumoniae* and *S. aureus*, shows no recent activity (NCT02853617). NDV-3A recombinant vaccine failed to prevent nasal acquisition of *S. aureus* in military recruits during Phase 2a trials (NCT03455309) (108). The four-antigen candidate SA4Ag was terminated during Phase 2b (NCT02388165) in 2019 due to futility (13). Phase 3 failure also occurred in the V710 IsdB vaccine (NCT00518687), as trials were terminated when interim analysis reported increased mortality and adverse side effects in vaccine recipients who developed an *S. aureus* infection. Another Phase 3 candidate against *S. aureus*, CP5-Epa and CP8-Epa vaccine, outside of the date range of the present review, was shown to confer partial immunity for approximately 40 weeks but is no longer under development (109).

At present, it is unclear what antigen targets would allow a vaccine to provide protection against *S. aureus* infection (13) In addition, correlates of protection are lacking, and vaccines that have shown protection in animal models have failed in clinical trials (37, 110, 111). Multiple candidate monoclonal antibodies against *S. aureus* have failed in clinical trials (112). Finally, *S. aureus* causes a diverse range clinical syndromes, including bacteraemia, skin infections, pneumonia and others, and it is not clear whether a vaccine against one would protect against others (113).
<table>
<thead>
<tr>
<th>Candidate vaccine</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Activity status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paragon Novel Vaccine</td>
<td><em>S. aureus</em>, <em>ETEC</em>, <em>ExPEC</em></td>
<td>Subunit/adjuvant platform</td>
<td>Immunethep; Merck</td>
<td>Private sector</td>
<td>Portugal; USA</td>
<td>Active</td>
</tr>
<tr>
<td>IBT-V02</td>
<td><em>S. aureus</em></td>
<td>Subunit; toxoid</td>
<td>Integrated BioTherapeutics</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>IBT-V02</td>
<td><em>S. aureus</em></td>
<td>Subunit vaccine</td>
<td>VLP Biotech</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>IBT-V02</td>
<td><em>S. aureus</em></td>
<td>Subunit; vaccine program</td>
<td>Biofarms</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>IBT-V02</td>
<td><em>S. aureus</em></td>
<td>Whole pathogen; ghost cells</td>
<td>Pan Chai University</td>
<td>Academic</td>
<td>China</td>
<td>Unknown</td>
</tr>
<tr>
<td>EVX-B1</td>
<td><em>S. aureus</em></td>
<td>RBC nanosponge</td>
<td>Evaxion Biotech</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>ABN-701</td>
<td><em>S. aureus</em></td>
<td>Indicated for SEB/Supe antigen toxin</td>
<td>Abion</td>
<td>Private sector</td>
<td>Republic of Korea</td>
<td>Active</td>
</tr>
<tr>
<td>CTI-005</td>
<td><em>S. aureus</em></td>
<td>Subunit; RBC nanosponge</td>
<td>Celsius Therapeutics</td>
<td>Private sector</td>
<td>USA</td>
<td>Active</td>
</tr>
<tr>
<td>CTI-026</td>
<td><em>S. aureus</em></td>
<td>Subunit; Antigen: Cogk (coproporphyrinogen oxidase), TP, triphosphate dehydrogenase, MAPS, multiple antigen presenting system, MRSA, methicillin-resistant <em>S. aureus</em>, RBC, red blood cells, SEB, staphylococcal enterotoxin B</td>
<td>University of Cologne</td>
<td>Academic</td>
<td>Germany</td>
<td>Active</td>
</tr>
<tr>
<td>Janssen Vaccines &amp; Prevention</td>
<td><em>S. aureus</em></td>
<td>Subunit vaccine</td>
<td>Janssen Vaccines &amp; Prevention</td>
<td>Private sector</td>
<td>Netherlands</td>
<td>Active</td>
</tr>
</tbody>
</table>

**Table 39. Preclinical development pipeline for *Staphylococcus aureus*.**

ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; MRSA: methicillin-resistant *S. aureus*; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; MAPS: multiple antigen presenting system; RBC: red blood cell; SEB: staphylococcal enterotoxin B.
Table 40. **Clinical development pipeline** for vaccine candidates actively undergoing clinical trials against *Staphylococcus aureus*.

<table>
<thead>
<tr>
<th>Vaccine candidate</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTSST-1 variant vaccine (ORG28077)</td>
<td>Subunit; recombinant. Detoxified toxic shock syndrome toxin-1 variant.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Biomedizinische ForschungsgmbH; Medical University of Vienna</td>
<td>Private sector</td>
<td>Austria, USA</td>
<td>2 NCT02814708</td>
</tr>
<tr>
<td>GSK3878858A</td>
<td>Subunit; recombinant. Sa-5Ag with/without adjuvant.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>GSK</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>1/2 NCT04420221</td>
</tr>
</tbody>
</table>

Ag: antigen; rTSST: recombinant toxic shock syndrome toxin; Sa: *Staphylococcus aureus*.

Table 41. **Clinical development pipeline** for vaccine candidates no longer under active development against *Staphylococcus aureus*.

<table>
<thead>
<tr>
<th>Vaccine candidate</th>
<th>Target pathogen(s)</th>
<th>Approach</th>
<th>Prophylactic/therapeutic</th>
<th>Route of administration</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>V710 IsdB</td>
<td><em>Staphylococcus aureus</em></td>
<td>Subunit; recombinant. Contains the highly conserved <em>S. aureus</em> 0657nI iron surface determinant B.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Merck Sharp &amp; Dohme</td>
<td>Private sector</td>
<td>USA</td>
<td>3 NCT00518687</td>
</tr>
<tr>
<td>SA4Ag (S. aureus 4-antigen vaccine) PF-06290510/SA4Ag</td>
<td><em>S. aureus</em></td>
<td>Subunit; conjugate. Four antigens: the adhesion molecule ClfA, the manganese transporter MntC and anti-phagocytic capsular polysaccharides 5 and 8. CP5 and CP8 conjugated to CRM197.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Pfizer</td>
<td>Private sector</td>
<td>USA</td>
<td>2b NCT02388165</td>
</tr>
<tr>
<td>NDV-3A (formerly NDV31 (108))</td>
<td><em>S. aureus</em></td>
<td>Subunit; recombinant. Recombinant candidal surface glycoprotein antigen A1s3p.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>NovaDigm Therapeutics</td>
<td>Private sector</td>
<td>USA</td>
<td>2 NCT03455309</td>
</tr>
<tr>
<td>AV0328</td>
<td><em>S. aureus; Streptococcus pneumoniae</em></td>
<td>Subunit; conjugate. dPNAG conjugated to TT.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Alopexx Vaccine</td>
<td>Private sector</td>
<td>USA</td>
<td>1/2 NCT02853617</td>
</tr>
<tr>
<td>rAT and rLukS-PV</td>
<td><em>S. aureus</em></td>
<td>Subunit; toxoid. Two <em>S. aureus</em> toxins, rAT and rLukS-PV, as monovalent and bivalent components.</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Nabi Biopharmaceuticals</td>
<td>Private sector</td>
<td>USA</td>
<td>1/2 NCT01011335</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Pathogen</td>
<td>Description</td>
<td>Type</td>
<td>Adjuvant</td>
<td>Sponsor</td>
<td>Country</td>
<td>NCT Number</td>
<td></td>
</tr>
<tr>
<td>---------</td>
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<td>-------------</td>
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<td></td>
</tr>
<tr>
<td>4C-Staph</td>
<td><em>S. aureus</em></td>
<td>Subunit; toxoid. Contains five conserved antigens known to have different roles in <em>S. aureus</em> pathogenesis: the secreted factors α-haemolysin (Hia), ess extracellular A (EssA) and ess extracellular B (EssB), and the two surface proteins ferric hydroxamate uptake D2 and conserved staphylococcal antigen 1A, with a novel TLR7-dependent adjuvant.</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>GSK</td>
<td>Private sector</td>
<td>United Kingdom</td>
<td>NCT01160172</td>
</tr>
<tr>
<td>STEB Vax (IBT-V01)</td>
<td><em>S. aureus</em></td>
<td>Subunit; recombinant. Recombinant mutated form of SEB containing three mutations in the major histocompatibility complex class II binding site, combined with an alum adjuvant (Alhydrogel).</td>
<td>Prophylactic</td>
<td>Parenteral</td>
<td>Integrated BioTherapeutics</td>
<td>Private sector</td>
<td>USA</td>
<td>NCT00974935</td>
</tr>
<tr>
<td>SA75</td>
<td><em>S. aureus</em></td>
<td>Whole pathogen</td>
<td>Prophylactic</td>
<td>Unknown</td>
<td>Vaccine Research International</td>
<td>Academic</td>
<td>United Kingdom</td>
<td>1</td>
</tr>
<tr>
<td>Recombinant <em>S. aureus</em> vaccine (114)</td>
<td><em>S. aureus</em></td>
<td>Subunit; recombinant. Hia, IsdB-N2 SpA5, mSEB, and MntC recombinant proteins and aluminium phosphate adjuvants.</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Chengdu Olymvax Biopharmaceuticals</td>
<td>Private sector</td>
<td>China</td>
<td>NCT02804711</td>
</tr>
</tbody>
</table>

### Vaccines in development

<table>
<thead>
<tr>
<th>Preclinical: 6; Phase 1: 0; Phase 2: 0; Phase 3: 0</th>
</tr>
</thead>
</table>

### Potential target population

1. A prophylactic vaccine given to children before *H. pylori* is acquired at a young age; or
2. A therapeutic vaccine given to adults who are infected and therefore at risk of cancer associated with *H. pylori*.

### Biological feasibility

Low

### Product development feasibility

High

### Access and implementation feasibility

High

Six vaccine candidates against *H. pylori* are in preclinical development, with active development occurring on at least two (Table 42). However, the approaches pursued are similar to some that have previously failed, and there is no evidence that these are more likely to succeed (37). The two candidates in active development are the surfome vaccine and the gastric cancer vaccine. A few of the potential antigens being explored in preclinical development against *H. pylori* and others which have been explored in mice, include yeast expressing ureB and ureA (115), Listeria expressing *H. pylori* antigens (116), a cyclic guanosine monophosphate-adenosine monophosphate adjuvanted urease vaccine (117) and OMVs (118).

Currently no *H. pylori* vaccines are in clinical development. Two vaccines have completed Phase 1 or Phase 1/2 clinical trials in the last 10 years. However, both are inactive or discontinued. Most recently, the IMX101 vaccine, which targets GGT (gamma-glutamyl transpeptidase) antigens (119), has had no reports of development since it was completed in 2018 (NCT03270800). Although the results of the clinical trial were promising, investment has been indefinitely postponed until a strategic partner is identified.

The sole Phase 3 clinical trial (NCT02302170) was not included in this analysis as it was completed in September 2008, which is outside the timeframe established by the search criteria. The trial took place in China, and recruited 4464 children (120), but was ultimately discontinued. The study showed that it is possible to induce vaccine-mediated protection against *H. pylori*, although overall vaccine development was hindered by the lack of known correlates of protection for the pathogen.

Two different *H. pylori* vaccines are theoretically possible: a prophylactic vaccine given to children before *H. pylori* is acquired at a young age, and a therapeutic vaccine given to adults who are infected and therefore at risk of cancer associated with *H. pylori*. The long time lag between infection in childhood and disease in adulthood contributes to the difficulty of vaccine development (12). *H pylori* infections affect over 50% of the population globally, with the highest rates concentrated in areas like Asia, where prevalence is highest. These high rates would facilitate a standard clinical trial design and demonstrate that there is a large potential market for a vaccine (37).
### Table 42. Preclinical development pipeline for *Helicobacter pylori*.

<table>
<thead>
<tr>
<th>Vaccine candidate</th>
<th>Approach</th>
<th>Developer</th>
<th>Sponsor type</th>
<th>Country of sponsor</th>
<th>Active status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotic vaccine delivery</td>
<td>Probiotic.</td>
<td>China Pharmaceutical University</td>
<td>Academic</td>
<td>China</td>
<td>Unknown</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> vaccine</td>
<td>Subunit; recombinant. HLA-binding epitopes.</td>
<td>EpiVax</td>
<td>Private sector</td>
<td>USA</td>
<td>Inactive</td>
</tr>
<tr>
<td><em>H. pylori</em> vaccine</td>
<td>Unknown</td>
<td>ImmBio</td>
<td>Private sector</td>
<td>UK</td>
<td>Inactive</td>
</tr>
<tr>
<td>Inactivated whole cell vaccine</td>
<td>Whole pathogen; inactivated. Mucosal vaccine.</td>
<td>University of Gothenburg</td>
<td>Academic</td>
<td>Sweden</td>
<td>Inactive</td>
</tr>
<tr>
<td><em>H. pylori</em> surfome antigens</td>
<td>Prophylactic mucosal vaccine.</td>
<td>Technical University of Munich</td>
<td>Academic</td>
<td>Germany</td>
<td>Active</td>
</tr>
<tr>
<td>Gastric cancer vaccine</td>
<td>Subunit. HtrA anti-gastritis vaccine.</td>
<td>Murdoch Children’s Research Institute</td>
<td>Academic</td>
<td>Australia</td>
<td>Active</td>
</tr>
</tbody>
</table>

HLA: human leucocyte antigen; HtrA: protease high temperature requirement A.

### Table 43. Clinical development pipeline for vaccine candidates no longer under active development against *Helicobacter pylori*.

<table>
<thead>
<tr>
<th>Candidates no longer under active development or discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine candidate</td>
</tr>
<tr>
<td>IMX101 (121)</td>
</tr>
</tbody>
</table>

GGT: gamma-glutamyl transpeptidase.
3. Discussion

AMR is an urgent threat with an increasing impact on global health (4). It is one of the leading causes of death around the world, with the highest burden in limited resource settings. This report highlights vaccine candidates in all stages of preclinical and clinical development that may be available in the future as tools to help combat AMR. The report also discusses some of the anticipated opportunities and challenges for innovation and R&D in this area.

In the analysis, pathogens in the WHO BPPL, have been broadly categorized in terms of feasibility (Table 44) (based on matching the progression of vaccine candidates in clinical and preclinical development and assessments of the feasibility of generating a vaccine based on analyses of biological, product development, and access and implementation feasibility (Table 1; see (26) for full methodology).

Table 44. Summary of pipeline findings and recommendations for pathogens on the BPPL.

<table>
<thead>
<tr>
<th>Pipeline Feasibility Group</th>
<th>Description</th>
<th>Pathogens</th>
<th>Recommendations</th>
</tr>
</thead>
</table>
| Very high                 | AMR priority pathogens for which licensed vaccines already exist | "Salmonella enterica ser. Typhi"  
"Streptococcus pneumoniae"  
"Haemophilus influenzae type b"  
"Mycobacterium tuberculosis" | Increase coverage of authorized vaccines in line with WHO immunization targets to maximise impact on AMR  
Accelerate the development of effective vaccines against TB. |
| High                      | AMR priority pathogens for which a vaccine candidate is in late-stage development (Phase 3) and vaccines would be suitable to target AMR infections caused by these priority pathogens in the coming years | "Extraintestinal pathogenic Escherichia coli (ExPEC)"  
"Salmonella enterica ser. Paratyphi A"  
"Neisseria gonorrhoeae"  
"Clostridioides difficile" | Accelerate the development of a vaccine for these pathogens |
| Moderate                  | AMR priority pathogens for which a vaccine candidate has either been identified in early clinical trials or been identified as a feasible vaccine target during expert review. Vaccines may be feasible solutions to target AMR infections, with moderate feasibility of vaccine development | "Enterotoxigenic Escherichia coli (ETEC)"  
"Klebsiella pneumoniae"  
"Non-typhoidal Salmonella"  
"Campylobacter spp."  
"Shigella spp." | Continue the development of a vaccine for these pathogens and expand knowledge of potential for vaccine impact and other tools to combat the AMR threat |
| Low                       | AMR priority pathogens for which no vaccine candidate has been identified in clinical development and therefore vaccines are not a feasible solution to target AMR infections in the foreseeable future, hence vaccine development feasibility is low | "Acinetobacter baumannii"  
"Pseudomonas aeruginosa"  
"Enterobacter spp."  
"Enterococcus faecium"  
"Staphylococcus aureus"  
"Helicobacter pylori" | Research and investment should explore alternative methods of control, including treatments and effective infection prevention, and should ensure access to clean water and adequate sanitation and hygiene facilities |
The vaccine development landscape in the context of AMR is multifaceted, with candidates against almost all pathogens in the WHO BPPL in early stages of development (preclinical) and with significantly fewer candidates in advanced stages of development (Table 45).

There are numerous scientific, technical and economic challenges to vaccine development for many of these pathogens (Fig. 8). Scientific challenges start in the preclinical phase where the process of target validation and proof of concept is complex and costly. Clinical assay determination and inter-individual biological variation bring additional complexity. Further to these challenges, the optimized vaccine candidate must be pure and delivered at a safe dose (potency), using an appropriate method of application, with an acceptable safety profile, in addition to having a stable shelf-life and being commercially viable.

For some pathogens, these challenges are so hard to overcome that other tools could be more appropriate for their management (Fig. 8). For example, *S. aureus* is a common commensal organism, which often colonizes human skin and for which antigen targets are unclear. Even though a large proportion of the population is exposed to *S. aureus* as a commensal, no lasting protective immune response is elicited. This adds to the biological challenge of developing a vaccine (13). Hence, multiple clinical trials have failed, and animal models have not been predictive of success. Another example is *E. faecium* which has a low biological feasibility for vaccine development as the extent of immunity from natural exposure is unknown and mechanisms of immunity are not fully understood (26).

In addition to the scientific challenges of vaccine development, there is also the long pathway for approval, which is often associated with uncertainty, high cost and financial risk. Lack of data on the long-term direct impact of the vaccines on populations adds to this uncertainty. Data is also needed on the impact of these vaccines on AMR emergence and burden, in the short and long term.

Mortality estimates have been established for many of the enteric pathogens with vaccine candidates in clinical trials, including ETEC, *Campylobacter* and *Shigella*. However, long term morbidity data, on stunting and cognitive impairment and data on the overall economic impacts, are also needed to support the value proposition for a vaccine and to encourage investment. Much of the disease burden is in LMICs. These markets are perceived to have limited commercial value by the private sector. Thus, investment is likely to require public and philanthropic funding support. Nonetheless, for some private investors, the lack of perceived return may be supplemented by more lucrative target product profiles (TPPs), including populations in HICs, such as MSM, travellers and military personnel. Some of these economic challenges could also be addressed through a multi-pathogen vaccine candidate which would increase the value proposition for a vaccine against enteric pathogens, as well as for *Salmonella* spp.

Many of the pathogens identified as priority due to AMR commonly cause hospital-acquired infections (HAIs), including *A. baumannii*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *E. faecium* and *Enterobacter* spp. The pathway to clinical development for vaccines against some of these pathogens is unclear (85) as large efficacy trials are likely to be required due to low disease incidence in target populations (12). In addition, target populations include critically ill patients, often with multiple co-morbidities and severely compromised immune systems. Many of these patients are also pre-treated with antibiotics and other medications. All of this makes the evaluation of clinical end points challenging (100, 101).

Identifying appropriate target populations and the timing of vaccine administration represent further challenges. Administering a vaccine to a critically ill patient at admission to an intensive care unit leaves limited time for an effective immunological response (105). Prophylactic use of a vaccine in advance of scheduled hospital procedures may be an alternative approach. However, there is currently no precedent nor evidence to support the use of prophylactic vaccines against HAIs in high-risk patients. Given the challenges of Phase 3 trials for vaccines against HAIs, alternative strategies may be useful to explore with regulatory authorities. For example, the use of correlates or surrogates of protection, and for the approved, the collection of post-licensure effectiveness data and real-world evidence. However, correlates of protection are lacking for most of these pathogens, and the clinical trial pathway to show proof of concept after Phase 1 and 2 is difficult.
Table 45. Vaccines and antibiotics in clinical development by pathogen and category.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>WHO Bacterial Priority Pathogens List</th>
<th>Vaccine development by Phase and licensed</th>
<th>Antibiotic development by phase and licensed since 20171</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii</td>
<td>Critical</td>
<td>Preclinical</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>Critical</td>
<td>Phase 1/2</td>
<td>Licensed US FDA 2017; EMA 2018</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>Critical</td>
<td>Preclinical</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>Critical</td>
<td>No vaccines in clinical/preclinical</td>
<td>Phase 3</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (ExPEC)</td>
<td>Critical</td>
<td>Phase 3</td>
<td>Phase 1</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (ETEC)</td>
<td>Critical</td>
<td>Phase 2b</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>High</td>
<td>Phase 3</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Campylobacter spp.</td>
<td>High</td>
<td>Preclinical</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>High</td>
<td>Phase 2</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Salmonella spp. (Typhi)</td>
<td>High</td>
<td>Licensed vaccine</td>
<td>No products in clinical development</td>
</tr>
<tr>
<td>Salmonella spp. (Paratyphi)</td>
<td>High</td>
<td>Phase 3</td>
<td>No products in clinical development</td>
</tr>
<tr>
<td>Salmonella spp. (non-typhoidal)</td>
<td>High</td>
<td>Phase 1</td>
<td>No products in clinical development</td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>High</td>
<td>No vaccines in clinical/preclinical</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>High</td>
<td>Preclinical</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>Medium</td>
<td>Phase 2</td>
<td>None</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Medium</td>
<td>Licensed vaccine</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Haemophilus influenzae, b</td>
<td>Medium</td>
<td>Licensed vaccine</td>
<td>Licensed US FDA 2019; EMA 2020</td>
</tr>
<tr>
<td>Clostridioides difficile</td>
<td></td>
<td>Phase 3</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td></td>
<td>Licensed vaccine</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

1 Information extracted from the WHO “2021 Antibacterial agents in clinical development and preclinical: an overview and analysis”. Licensed means since 1 July 2017. The Phase of development was that of November 2021. Some of these are developed as broad-spectrum to target more than one pathogen. If there was a pathogen specific antibiotic, it was included in the table instead of the broad-spectrum compound, despite the phase of development. The broad-spectrum antibiotics are: Cefiderocol for MDR Acinetobacter, and Enterobacterales, as well as Stenotrophomonas maltophilia (licensed US FDA (11/2019, cUTI); 9/21 HAP/VAP) EMA (4/2020)); Taniborbatam + cefepime for carbapenem-resistant Gram-negative bacilli (Phase 2); CAL02 for *S. pneumoniae, P. aeruginosa, A. baumannii, Enterobacterales, and S. aureus* (Phase 1); TRL1068 for both Gram-negative and Gram-positive bacteria (Phase 1); Rhu-pGSK for both Gram positive and Gram-negative bacteria (Phase 1/2); TRL1068 for Gram positive and Gram-negative bacteria biofilms (Phase 1/2); Lefamulin for *Streptococcus pneumoniae, methicillin-susceptible Staphylococcus aureus, Haemophilus influenzae, Legionella pneumophila, Mycoplasma pneumoniae, and Chlamy phila pneumoniae* (US FDA 18/2019 EMA 7/2020). In addition, it has activity against methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), multidrug-resistant *Neisseria gonorrhoeae, and Mycoplasma genitalium*.  

3. Discussion
**Fig. 8.** The feasibility of producing a vaccine as assessed by expert consultation. Scale from very low (1) to very high (5). See the "Methodology" section for a description of feasibility assessments and (26). It should be noted that ordering of pathogens by total score does not indicate total feasibility, as very low feasibility in one indicator may present a greater hurdle to further development than moderate scores throughout. Enterobacter spp. are not included in this analysis.

*A. baumannii* 1 refers to a vaccine against bloodstream infections; *A. baumannii* 2 is against hospital-acquired pneumonia. ExPEC 1 is against UTI; ExPEC 2 is against sepsis. *K. pneumoniae* 1 is a maternal vaccine to protect neonates; *K. pneumoniae* 2 is against hospital-acquired infections. *S. pneumoniae* 1 protects against at least 10 of the most common serotypes; *S. pneumoniae* 2 protects against all serotypes. *M. tuberculosis* 1 protects against active pulmonary TB; *M. tuberculosis* 2 protects against all forms of active TB. ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; M. tuberculosis; NTS: non-typhoidal *Salmonella*; spp.: species; TB: tuberculosis; UTI: urinary tract infection.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Advanced Candidates</th>
<th>Immunity from natural exposure</th>
<th>Understanding of immunity</th>
<th>Likelihood of protection against most strains</th>
<th>Overall Biological Feasibility</th>
<th>Animal models</th>
<th>In vitro assays</th>
<th>Ease of Clinical Development</th>
<th>Human challenge models</th>
<th>Overall Product Development Feasibility</th>
<th>Existing delivery systems</th>
<th>Commercial attractiveness</th>
<th>Clarity of licensure and policy decision</th>
<th>Ease of uptake</th>
<th>Overall Access &amp; Implementation Feasibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hib</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>3</td>
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<td>2</td>
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<td>S. Typhi</td>
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</tr>
<tr>
<td>ExPEC 2</td>
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<tr>
<td>H. pylori</td>
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<td>5</td>
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<tr>
<td>NTS</td>
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<td>Shigella spp.</td>
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<td>NA</td>
<td>5</td>
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<tr>
<td>Campylobacter spp.</td>
<td>4</td>
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</tr>
<tr>
<td>K. pneumoniae 1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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Finally, there are number of challenges unique to some pathogens/infection syndromes. For example, for commensal pathogens, such as *E. coli*, the effect of immunization on the composition of the microbiome and the consequences for health of such impacts are not well understood. For other pathogens, such as *C. difficile*, the role of the microbiome in disease progression is also poorly understood. Developing a toxin mediated vaccine for diarrhoeal disease or a vaccine to address UTI in an otherwise healthy individual, is likely to be different from developing a vaccine to address Gram-negative infections in immunocompromised hosts, where the immune response might be compromised, and infections may involve multiple pathogens.

Another example of unique challenges is the development of maternal vaccines. *K. pneumoniae* is associated with a high burden of neonatal sepsis in developing countries. For vaccine development against *K. pneumoniae*, clinical trials involving neonates are challenging, and commercial attractiveness is limited (37). Preclinical trials in animal models have shown that maternal vaccination may offer protection to neonates against Gram-negative bacteria, including *Klebsiella* spp., *E. coli* and *P. aeruginosa* (122). However, there are challenges associated with the lack of clinical trials in high-burden settings, as neonatal infections predominantly occur in lower resourced settings with weak health systems and non-lucrative markets for private investors (37). In HICs, data indicate that *K. pneumoniae* infections are most often hospital acquired and tend to affect a different sub-set of the population, including the elderly and immunocompromised. The lack of a clearly defined target population makes recruitment for clinical trials and the cost-effectiveness case for a vaccine challenging.

Despite these challenges, for many of the pathogens clustered into Group A in this analysis, a vaccine candidate could be possible. Vaccines already exist for four of the pathogens on the WHO BPPL and their impact on AMR is already established. These include PCVs against *S. pneumoniae*, TCVs against Typhoid, Hib vaccines against *H. influenzae* type b and BCG for *M. tuberculosis*. PCVs have dramatically reduced mortality in the USA and Europe in comparison to other regions, where the vaccine is not widely available and used. However, resistant *S. pneumoniae* continues to be one of six leading causes of deaths associated with AMR globally (5) and the number one cause of death due to any AMR infection in western sub-Saharan Africa (5). The development of vaccines against resistant pathogens is not enough to prevent the emergence of AMR and associated deaths. Ensuring vulnerable populations have access is also essential to save lives and prevent the further spread of AMR.

**FUTURE INNOVATION AND THE POTENTIAL OF mRNA VACCINES**

Innovation is occurring in the development of novel vaccines against AMR pathogens, but there are biological, clinical development-related and economic challenges which differ from one pathogen to another. While incentive-based policies might be needed for some vaccines, for others alternative interventions may be more appropriate.

One possibility for innovation is to employ the new mRNA vaccine technology, which can be either developed and scaled up to manufacture products faster than with conventional vaccines (123) and cost less to produce (124). In the present analysis only one mRNA vaccine candidate was identified against *M. tuberculosis*, however, further candidates using this technology are likely to emerge in the future.

Antigen expression of mRNA vaccines occurs in vivo, which removes the need for some costly and time-consuming manufacturing requirements associated with other vaccine platforms requiring in vitro expression (125). However, research is needed to improve the thermostability of mRNA vaccines, which currently require ultra-cold chain for long-term storage. Further research is also needed to incorporate multiple antigens into mRNA vaccines and assess safety in infants and children (125). In addition, the only currently licensed mRNA vaccines are against viral pathogens, further research is needed to understand if viable mRNA bacterial vaccines can be effective.
4. Conclusions

This report has identified the following four broad groups of pathogens in the WHO BPPL on basis of the preclinical and clinical development pipeline and assessments of vaccine development feasibility. There are vaccines already licensed against four priority pathogens for AMR (Group A) (S. enterica ser. Typhi, S. pneumoniae, Hib and M. tuberculosis). For these existing vaccines coverage should be increased to WHO immunization targets and optimised to reduce AMR, and the development of more effective vaccines against M. tuberculosis should be accelerated. Group B constitutes pathogens with vaccine candidates in late-stage clinical development (ExPEC, S. enterica ser. Paratyphi A, N. gonorrhoeae and C. difficile). Research on those vaccines currently in late clinical trials should be accelerated. Group C constitutes five pathogens for which vaccine candidates have moderate to high feasibility for vaccine development and most of these are in early clinical trials (ETEC, K. pneumoniae, NTS, Campylobacter spp. and Shigella spp.). There may be vaccines against these pathogens that become available in the long term, however, short term solutions to prevent resistance should focus on interventions other than vaccines. The remaining six pathogens from the WHO priority pathogens list represent Group D (A. baumannii, P. aeruginosa, Enterobacter spp., E. faecium, S. aureus, and H. pylori). These pathogens were found to have low feasibility for vaccine development due to biological and other product development challenges. Vaccines are not likely to be available for the foreseeable future against these pathogens and research is needed into alternative methods of AMR control.
5. Methodology

Scope

Pathogen scope

The pathogens included in this analysis were limited to the WHO BPPL (7), as well as *M. tuberculosis* and *C. difficile*, as used in prior WHO antibacterial pipeline analyses (126). Although other national lists identify further drug-resistant bacteria as priority threats according to local needs (127, 128), including Group A and Group B *Streptococcus*, these were outside the scope of the present analysis. This analysis focused on bacterial pathogens prioritized due to AMR. However, vaccines against viruses, parasites and fungi also have an impact on AMR by reducing consumption of antibiotics, a key driver of resistance (8).

A key difference between the mechanism of action for vaccines and antibiotics is that vaccines typically have a more specific target and may provide protection only against a specific serotype or strain of a pathogen; a single antibiotic may be effective against various bacterial species susceptible to the mode of action of the antibiotic. The WHO BPPL was designed to prioritize pathogens to guide R&D of new therapeutics rather than vaccines and considers pathogens by resistance, for example carbapenem-resistant *Enterobacterales*. For the purposes of tailoring this list to a vaccine-specific analysis, some of the pathogen groups in the WHO priority list have been sub-divided. The *Enterobacterales* have been split and condensed into the most encountered species: *K. pneumoniae*, *Enterobacter* spp., ETEC and ExPEC. Multiple serotypes exist among the *Salmonella* species with significantly different epidemiology and clinical presentation, presenting substantially different targets for vaccine development. Here, the most common serovars of *S. enterica* ser. Typhi, NTS serovars and *S. enterica* ser. Paratyphi A are considered. Of the *Shigella* species, *S. flexneri*, *S. sonnei* and *S. dysenteriae* were considered, each of which presents distinct antigenic targets for vaccination.

Inclusion/exclusion criteria

This report only considers novel vaccine candidates, unlicensed against the pathogen considered anywhere in the world. Clinical candidates in Phases 1 to 3 that were active or inactive/discontinued for which development occurred in the last 10 years were included. Novel adjuvants, dosing regimens or new combinations were not considered unless the formulation of the vaccine was changed. This particularly applies to BCG, where there are trials looking at booster vaccination and to some of the current clinical trials for *H. influenzae* and *S. pneumoniae*. Monoclonal antibodies or candidates for passive immunization were not included in this analysis; however, these are captured in the WHO antibacterial preclinical pipeline report (9).

Research on a candidate was considered to be active if any clinical development activity had taken place in the last 3 years, they were listed on the developer’s pipeline as active or they were confirmed to be active by consulted experts. Candidates were identified as inactive if no clinical development activity had been identified in the last 3 years or experts identified them as inactive. Candidates were labelled as discontinued if they were no longer listed in the industry development pipeline or the literature search or if the expert consultation indicated development had ceased. Inactive and discontinued candidates are listed separately to candidates currently in active development.

The preclinical pipeline considers vaccine candidates in late stages of active preclinical development and is a snapshot of some of the current research. The list is not exhaustive, as preclinical research is highly dynamic.
Search strategy

Clinical pipeline

Clinical trials

A search was performed of the International Clinical Trials Registry Platform (ICTRP), which includes clinical trial databases from Australia, Brazil, China, Cuba, Germany, European Union, India, Islamic Republic of Iran, Japan, Lebanon, New Zealand, Pan African Clinical Trial Registry, Peru, Thailand, The Netherlands, Republic of Korea, and Sri Lanka as primary registries and the USA (Clinicaltrials.gov) as a data provider. In addition, a search was conducted of clinicaltrials.gov, and Japanese and Russian databases in local languages. Industry repositories of clinical trials were also consulted.

Literature review

The report included data identified through a systematic review and analysis of grey literature. A search of PubMed included only papers written in English, from 2010 onwards. Search terms incorporated pathogen names as follows: ((vaccine) AND ((candidate) OR (pipeline) OR (research) OR (landscape))) AND (pathogen name) AND ((phase 1) OR (phase 2) OR (phase 3) OR (clinical)). Title and abstract were then screened for relevance before the full text articles were reviewed. Papers were scanned for clinical and preclinical vaccine candidates targeting the pathogens in scope. Data were extracted and cleaned to remove duplicates or entries that did not meet the inclusion criteria. The grey literature was consulted in the form of reports, documents and slides from Product Development for Vaccines Advisory Committee (PDVAC) meetings; reports, including Vaccines to tackle drug resistant infections by the Wellcome Trust (12), the Pew Charitable Trusts report (10) and the Access to Medicine Foundation’s benchmark report (11); the WHO tracker database (up to 2018) and any other grey literature referenced or suggested by experts. Data were also included from AdisInsight, accessible from the WHO Global Observatory on Health R&D, and the Dynamic Dashboard from the Global AMR R&D Hub.

Preclinical pipeline

A direct search of the literature was not performed for the preclinical pipeline. Candidates that emerged from the search processes outlined in the "Literature review" section for the clinical pipeline that were still in preclinical development were included in the preclinical pipeline. Candidates identified in the previous pipeline for antibacterial agents in clinical and preclinical development were also included (9).

A note on previous studies

The number of vaccine candidates in clinical development (61) identified in this report is similar to the 64 clinical-stage vaccine candidates against AMR pathogens cited in the 2018 Wellcome Trust report, although this did not include vaccines against C. difficile (12) and the timeframe was from 2013 to 2018. The report of the Pew Charitable Trusts found 10 vaccines in development against drug-resistant pathogens (10), and the AMR Industry Alliance reported 11 candidates (129). These differences are due to the broader scope of this report, which is not limited to members of the AMR Industry Alliance and includes all pathogens on the WHO priority list, in addition to C. difficile and M. tuberculosis, while Pew included only clinical candidates and did not include H. pylori or M. tuberculosis. Finally, the report has identified 50 vaccine candidates for which development was discontinued after clinical trials had started that are listed in this report as inactive candidates.

Data collection

The following data points were collected: pathogen, other pathogens targeted, candidate vaccine name, approach (live attenuated, mRNA, etc.), prophylactic / therapeutic, route of administration (oral / parenteral / nasal / other), clinical trial registry ID (relevant clinical trials in the last 10 years), non-exhaustive list of relevant publications (publication year, lead author and full publication link / PMID), activity status (active / inactive / discontinued).

For each candidate in clinical trials, where available the following data were gathered for the most recent clinical trial in the highest phase of development: registry link, trial status (open, recruiting; open, not recruiting / completed / terminated / withdrawn / unknown), developer name, sponsor location, sponsor type (academic / industry / government / other / unknown), Phase (1 / 2 / 2b / 3), study start date, completion date (anticipated or actual) and, for trials in Phase 3: age, enrolment size and location.
Feedback
A draft clinical and preclinical pipeline report was generated and shared for feedback with stakeholders across industry, academia, funding agencies, policymakers, and other experts. Comments were reviewed and incorporated into the final data set and report.

Limitations
This clinical and preclinical pipeline analysis was reliant on data available in the public domain or from the contacted experts. Although this was a global review, many regional databases and research hubs exist, and it is highly possible that products in clinical development have been missed. Targeted searches from Japan and the Russian Federation have attempted to broaden the search. This report does not attempt to present a complete picture of products in preclinical development as this space is highly dynamic. The preclinical pipeline relied on results from the searches performed specifically for the clinical pipeline, and it is possible some candidates may have been missed.

Not all data points could be found for every candidate entry, and unknowns have been left blank. In some cases data on the current state of development are limited, which may affect how accurately candidates are classified as active, inactive or discontinued.

Feasibility assessments
A full methodology and description of feasibility assessments is published and described here (26). The indicators and sub-indicators used to assess biological, product development, and access and implementation feasibility are shown in Table 1. These indicators and sub-indicators were rated very low, low, medium, high or very high by pathogen-specific experts, and associated scores from 1 (very low) to 5 (very high) were given. The indicators and thresholds for the indicators were developed by PATH, the London School of Hygiene & Tropical Medicine and the WHO Working Group on Vaccines and AMR. The assessments of feasibility were made by pathogen-specific experts. Although efforts have been made to align ratings by sharing a common methodology and agreed thresholds, there is inevitably a level of subjectivity. Different amounts of information are available for different pathogens and challenges differ, though synergies also exist.
References


6. How drug-resistant infections are undermining modern medicine – and why more research is needed now. London: Wellcome Trust; 2021.


