

Bacterial vaccines in clinical and preclinical development 2021

An overview and analysis



World Health
Organization

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2021 Bacterial vaccines in clinical and preclinical development: an overview and analysis

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Abbreviations

Ag	antigen	HICs	high-income countries
AMR	antimicrobial resistance	HKMS	heat-killed multi-serotype <i>Shigella</i> immunogens
BCG	Bacillus Calmette–Guérin	HLA	human leucocyte antigen
BMGF	Bill & Melinda Gates Foundation	HtrA	protease high temperature requirement A
CF	colonization factor	IATS	International Antigenic Typing Schema
CFA	colonization factor antigen	IAVI	International AIDS Vaccine Initiative
CgoX	coproporphyrinogen oxidase	ICMR	Indian Council of Medical Research
CHIM	Controlled Human Infection Model	ICU	intensive care unit
CJCV	capsule conjugate <i>Campylobacter</i> vaccine	IDRI	Infectious Disease Research Institute
CMV	cytomegalovirus	iNTS	invasive non-typhoidal <i>Salmonella</i>
COPS	Group D core + O-polysaccharide	IPD	invasive pneumococcal disease
COVID-19	coronavirus disease	IVI	International Vaccine Institute
CP, CPS	capsular polysaccharide	LMICs	low- and middle-income countries
CS	coli surface	LPS	lipopolysaccharide
dmLT	double-mutant <i>Escherichia coli</i> heat-labile toxin	LT	<i>Escherichia coli</i> heat-labile toxin
dPNAG	deacylated poly-N- β -(1-6)-acetylglucosamine	MAPS	multiple antigen presenting system
DT	diphtheria toxoid	MDR	multidrug-resistant
EPA	ExoProtein A; a detoxified form of <i>Pseudomonas aeruginosa</i> Exotoxin A	MEFA	multiepitope fusion antigen
ETEC	enterotoxigenic <i>Escherichia coli</i>	MIP	<i>Mycobacterium indicus pranii</i>
ExPEC	extraintestinal pathogenic <i>Escherichia coli</i>	MSM	men who have sex with men
FTA	fimbrial tip adhesin	Mtb	<i>Mycobacterium tuberculosis</i>
GAPDH	glyceraldehyde 3-phosphate dehydrogenase	MVA	modified Vaccinia virus Ankara
Gates MRI	Bill & Melinda Gates Medical Research Institute	NDA	New Drug Application
Gavi	Gavi, the Vaccine Alliance	NIAID	National Institute of Allergy and Infectious Disease
GGT	gamma-glutamyl transpeptidase	NICED	National Institute of Cholera and Enteric Diseases
GHIT	Global Health Innovative Technology Fund	NICHD	National Institute of Child Health and Human Development
GMMA	generalized modules for membrane antigens	NIH	National Institutes of Health
GVGH	GSK Vaccine Institute for Global Health	NIHCC	NIH Clinical Center
Hib	<i>Haemophilus influenzae</i> type B	NMRC	Naval Medical Research Center
		NOMVs	native outer membrane vesicles
		NRA	national regulatory authority
		NTS	non-typhoidal <i>Salmonella</i>

OMP	outer membrane protein	virG	<i>Shigella</i> outer membrane protein essential for bacterial spreading
OMV	outer membrane vesicle	WHO	World Health Organization
PBPV	protein-based pneumococcal vaccine	WHO SAGE	WHO Strategic Advisory Group of Experts on Immunization
PCV	pneumococcal conjugate vaccine	WHO BPPL	WHO Bacterial Priority Pathogens List
PDVAC	Product Development for Vaccines Advisory Committee	WRAIR	Walter Reed Army Institute of Research
Pephyd	peptidoglycan hydrolase		
PPrV	pneumococcal protein vaccine		
PSSP-1	pan- <i>Shigella</i> surface protein 1		
PPSV	pneumococcal polysaccharide vaccine		
R&D	research and development		
rBCG	recombinant BCG		
rTSST-1v	recombinant toxic shock syndrome toxin-1 variant		
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2		
SEB	staphylococcal enterotoxin B		
ser.	serovar		
spp.	species		
SSI	Staten Serum Institute		
SsIE	secreted and surface-associated lipoprotein from <i>Escherichia coli</i>		
ST	<i>Escherichia coli</i> heat-stable toxin		
TB	tuberculosis		
TBVI	TuBerculosis Vaccine Initiative		
TCV	typhoid conjugate vaccine		
TLR	toll-like receptor		
TPI	triose-phosphate isomerase		
TPP	target product profile		
TPV	typhoid polysaccharide vaccine		
TT	tetanus toxoid		
UPEC	uropathogenic <i>Escherichia coli</i>		
US FDA	US Food and Drug Administration		
UTI	urinary tract infection		
Vi	capsular virulence antigen		
ViPS	Vi polysaccharide		

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).

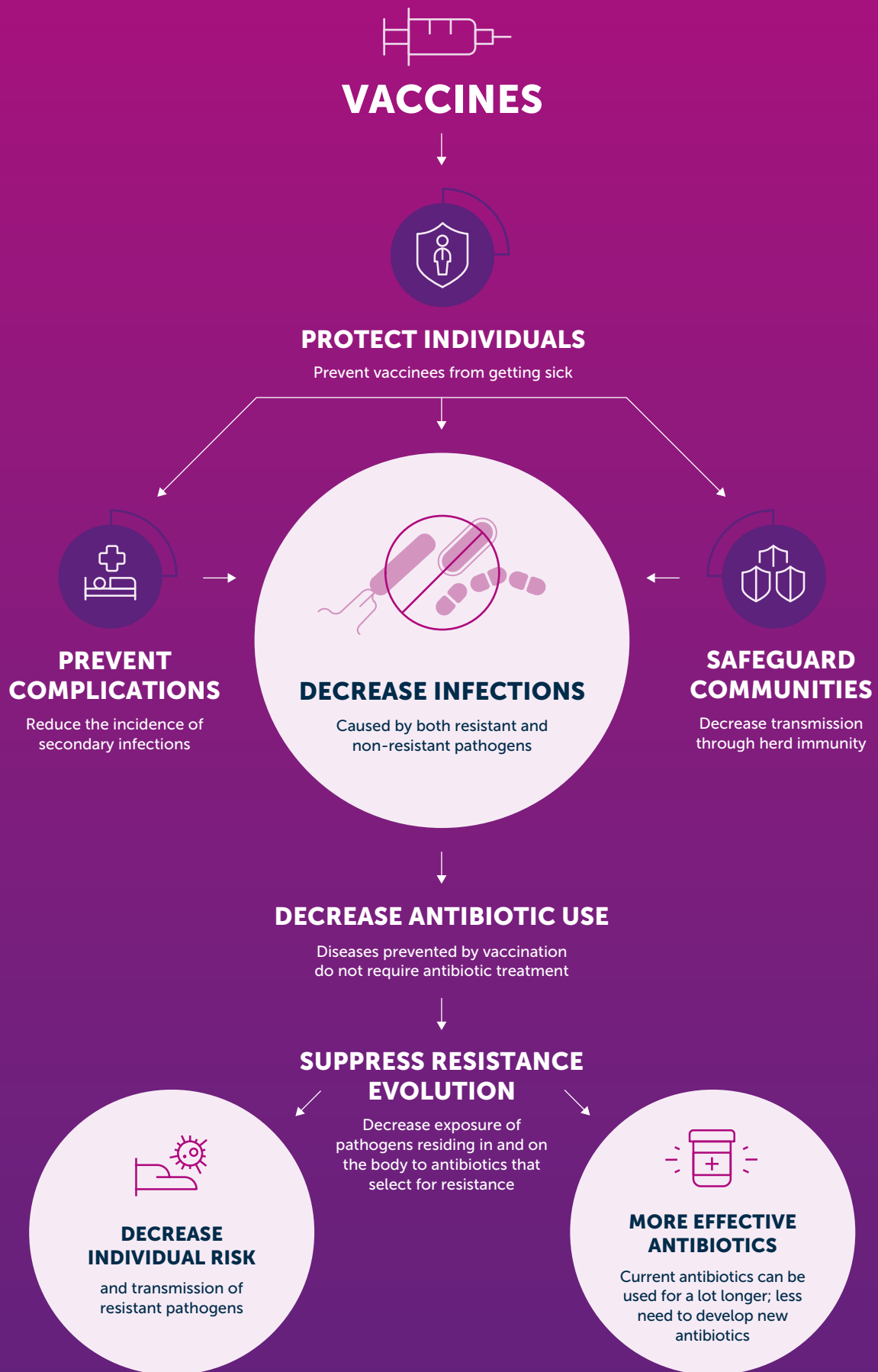
The challenge of AMR is not limited to the threat that we are running out of effective treatments for infectious diseases. AMR also compromises other modern medical procedures that rely on effective control of secondary infections, including surgery, organ transplants and treatment for HIV, liver and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

FIG 1. MECHANISMS OF VACCINE IMPACT ON AMR (8).



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	 Product Development Feasibility	 Access and Implementation Feasibility
<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • 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.

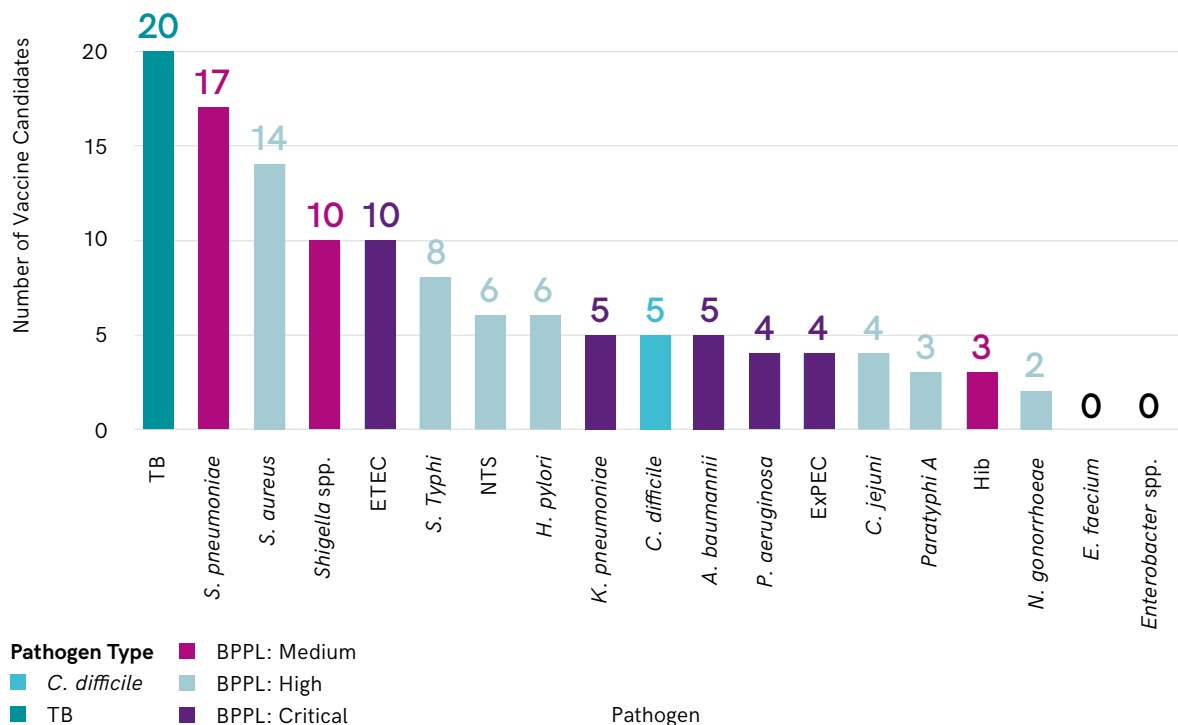


Fig. 3. (a) Total number of candidates in active clinical development by pathogen.

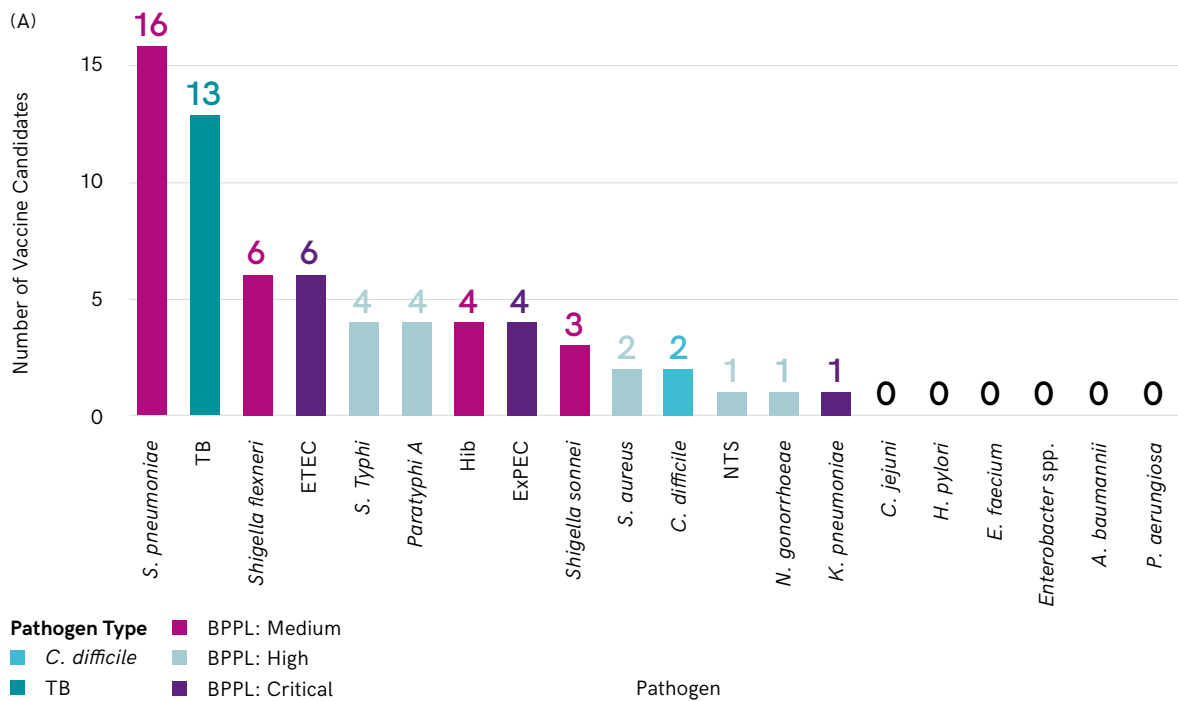
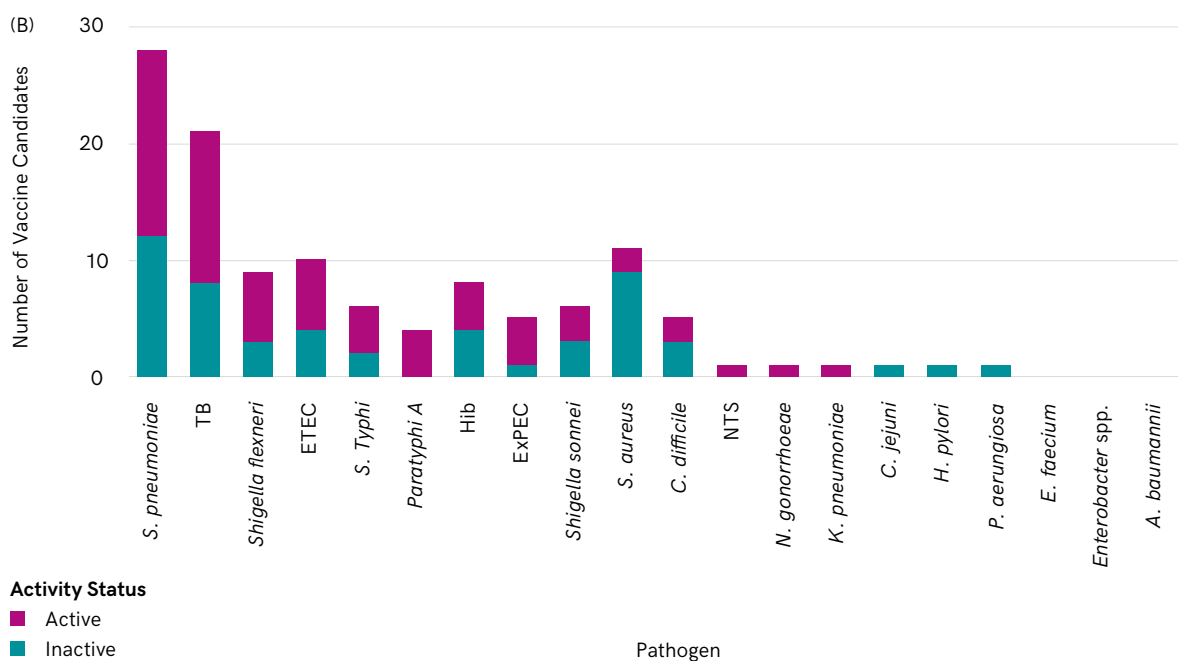


Fig. 3. (b) Total number of candidates both in active clinical development and that have become inactive or discontinued over the last 10 years, by pathogen. Note that some vaccine candidates are double counted here as they target more than one pathogen. Pathogen type refers to status as defined by the 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

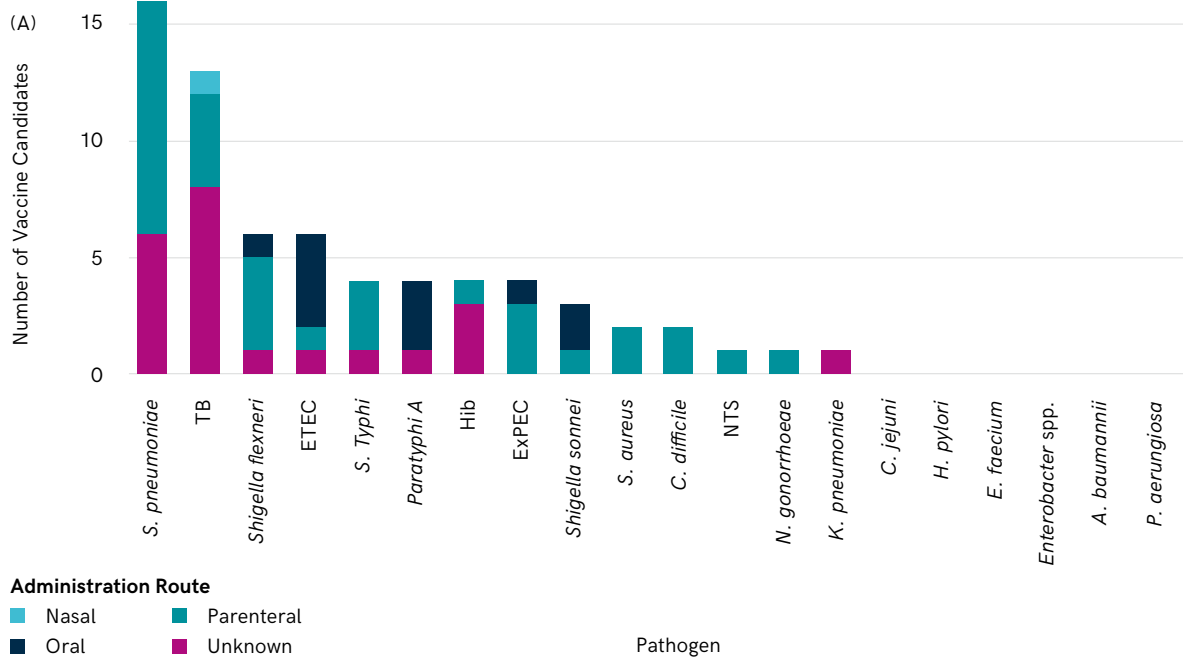
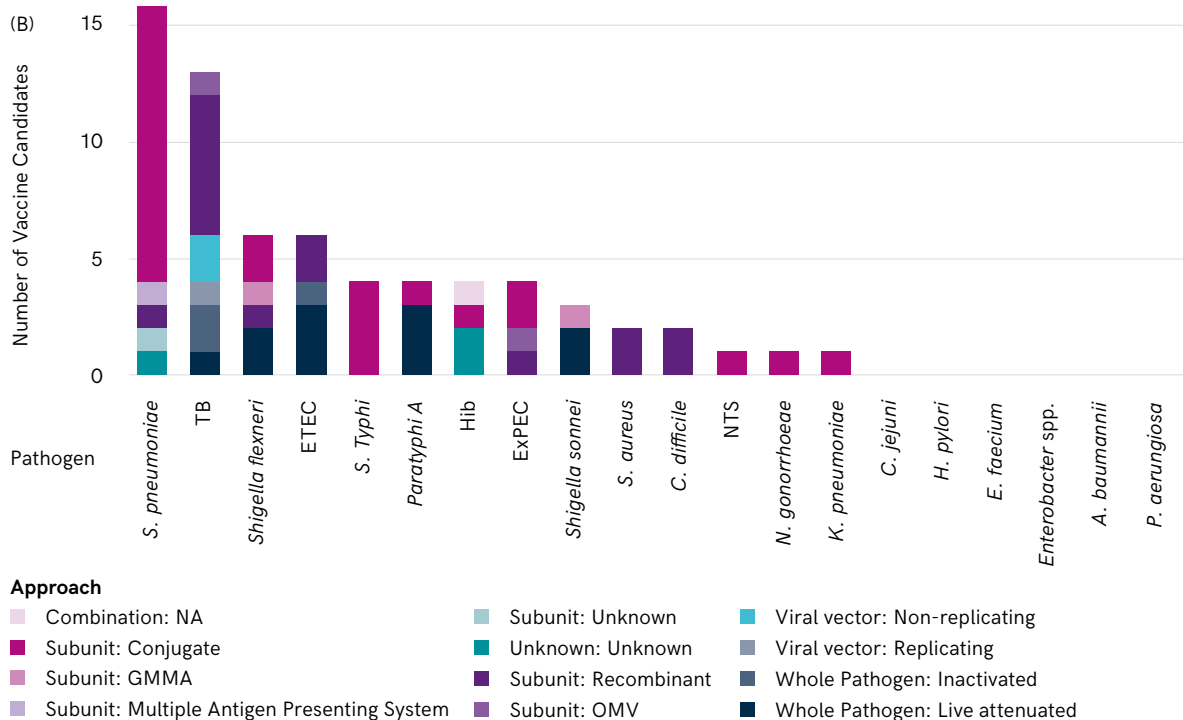


Fig. 5. (b) Total number of candidates in active clinical development, by pathogen and approach. The approach is split into two levels; the first level describes whether the vaccine candidate approach is subunit, viral vector or whole pathogen and the following description describes more specifically 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.



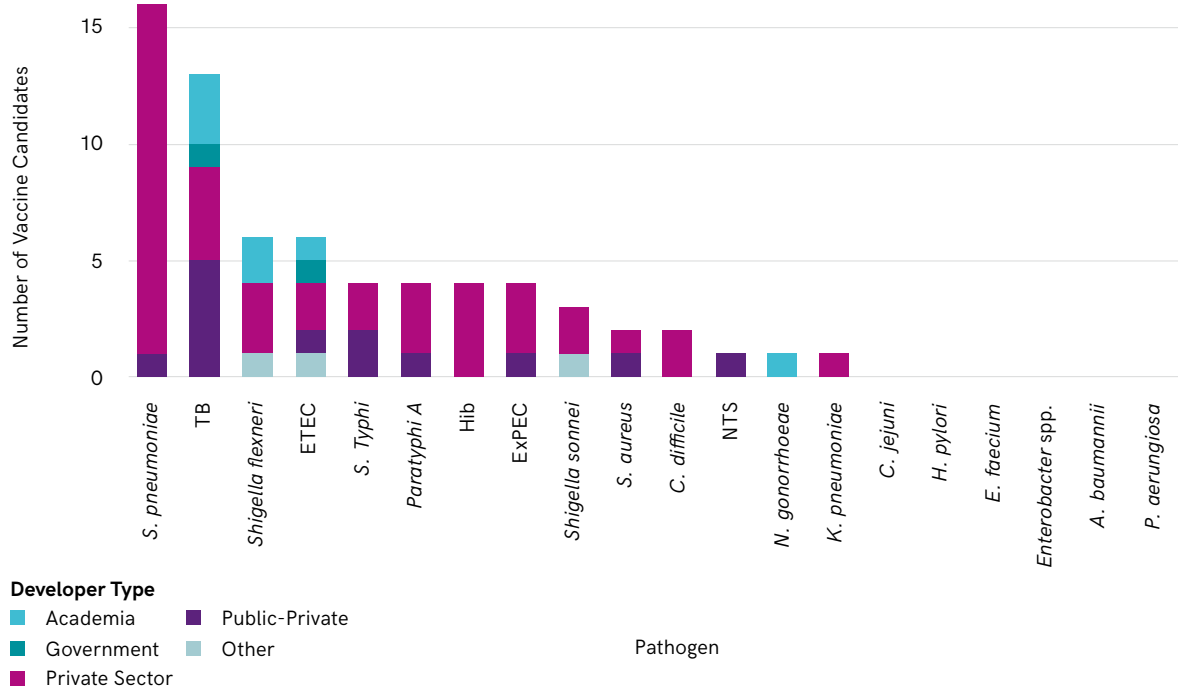
The broader picture of investment is shown in Fig. 3b, which shows both active and inactive or discontinued candidates. As previously mentioned, currently there are no candidates in clinical development against *Shigella dysenteriae*, *H. pylori*, and the critical priority pathogen, *P. aeruginosa*. 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.

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.



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 *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.

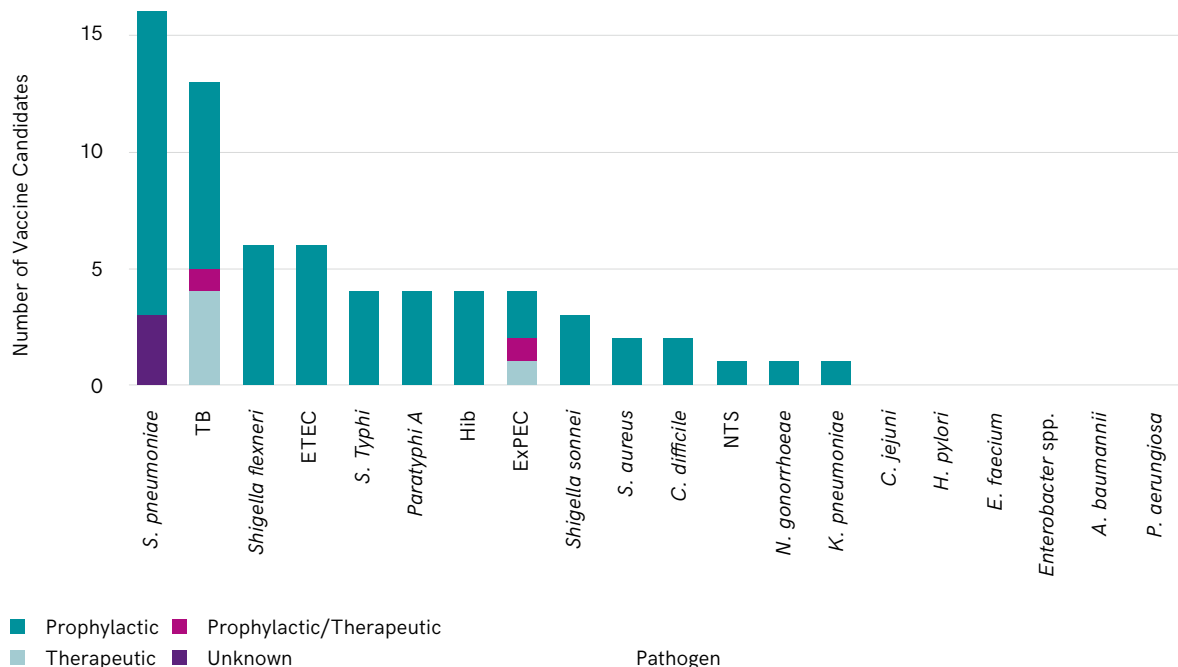
Developers

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 *M. tuberculosis*, ETEC, *S. enterica* ser. Paratyphi A, NTS, *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.

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 *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; Hib: *Haemophilus influenzae* type b; NTS: non-typhoidal *Salmonella*; TB: tuberculosis.



Vaccines being developed against WHO bacterial priority pathogens

Group A: Pathogens with licensed vaccines

Salmonella enterica ser. Typhi

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

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 2. Preclinical development pipeline for *Salmonella enterica* ser. Typhi.

Candidate vaccine	Target pathogen(s)	Approach	Developer	Sponsor type	Country of sponsor	Activity status
iNTS-TCV	<i>Salmonella enterica</i> ser. Typhi and Typhimurium	Subunit; conjugate	GVGH	Private sector	Italy	Active
Trivalent conjugate vaccine	<i>S. enterica</i> ser. Typhi, Typhimurium and Enteritidis	Subunit; conjugate. Trivalent conjugate vaccine building on SK Bioscience Vi-DT vaccine.	SK Bioscience	Private sector	Republic of Korea	Active
iNTS-GMMA	<i>S. enterica</i> ser. Typhi, Typhimurium and Enteritidis	Subunit; conjugate; GMMA. Three-component vaccine based on iNTS-GMMA and TCV.	GVGH	Private sector	Italy	Active
Vi-PsaA-PdT	<i>S. enterica</i> ser. Typhi	Subunit; conjugate	Harvard Medical School	Academic	USA	Active
O:2,12-DT + Vi-DT	<i>S. enterica</i> ser. Typhi and Paratyphi A	Subunit; conjugate. O:2 of <i>S. enterica</i> ser. Paratyphi A conjugated to diphtheria toxoid (O:2-DT), with an adpic acid dihydrazide linker.	International Vaccine Institute	Private sector	Republic of Korea	Active
O:2,12-CRM197 + Vi-CRM197	<i>S. enterica</i> ser. Typhi and Paratyphi A	Subunit; conjugate. Two surface polysaccharide antigens, Vi and O:2, targeting <i>S. enterica</i> ser. Typhi and Paratyphi A, respectively, each conjugated individually to CRM197, the mutant diphtheria toxin protein.	Biological E.; GVGH	Private sector	India; Italy	Active
<i>S. enterica</i> ser. Typhi and Paratyphi vaccine	<i>S. enterica</i> ser. Typhi and Paratyphi A	Bivalent vaccine	University of Oxford	Academic	United Kingdom	Active
Recombinant Ty21a typhoid vaccine expressing <i>Shigella</i> LPS	<i>S. enterica</i> ser. Typhi, <i>Shigella sonnei</i> and <i>S. flexneri</i>	Whole pathogen; live attenuated. Chimeric vector. <i>Salmonella enterica</i> ser. Typhi Ty21a construct comprising a <i>Shigella sonnei</i> O-antigen biosynthetic gene region.	Protein Potential	Private sector	USA	Active

DT: diphtheria toxoid; GVGH: GSK Vaccine Institute for Global Health; iNTS: invasive non-typhoidal *Salmonella*; GMMA: generalized modules for membrane antigens; LPS: lipopolysaccharide; PsaA-PdT: fusion protein PsaA-PdT; ser.: serovar; TCV: typhoid conjugate vaccine; TPV: typhoid polysaccharide vaccine; Vi: virulence factor.

Table 3. **Clinical development pipeline** for vaccine candidates actively undergoing clinical trials against *Salmonella enterica* ser. Typhi.

Candidates actively undergoing clinical trials									
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
EuTCV	<i>Salmonella enterica</i> ser. Typhi	Subunit; conjugate Vi-TT	Prophylactic	Parenteral	EuBiologics	Private sector	Republic of Korea	3	NCT04830371
Vi-DT (27, 28)	<i>S. enterica</i> ser. Typhi	Subunit; conjugate	Prophylactic	Parenteral	PT Bio Farm; Indonesia University; SK Bioscience; BMGF/IVI	Private sector	Indonesia; Philippines; USA; Republic of Korea	3	NCT04051268 NCT04204096
Typhoid Vi conjugate vaccine	<i>S. enterica</i> ser. Typhi	Subunit; conjugate	Prophylactic		CNBG; Sinopharm	Private sector	China	3	
Entervax (previously M01ZH09) (29)	<i>S. enterica</i> ser. Typhi and Paratyphi A	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 flagella) from <i>S. enterica</i> ser. Paratyphi A (ZH9PA).	Prophylactic	Oral	Prokarium	Private sector	United Kingdom	2b	NCT01405521
CVD 1000	<i>S. enterica</i> ser. Typhi, Typhimurium and Enteritidis	Subunit; conjugate. Trivalent conjugate vaccine (<i>S. enterica</i> ser. Enteritidis conjugate - Group D core + O-polysaccharide (COPS) linked to Enteritidis Phase 1 flagellin. <i>S. enterica</i> ser. Typhimurium conjugate - Group B COPS linked to Typhimurium Phase 1 flagellin. <i>S. enterica</i> ser. Typhi Vi-TT conjugate - ViPS linked to tetanus toxoid (Tybpar TCV).	Prophylactic	Parenteral	Bharat Biotech; CVD; University of Maryland	Private sector	India; USA	1	NCT03981952â

BMGF/IVI: Bill & Melinda Gates Foundation/International Vaccine Institute; CNBG: China National Biotec Group; DT: diphtheria toxoid; LPS: lipopolysaccharide; O PS: O-polysaccharide; ser.: serovar; TCV: typhoid conjugate vaccine; TT: tetanus toxoid; Vi, ViPS: virulence factor capsular polysaccharide.

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

Candidates no longer under active development or discontinued									
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/ therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
TyphETEC-ZH9 typhoid-LT/ ST toxoid	<i>S. enterica</i> ser. Typhi and ETEC	Subunit; toxoid. ZH9 typhoid vectoring LT/ST toxoid and CF/CS antigens.	Prophylactic		Prokarium	Private sector	United Kingdom	1	
Typhvax (30)	<i>S. enterica</i> ser. Typhi	Subunit; protein capsular matrix	Prophylactic	Parenteral	Matrivax	Private sector	USA	1	NCT03926455

BMGF/IVI: Bill & Melinda Gates Foundation/International Vaccine Institute; CNBG: China National Biotec Group; DT: diphtheria toxoid; LPS: lipopolysaccharide; O PS: O-polysaccharide; ser.: serovar; TCY: typhoid conjugate vaccine; TT: tetanus toxoid; V₁, VIPS: virulence factor capsular polysaccharide.

***Haemophilus influenzae* type b**

Vaccines in development	Preclinical: 3, Phase 1: 1; Phase 2: 0; Phase 3: 3
Potential target population	1-12 months
Biological feasibility	Very high
Product development feasibility	Very high
Access and implementation feasibility	Very high

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 5. Preclinical development pipeline for *Haemophilus influenzae* type b.

Candidate vaccine	Approach	Developer	Sponsor type	Country of sponsor	Activity status
DTcP-Hib (<i>Haemophilus influenzae</i> type b) combo vaccine and MCV2-Hib combination vaccine	Subunit; conjugate	CanSino	Private sector	China	Active
Hib vaccine	Unknown	Wellstat Therapeutics	Private sector	USA	Active
Hib vaccine	Unknown	HanaVax	Private sector	Japan	Active

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.

Candidates actively undergoing clinical trials								
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
Shan 6	Hib	Paediatric hexavalent vaccine	Prophylactic	Unknown	Sanofi Pasteur	Private sector	France	3 NCT04429295
Freeze-dried <i>Haemophilus influenzae</i> type b (Hib) combined vaccine	Hib		Prophylactic	Unknown	Beijing Zhifei Lvzhu Bio-pharmaceutical	Private sector	China	3 Chi-CTR20-00032281
MT-2355 (BK1310)	Hib	Subunit; conjugate	Prophylactic	Parenteral	Mitsubishi Tanabe Pharma	Private sector	Japan	3 NCT03891758
LBVD	Hib	DTP-HepB-IPV-Hib vaccine	Prophylactic	Unknown	LG Chem	Private sector	Republic of Korea	1 NCT04429295

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.

Candidates no longer under active development or discontinued								
Candidate vaccine	Approach	Prophylactic/ therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
<i>Haemophilus influenzae</i> type b (Hib) conjugate vaccine	Subunit, conjugate	Prophylactic	Parenteral	Jiangsu Province Center for Disease Control and Prevention; Chengdu Olymvox Biopharmaceuticals	Private sector	China	3	NCT01732198
VN-0105	Paediatric pentavalent vaccine	Prophylactic	Unknown	Sanofi; Kitasato; Daiichi Sankyo	Private sector	Japan	3	
Hib vaccine (Bio Farma), single shot	Immunostimulants	Prophylactic	Parenteral	PT Bio Farma	Private sector	Indonesia	3	NCT01986335
Investigational Hib vaccine (NU300)	Subunit, conjugate	Prophylactic	Unknown	Nuron Biotech	Private sector	USA	2	NCT01732198

Streptococcus pneumoniae

Vaccines in development	Preclinical: 17; Phase 1: 4; Phase 2: 8; Phase 3: 4
Potential target population	<p>1-12 months for the existing vaccine, or a vaccine with improved efficacy against invasive pneumococcal disease, lobar pneumonia and acute otitis media could be extended to 1-59 months.</p> <p>The target population could also include older adults with underlying comorbidities such as chronic lung disease.</p> <p>In high-income countries (HICs), such as the USA, Pfizer's Prevnar 20 is recommended for adults aged 65 and older and adults aged 19-64 with certain risk conditions.</p>
Biological feasibility	<p>Covering 10 major serotypes: very high</p> <p>Covering all major serotypes: medium</p>
Product development feasibility	<p>Covering 10 major serotypes: medium</p> <p>Covering all major serotypes: low</p>
Access and implementation feasibility	<p>Covering 10 major serotypes: medium</p> <p>Covering all major serotypes: medium</p>

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*.

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

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*.

Candidates actively undergoing clinical trials									
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
23-Valent pneumococcal polysaccharide vaccine (PPSV23)	<i>S. pneumoniae</i>	Subunit	Unknown	Parenteral	Beijing Zhifei Lvzhu Bio-pharmaceutical	Private sector	China	3	NCT04278248
15-Valent pneumococcal conjugate vaccine (PCV)	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Parenteral	Beijing Zhifei Lvzhu Bio-pharmaceutical	Private sector	China	3	NCT04357522
14-Valent PCV (adsorbed)	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Parenteral	Biological E.	Private sector	India	3	
13-Valent PCV	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Parenteral	Beijing Minhai Biotechnology	Private sector	China	3	NCT02494999
ASP3772	<i>S. pneumoniae</i>	Subunit; pneumococcal MAPS vaccine	Prophylactic	Parenteral	Affinivax; Astellas Pharma	Private sector	USA; Japan	2	NCT03803202
Multivalent PCV	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Unknown	LG Chem	Private sector	Republic of Korea	2	NCT03467984
Polyvalent PCV V116	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Unknown	Merck Sharp & Dohme	Private sector	USA	2	NCT04168190
Nucovac	<i>S. pneumoniae</i>	Subunit; conjugate 11-valent PPSV	Prophylactic	Parenteral	Panacea Biotech	Private sector	India	2	CTRI/2013/05/003711
Pneumococcal recombinant protein vaccine (PPrV) (35)	<i>S. pneumoniae</i>	Protein-based pneumococcal vaccine; trivalent protein vaccine carrying combined recombinant proteins PcpA, PhtD and PlyD1	Prophylactic	Parenteral	Sanofi Pasteur	Private sector	France	2	NCT01446926
SP0202, SKYPAC	<i>S. pneumoniae</i>	Subunit; next generation conjugate vaccine	Prophylactic	Parenteral	Sanofi Pasteur; SK Bioscience; SK Chemical	Private sector	France; Republic of Korea	2	NCT04583618 NCT04398706
15-Valent PCV	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Parenteral	Tergene Biotech; Aurobindo Pharma	Private sector	India	2	CTRI/2019-02-017527

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

PF-06842433	<i>S. pneumoniae</i>	Unknown	Prophylactic	Unknown	Pfizer	Private sector	USA	2 EudraCT 2020-005039-59
13-Valent PCV	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Unknown	CanSino	Private sector	China	1 NCT04100772
Protein-based pneumococcal vaccine (PBPV)	<i>S. pneumoniae</i>	PBPV	Prophylactic	Parenteral	CanSino; Henan Center for Disease Control and Prevention	Private sector	China	1 NCT04087460
13-Valent PCV	<i>S. pneumoniae</i>	Subunit; conjugate	Unknown	Unknown	China National Biotec Group (CNBG)	Private sector Private sector	China	1
euPCV15	<i>S. pneumoniae</i>	Subunit; conjugate	Unknown	Unknown	EuBiologics	Private sector	Republic of Korea	1 NCT04830358

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

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

Candidates no longer under active development or discontinued									
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
GEN-004, SP0148, 1912, 2108	<i>S. pneumoniae</i>	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.	Unknown	Unknown	Genocea Biosciences	Private sector	USA	3	NCT01995617
PCV7 (VCN7-T)	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Intramuscular	Biomolecular Chemistry Center (CQB)	Academic	Cuba	2/3	RPCCEC0000-182

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

dPly (pneumolysin)/ PHdW/PHID-CV (GSK2189242A)	<i>S. pneumoniae</i>	Subunit conjugate. PHID-CV: 10-valent PCV (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F)	Unknown	Intramuscular	GSK	Private sector	United Kingdom	2 NCT00307528
Pneumo Nexgen multivalent pneumococcal conjugate vaccine (PCV20)	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Parenteral	Pfizer	Private sector	USA	2 NCT03550313
IC47	<i>S. pneumoniae</i>	Subunit; recombinant/purified protein vaccine (PcsB, StkP, PsaA)	Unknown	Intramuscular	Valneva Austria; PATH	Private sector	Austria; USA	1 NCT00873431
RASV (recombinant avirulent <i>S. enterica</i> ser. Typhi)	<i>S. pneumoniae</i>	Whole cell; recombinant attenuated <i>Salmonella enterica</i> ser. Typhi vaccine vectors producing <i>Streptococcus pneumoniae</i> PspA	Prophylactic	Oral	Arizona State University	Academic	USA	1 NCT01033409
PCV13a	<i>S. pneumoniae</i>	Subunit; conjugate	Prophylactic	Parenteral	Beijing Chaoyang District Centre for Disease Control and Prevention	Other	China	1 NCT02544698
AV0328	<i>S. aureus</i> , <i>S. pneumoniae</i>	dPNAG conjugated to TT	Prophylactic	Parenteral	Alopecx Vaccine	Private sector	USA	1/2 NCT02853617
<i>S. pneumoniae</i> whole cell vaccine + Alum (SPWCV)	<i>S. pneumoniae</i>	Whole pathogen; inactivated	Prophylactic	Parenteral	PATH; Intercell; Novartis	Private sector	USA; United Kingdom; Austria	1/2 NCT02543892
PhuBiovax	<i>S. pneumoniae</i>	Vaccine containing multiple protein antigens. Mutated the pneumococcal toxin, pneumolysin, of <i>S. pneumoniae</i> serotype 4 TIGR4 strain into a nontoxic form.	Prophylactic	Parenteral	ImmunoBiology; Simbec Research; Oxford Therapeutics Consulting; ORION Clinical Services	Private sector	United Kingdom	1 NCT02572635
Pneumococcal vaccine programme	<i>S. pneumoniae</i>	Unknown	Unknown	Unknown	Instituto Butantan	Academic	Brazil	1
Bioconjugate pneumococcal vaccine	<i>S. pneumoniae</i>	Multivalent polysaccharide	Prophylactic	Unknown	LimmaTech Biologics	Private sector	Switzerland	1 NCT03030976

PpSV: pneumococcal polysaccharide vaccine; TLR: toll-like receptor; TT: tetanus toxoid

Mycobacterium tuberculosis

Vaccines in development	Preclinical: 20; Phase 1: 2; Phase 2: 7; Phase 3: 4
Potential target population	<ol style="list-style-type: none"> 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) (45). 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) (46). 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) (47). 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 (CTRI/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 11. Preclinical development pipeline for Mycobacterium tuberculosis.

Candidate vaccine	Approach	Developer	Sponsor type	Country of sponsor	Activity status
Tuberculosis (TB) vaccine	Unknown	EpiVax	Private sector	USA	Active
GI-19000 TB vaccine	Unknown	GlobalImmune	Private sector	USA	Active
T-BioVax	Unknown	ImmBio	Private sector	United Kingdom	Active
Lipovax-Fg115-TB	Unknown	Lipotek	Private sector	Australia	Active
Lipovax-FliC-TB	Unknown	Lipotek	Private sector	Australia	Active
TB research programme	Unknown	Longhorn Vaccines and Diagnostics	Private sector	USA	Active
Therapeutic MDR TB programme	Unknown	TheraVectys	Private sector	France	Active
TVI-Tuberculosis-1	Unknown	TVAX Biomedical	Private sector	USA	Active
MTbuVax	Unknown	Vaxil Bio	Private sector	Israel	Active
TB vaccine	Unknown	Greffex	Private sector	USA	Active
TB vaccine	RNA-based therapeutics	Janssen; Synthetic Genomics	Private sector	Belgium	Active
TB vaccine	Unknown	HanaVax	Private sector	Japan	Active
H107	Unknown	SSI; TBVI	Other	Denmark	Active
CysVac2/Ad	Unknown	University of Sydney; TBVI	Academic	Australia	Active
MVA Multivac	Unknown	Transgene; TBVI	Private sector	France	Active
BCG-ZMP1	Unknown	University of Zurich; TBVI	Academic	Switzerland	Active
BCG, ChAdOx/MVA PPE15-85A	Unknown	University of Oxford; TBVI	Academic	United Kingdom	Active
TB vaccine	mRNA-based vaccine	BioNTech	Private sector	Germany	Active
PDS0201	Versamune platform with bacillus <i>M. tuberculosis</i> antigens	PDS Biotechnology	Private sector	USA	Active
CMV-TB	Unknown	Vir Biotechnology	Private sector	USA	Active

BCG: Bacillus Calmette-Guérin; CMV: cytomegalovirus; MDR: multidrug-resistant; MVA: modified Vaccinia virus Ankara; SSI: Staten Serum Institute; TB: tuberculosis; TBVI: TuBerculosis Vaccine Initiative.

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

Candidates actively undergoing clinical trials							
Candidate vaccine	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
VPM 1002 (rBCG)	Recombinant BCG (BCG Δ ureC::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.	Prophylactic	Intradermal	Serum Institute of India; VPM; IAVI; Biofabri; Universidad de Zaragoza	Private sector	India; Germany	3 NCT04351685
Immuvac (MIP)	Heat-killed <i>Mycobacterium indicus pranii</i> vaccine	Prophylactic	Intradermal	ICMR; Cadila Pharmaceuticals	Public-private	India	3 CTRI/2019/01/017026
RUTI	Inactivated partial target organism, i.e. cell wall fragments of <i>M. tuberculosis</i> (Mtb) formulated in a liposome suspension.	Therapeutic	Intramuscular	University Medical Center Groningen	Academic	Netherlands	2b NCT02711735
H56:IC31 (47)	Recombinant subunit; adjuvanted fusion protein consisting of three highly immunogenic Mtb 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.	Therapeutic	Parenteral	SSI; IAVI	Private sector	Global	2b NCT03512249
M72/AS01E (originally GSK TB vaccine 692342 [later M72])	Recombinant subunit; fusion protein expressing two immunogenic Mtb 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.	Prophylactic	Intramuscular	GSK; IAVI; Gates MRI	Private sector	USA; United Kingdom	2b NCT01755598
DAR-901 booster	Heat inactivated non-Mtb, killed whole cell	Prophylactic	Intradermal	University of Dartmouth Hitchcock Medical Center; IAVI; GHIT	Academic	USA	2b NCT02712424
ChadOx1.85A MVA 85A (AERAS 485, MVA 85A-IMX-313)	Viral vectored vaccine	Prophylactic	Parenteral	University of Oxford	Academic	United Kingdom; Uganda	2a NCT03681860

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

MTBVAC	Live, attenuated target organism. Genetically modified Mtb clinical isolate with deletions of the <i>phoP</i> gene, needed to control the transcription of key Mtb virulence genes, permitting its survival in host cells; and the <i>fadD26</i> gene, required for the synthesis of cell surface lipids that play a critical role in Mtb pathogenicity (includes ESAT6 and CFP10).	Prophylactic	Intradermal	IAVI; Biofabri; TBVI; Universidad de Zaragoza	Private sector	Global	3 NCT04975178
ID93 + GLA-SE (45)	Recombinant subunit; fusion of four Mtb antigens: Rv1813, an antigen upregulated under hypoxic conditions; Rv2608, the PPE protein, probably associated with the Mtb outer membrane; Rv3619 and Rv3620, included in the Esx protein family of secreted virulence factors.	Prophylactic/therapeutic	Parenteral	Quratis; IDRI	Private sector	USA	2a NCT03806686
GamTBvac	Recombinant subunit vaccine containing dextran-binding domain-modified Ag85a and ESAT6-CFP10 MTB antigens and CpG ODN adjuvant with dextrans.	Prophylactic	Subcutaneous	Ministry of Health, Russia		Russia	3 NCT04975737
TB/Flu-04L	Live recombinant influenza-vectored TB vaccine expressing antigens Ag85A and ESAT-6.	Therapeutic	Intranasal	Research Institute for Biological Safety Problems; Research Institute of Influenza	Academic	Kazakhstan	2 NCT02501421
TB/Flu-04L AdHu5Ag85A (Ad5 Ag85A)	Viral vectored vaccine	Prophylactic	Nasal	McMaster; CanSino	Industry	China; Canada	1 NCT02337270
AEC/BC02	Recombinant subunit	Prophylactic	Intradermal	AnHui Zhifei Longcom Biologic Pharmacy	Private sector	China	1b NCT04239313

BCG: *Bacillus Calmette-Guérin*; Gates MRI: Bill & Melinda Gates Medical Research Institute; GHIT: Global Health Innovative Technology Fund; IAVI: International AIDS Vaccine Initiative; ICMR: Indian Council of Medical Research; MIP: *Mycobacterium indicus pranii*; MVA: modified Vaccinia virus Ankara; ODN: oligodeoxynucleotide; PPE: proline-proline-glutamate protein; rBCG: recombinant BCG; SSI: Staten Serum Institute; TB: tuberculosis; TBVI: Tuberculosis Vaccine Initiative; TLR: toll-like receptor.

Table 13. **Clinical development pipeline** for vaccine candidates no longer under active development against *Mycobacterium tuberculosis*.

Candidates no longer under active development or discontinued							
Candidate vaccine	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
AERAS-422	Recombinant BCG; rBCG over-expressing TB antigens Ag85A, Ag85B and Rv3407, and expressing mutant perfringolysin.	Prophylactic	Intradermal	Aeras Global TB Vaccine Foundation	Other	USA	1 NCT01340820
GX-70	DNA vaccine	Therapeutic	Intramuscular	Yonsei University	Academic	Republic of Korea	1 NCT03159975
Ag85B-ESAT-6 + IC31	Adjuvanted TB subunit vaccine	Prophylactic	Intramuscular	SSI	Academic	Denmark	1 NCT01049282
H4:IC31 (AERAS-404)	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).	Prophylactic	Parenteral	Aeras; SSI; Sanofi-Pasteur; Intercell	Private sector	USA	2 NCT02378207 NCT01861730
MVA85A + BCG	Recombinant viral vector	Prophylactic	Parenteral	Aeras; University of Oxford	Academic	United Kingdom; USA	2 NCT01650389
Tubivac (V7) (49)	Heat-inactivated <i>Mycobacterium vaccae</i>	Therapeutic	Oral	Immunitor	Private sector	Canada	3 NCT01977768
H1-IC31 (ESAT-6, Ag85B) (47)	Protein subunit	Prophylactic/therapeutic	Parenteral	SSI	Academic	USA	2 PACTR20140-3000464306 DoH-27-0612-3947
KCMC-001 (HVJ-E/HSP65 DNA + IL-12 DNA vaccine)	DNA vaccine	Therapeutic	Parenteral	National Hospital Organization, Ibaraki Higashi Hospital	Academic	Japan	1 JPRN-jRCT20-53190023

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)

Vaccines in development	Preclinical: 4; Phase 1: 1; Phase 2: 2; Phase 3: 1
Potential target population	<ol style="list-style-type: none"> 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 Uro-Vaxom 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).

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

ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; SsIE: 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).

Candidates actively undergoing clinical trials						
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Phase
ExPEC9V	ExPEC	Subunit; conjugate. Nine-valent O-polysaccharide conjugate vaccine.	Prophylactic	Parenteral	Johnson & Johnson	3 NCT04899336
UTI Vx, FimH vaccine (FimCH) (55)	ExPEC	Subunit; recombinant. FimH, a bacterial adhesin protein, and TLR4 agonist as adjuvant.	Therapeutic	Parenteral	Sequoia Sciences	2
Uro-Vaxom (OM-89) (56, 57)	ExPEC	Subunit; OMV. Bacterial vaccine containing 6 mg heat-inactivated <i>E. coli</i> membrane glycoproteins derived from 18 different strains.	Prophylactic/therapeutic	Oral	Vifor Pharma; OM Pharma; Buckinghamshire Healthcare NHS Trust	2 NCT02591901
ExPEC10V (VAC52416, JNJ-69968054)	ExPEC	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 <i>P. aeruginosa</i> .	Prophylactic	Parenteral	Johnson & Johnson	1/2 NCT03819049 NCT04306302

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).

Candidates no longer under active development or discontinued						
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Phase
ExPEC4V (JNJ-63871860)	ExPEC	Subunit; conjugate. Four-valent O-polysaccharide conjugate vaccine	Prophylactic	Parenteral	Johnson & Johnson	2 NCT02546960

ExPEC: extraintestinal pathogenic *Escherichia coli*.

Salmonella enterica ser. Paratyphi A

Vaccines in development	Preclinical: 4; Phase 1: 1; Phase 2: 1; Phase 3: 1
Potential target population	1–59 months in endemic settings
Biological feasibility	Medium
Product development feasibility	Medium
Access and implementation feasibility	Medium

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 17. Preclinical development pipeline for *Salmonella enterica* ser. Paratyphi A.

Candidate vaccine	Target pathogen(s)	Approach	Developer	Sponsor type	Country of sponsor	Activity status
O:2, 12-DT + Vi-DT	<i>Salmonella enterica</i> ser. Paratyphi A and Typhi	Subunit; conjugate. O:2 of <i>S. enterica</i> ser. Paratyphi A conjugated to diphtheria toxoid (O:2-DT), with an adipic acid dihydrazide linker.	International Vaccine Institute	Private sector	Republic of Korea	Active
O:2, 12-CRM197 + Vi-CRM197	<i>S. enterica</i> ser. Paratyphi A and Typhi	Subunit; conjugate. Two surface polysaccharide antigens, Vi and O:2, targeting <i>S. enterica</i> ser. Typhi and <i>S. enterica</i> ser. Paratyphi A, respectively, each conjugated individually to CRM197, the mutant DT protein.	Biological E., GVGH	Private sector	India; Italy	Active
<i>Salmonella enterica</i> ser. Typhi and Paratyphi vaccine	<i>S. enterica</i> ser. Paratyphi A and Typhi	Bivalent vaccine	University of Oxford	Academic	United Kingdom	Active
<i>S. enterica</i> ser. Paratyphi A	<i>S. enterica</i> ser. Paratyphi A	Subunit; Conjugate. OPS-Nanoparticle conjugate	KJ Biosciences	Private sector	USA	Active

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									
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
O:2,12-TT	<i>S. enterica</i> ser. Paratyphi A	Subunit; conjugate	Prophylactic		Lanzhou Institutes of Biological Products	Private sector	China	3	
Entervax (previously M01ZH09) (29)	<i>S. enterica</i> ser. Paratyphi A and Typhi	Whole pathogen; live attenuated. Typhi ZH9 plus an engineered derivative providing an immune response to the key antigens (LPS O:2 and Hi:a flagella) from <i>S. enterica</i> ser. Paratyphi A (ZH9PA).	Prophylactic	Oral	Prokarium	Private sector	United Kingdom	2b NCT01405521	
CVD 1902 (VASP: Vaccine against <i>S. enterica</i> ser. Paratyphi A) (59)	<i>S. enterica</i> ser. Paratyphi A	Whole pathogen; live attenuated strain with two independently attenuating mutations in guaBA and clipX.	Prophylactic	Oral	University of Oxford; University of Maryland; Bharat Biotech	Academic	United Kingdom; USA; India	1 NCT01129453	

LPS: lipopolysaccharide; TT: typhoid toxin.

Candidates no longer under active development or discontinued: None

Neisseria gonorrhoeae

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

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*.

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

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

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

Candidates actively undergoing clinical trials								
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
4CMenB (Bexsero)	<i>N. gonorrhoeae</i>	Subunit; conjugate	Prophylactic	Parenteral	Kirby Institute	Academic	China Australia	3 NCT04415424

Candidates no longer under active development or discontinued: None

Clostridioides difficile

Vaccines in development	Preclinical: 5; Phase 1: 1; Phase 2: 0; Phase 3: 1
Potential target population	Adults over 45 years of age
Biological feasibility	Medium
Product development feasibility	Low
Access and implementation feasibility	Low

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*.

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

MAPS: multiple antigen presenting system.

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

Candidates actively undergoing clinical trials							
Candidate vaccine	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
PF-06425090 (+/- adjuvant) (62-64, 68)	Subunit; recombinant toxin; genetically and chemically detoxified TcdA and TcdB toxins	Prophylactic	Parenteral	Pfizer	Private sector	USA	3 NCT03090191
GSK2904545A +/- adjuvant AS01B (CDIFF Ag - GSK)	Subunit; recombinant protein F2 antigen	Prophylactic	Parenteral	GSK	Private sector	United Kingdom	1 NCT04026009

Ag: antigen.

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

Candidates no longer under active development or discontinued							
Candidate vaccine	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
ACAM-CDIFF	Subunit; toxoid. Chemically detoxified TcdA and TcdB.	Therapeutic	Parenteral	Sanofi Pasteur	Private sector	France	3 NCT01887912
VLA84 (IC84)	Subunit; recombinant. Recombinant chimeric protein linking the binding domains of TcdA and TcdB.	Prophylactic	Parenteral	Valneva Austria	Private sector	Austria	2 NCT02316470
CDVAX	Recombinant spores of the bacterium <i>Bacillus subtilis</i> that have been engineered to display an antigen which is part of TcdA	Prophylactic	Oral	Royal Holloway University	Academic	United Kingdom	1 NCT02991417

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)

Vaccines in development	Preclinical: 10; Phase 1: 4; Phase 2: 2; Phase 3: 0
Potential target population	6–24 months old in endemic countries and international travellers
Biological feasibility	Medium
Product development feasibility	High
Access and implementation feasibility	Medium

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 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 24. Preclinical development pipeline for Enterotoxigenic *Escherichia coli* (ETEC).

Candidate vaccine	Target pathogen(s)	Approach	Developer	Sponsor type	Country of sponsor
Paragon Novel Vaccine	<i>S. aureus</i> , ETEC, ExPEC	Subunit. Peptide-based candidate vaccine, elicits bacterial GAPDH-specific blocking antibodies to protect the host from infection.	Immunethep; Merck	Private sector	Portugal; USA
ETEC vaccine	ETEC	Unknown	Hilleman Laboratories	Private sector	India
MecVax (Multi-Epitope Antigen [MEFA] vaccine)	ETEC	Subunit; toxoid. Tag-less toxoid fusion 3xStaN12S-mnLTR192G/L211A and CFA/II/IV MEFA induce neutralizing antibodies to seven adhesins (CFA/I, CST-1-CS6) and both enterotoxins (LT, STa) of ETEC	University of Illinois; Johns Hopkins University	Academic	USA
LT/ST toxoids	ETEC	Subunit; conjugate	ENTVAC Consortium; GLOBVAC; STOPENTERICS; PATH	Academic	Global
Fimbrial tip adhesins	ETEC	Unknown	NMRC; PATH	Other	USA
ETEC vaccine	ETEC	Subunit; conjugate. ST/LT toxoid (fusion, conjugate or vectored).	University of Bergen	Academic	Norway
ETEC vaccine	ETEC	Subunit; recombinant. Mix of conserved ETEC antigens: EtpA and EatA.	Washington University School of Medicine	Academic	USA
<i>Campylobacter</i> /ETEC vaccines	<i>C. jejuni</i> , ETEC	Unknown	Immuron; Naval Medical Research Centre	Private sector	Australia
Glycoconjugate vaccine	<i>C. jejuni</i> , ETEC, <i>S. flexneri</i>	Subunit; glycoconjugate	NMRC; WRAIR	Other	USA
Glycoprotein-based candidate	ETEC, ExPEC	Subunit; conjugate. Conserved YghJ (SsIE) shared by UPEC and ETEC.	GlyProVac	Private sector	Denmark

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 25. **Preclinical development pipeline** for vaccine candidates actively undergoing clinical trials against Enterotoxigenic *Escherichia coli* (ETEC).

Candidates actively undergoing clinical trials									
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
ETVAX/dmLT; ETVAX (OEV-122); ETVAX (OEV-123); ETVAX (OEV-121); (OEV-124) (69)	Enterotoxigenic <i>Escherichia coli</i> (ETEC)	Whole cell; inactivated four <i>E. coli</i> strains overexpressing the most prevalent colonization factors (CFs) (CFA/I, CS3, CS5 and CS6) and a hybrid LTB/CTB toxoid administered with dmLT enterotoxin as both an immunogen and an adjuvant.	Prophylactic	Oral	Scandinavian Biopharma; Gothenburg University; United Medix Laboratories; Oy Medfiles; University of Helsinki; University of Virginia	Private sector	Sweden; Finland; USA	2b PACTR202010819218562	
Phase 1: CfaE + mLT (ID); CssBA + dmLT; Phase 2: CfaE + mLT (74)	ETEC	Subunit; recombinant (fimbrial and non-fimbrial) targeting CFA/I (dscCfaE) and CS6 (CssBA) using modified <i>E. coli</i> LT enterotoxin LTR192G or LTR192/L211A.	Prophylactic	Parenteral	NMRC; US Army Surgeon General; PATH	Private sector	USA	2 NCT01922856	
<i>Shigella</i> -ETEC	ETEC, <i>S. sonnei</i> , <i>S. flexneri</i>	Whole pathogen; live attenuated <i>Shigella</i> vaccine expressing ETEC antigens.	Prophylactic	Unknown	Emergent Biosolutions	Private sector	USA	Phase 1 Not yet registered	
ShigEETEC (75, 76)	ETEC, <i>S. sonnei</i> , <i>S. flexneri</i>	Whole pathogen; live attenuated vaccine. Attenuated by mutation to the LPS antigen and invasion proteins.	Prophylactic	Oral	EveliQure Biotechnologies	Private sector	Austria	1 EudraCT: 2020-000248- 79	
CVD 31000 (CVD 1208S-122)	ETEC, <i>S. flexneri</i>	Whole pathogen; live attenuated <i>S. flexneri</i> 2a expressing ETEC antigens.	Prophylactic	Oral	University of Maryland	Academic	USA	1 NCT04634513	
dmLT (LTR192G/ L211A) (77)	ETEC	Subunit; recombinant dmLT enterotoxin (R192G/L211A).	Prophylactic	Oral	NIAID	Other	USA	1 NCT03548064	

CTB: 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; mLT: 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).

Candidates actively undergoing clinical trials									
Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
ETEC vaccine	ETEC	Unknown	Unknown	Unknown	EuBiologics	Private sector	Republic of Korea	3	
VLA1701	ETEC	Whole pathogen; inactivated. Inactivated <i>Vibrio cholerae</i> and recombinant cholera toxin B subunit.	Prophylactic	Oral	Valneva Austria; Johns Hopkins University; NMRC.	Private sector	Austria	2 NCT03576183	
ACE527-102 (71)	ETEC	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.	Prophylactic	Oral	TD Vaccines; Pierrrel Research USA; Johns Hopkins University	Private sector	USA	2 NCT01060748 NCT01739231	
TyphETEC-ZH9 typhoid-LT/ST toxoid	ETEC, <i>Salmonella enterica</i> ser. Typhi	Subunit; toxoid. ZH9 typhoid vectoring LT/ST toxoid and CF/CS antigens.	Prophylactic	Unknown	Prokarium	Private sector	United Kingdom	1	

CTB: 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; mLT: mutant LT; NIAID: National Institute of Allergy and Infectious Diseases; NMRC: Naval Medical Research Center; O-Ag: O-antigen.

Klebsiella pneumoniae

Vaccines in development	Preclinical: 5; Phase 1: 1; Phase 2: 0; Phase 3: 0
Potential target population	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
Biological feasibility	Maternal immunization: low Patient immunization: medium
Product development feasibility	Maternal immunization: medium Patient immunization: medium
Access and implementation feasibility	Maternal immunization: medium Patient immunization: medium

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*.

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

LPS: lipopolysaccharide; MAPS: multiple antigen presenting system.

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

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

Candidates no longer under active development or discontinued

Non-typhoidal *Salmonella*

Vaccines in development	Preclinical: 5; Phase 1: 1; Phase 2: 0; Phase 3: 0
Potential target population	1–59 months in endemic settings
Biological feasibility	Medium
Product development feasibility	Medium
Access and implementation feasibility	High

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*.

Candidate vaccine	Target pathogen(s)	Approach	Developer	Sponsor type	Country of sponsor	Activity status
iNTS-TCV vaccine	<i>S. enterica</i> ser. Typhi and Typhimurium	Subunit; conjugate	GSK	Private sector	Italy	Active
Trivalent conjugate vaccine	<i>S. enterica</i> ser. Typhi, Typhimurium and Enteritidis	Subunit; conjugate. Trivalent conjugate vaccine building on SK Bioscience Vi-DT vaccine.	SK Bioscience	Private sector	Republic of Korea	Active
iNTS-GMMA and TCV	<i>S. enterica</i> ser. Typhi, Typhimurium and Enteritidis	Subunit; conjugate. Three-component vaccine based on iNTS-GMMA and TCV.	GSK	Private sector	Italy	Active
CVD 1944 (derived from <i>S. enterica</i> ser. Enteritidis) and CVD 1931 (derived from <i>S. enterica</i> ser. Typhimurium) (86)	<i>S. enterica</i> ser. Typhimurium and Enteritidis	Whole pathogen; live attenuated	University of Maryland	Academic	USA	Active
OmpD (87)	<i>S. enterica</i> ser. Typhimurium	Subunit; recombinant	University of Birmingham	Academic	United Kingdom	Active

DT: diphtheria toxoid; GMMA: generalized modules for membrane antigens; GVGH: 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*.

Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
CVD 1000	<i>S. enterica</i> ser. Typhi, <i>S. enterica</i> ser. Typhimurium and <i>S. enterica</i> ser. Enteritidis	Trivalent conjugate vaccine (S. <i>enterica</i> ser. Enteritidis conjugate – Group D core + O PS (COPS) linked to Enteritidis Phase 1 flagellin. <i>S. enterica</i> ser. Typhimurium conjugate – Group B COPS linked to Typhimurium Phase 1 flagellin. <i>S. enterica</i> ser. Typhi Vi-TT conjugate – ViPS linked to tetanus toxoid (Tybbar TCV).	Prophylactic	Parenteral	Bharat Biotech; CVD; University of Maryland	Private sector	India; USA	1 NCT03981952

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.**

Vaccines in development	Preclinical: 4; Phase 1: 0; Phase 2: 0; Phase 3: 0
Potential target population	Infants of 6–12 months and international travellers
Biological feasibility	Medium
Product development feasibility	High
Access and implementation feasibility	Medium

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.

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

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.

Candidate vaccine	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
CJCV	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.	Prophylactic	Parenteral	NMRC; WRAIR	Government	USA	1 NCT02067676

CJCV: capsule conjugate *Campylobacter* vaccine; CPS: capsular polysaccharide; GYGH: 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.

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

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. ShigE_{TEC}, 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 33. Preclinical development pipeline for *Shigella* spp.

Candidate vaccine	Target pathogen(s)	Approach	Developer	Sponsor type	Country of sponsor	Activity status
Glycoconjugate vaccine	<i>Campylobacter jejuni</i> , ETEC, <i>S. flexneri</i>	Subunit; glycoconjugates	NMRC; WRAIR	Other	USA	Active
DB Fusion. Serotype-independent <i>Shigella</i> vaccine candidate	<i>S. sonnei</i> , <i>S. flexneri</i>	Subunit; DB Fusion and adjuvant. Fusion protein of two Type III secretion system antigens, invasion plasmid antigens B (Ipa B) and D (Ipa D).	PATH; Oklahoma State University	Other	USA	Active
ShigOraVax	<i>S. sonnei</i> , <i>S. flexneri</i>	Whole pathogen; inactivated	European Vaccine Initiative; Leiden University Medical Center; Group de Recherche Action en Santé; Centre for Infectious Disease Research in Zambia; University of Gothenburg; Hilleman Laboratories	Private sector	Germany; Netherlands; Burkina Faso; Zambia; Sweden; India	Active
34 kDa OMP	<i>S. flexneri</i>	Subunit; OMP	NICED	Academic	India	Active
Truncated mutant	<i>S. sonnei</i> , <i>S. flexneri</i> , <i>S. dysenteriae</i>	Whole pathogen; truncated <i>Shigella</i> targets OMP for universal <i>Shigella</i> vaccine	IVI	Other	Republic of Korea	Active
OMV Sfl2a	<i>S. flexneri</i>	Subunit; OMV	University of Navarra	Academic	Spain	Active
PSSP-1	<i>S. sonnei</i> , <i>S. flexneri</i> , <i>S. dysenteriae</i>	Subunit; OMV	IVI	Other	Republic of Korea	Active
HKMS	<i>S. sonnei</i> , <i>S. flexneri</i> , <i>S. dysenteriae</i>	Whole pathogen; inactivated. Heat-killed multi-serotype <i>Shigella</i> immunogens.	NICED	Academic	India	Active
Ty21a typhoid vaccine expressing <i>Shigella</i> LPS	<i>Salmonella enterica</i> ser. Typhi, <i>Shigella flexneri</i> , <i>S. sonnei</i>	Whole pathogen; live attenuated. Chimeric vector. <i>Salmonella enterica</i> ser. Typhi Ty21a construct comprising a <i>Shigella sonnei</i> O-Ag biosynthetic gene region.	Protein Potential	Private sector	USA	Active
<i>S. flexneri</i> 2a and <i>S. sonnei</i> conjugate	<i>S. sonnei</i> , <i>S. flexneri</i>	Subunit; conjugate	ZFSW	Private sector	China	Active

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.

Candidates actively undergoing clinical trials									
Vaccine candidate	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase	
GlycoShig3 (SF2a-TT15) (96)	<i>Shigella flexneri</i>	Subunit; glycoconjugate recombinant. Functional oligosaccharide mimic of O-Ag, the bacterial OMP, coupled to TT.	Prophylactic	Parenteral	Pasteur Institute	Academic	France	2	NCT04602975
WRSS2/WRSS3 (VirG series) (97)	<i>S. sonnei</i>	Whole cell; live attenuated. WRSS2 and WRSS3; virG based.	Prophylactic	Oral	WRAIR; NIAID	Other	USA	2	NCT04242264
Shigella-E TEC	E TEC, <i>S. sonnei</i> , <i>S. flexneri</i>	Whole pathogen; live attenuated <i>Shigella</i> vaccine expressing ETEC antigens.	Prophylactic	Unknown	Emergent Biosolutions	Private sector	USA	1	Not yet registered
ShigE TEC (75, 76)	E TEC, <i>S. sonnei</i> , <i>S. flexneri</i>	Whole pathogen; live attenuated, mutation to the LPS antigen and invasion proteins.	Prophylactic	Oral	EveliQure Biotechnologies	Private sector	Austria	1	EudraCT: 2020-000248-79
CVD 31000 (CVD 1208S-122)	E TEC, <i>S. flexneri</i>	Whole pathogen; live attenuated. <i>S. flexneri</i> 2a expressing ETEC antigens.	Prophylactic	Oral	University of Maryland	Academic	USA	1	NCT04634513
InvaplexAR; InvaplexAR-DETOX (98)	<i>S. flexneri</i>	Subunit; recombinant. <i>Shigella</i> LPS and the Type 3 secretion system proteins (Ipa B, Ipa C).	Prophylactic	Parenteral	WRAIR; PATH	Other	USA	1	NCT03869333
Shigella4V (GSK4069327A) (94, 98)	<i>S. flexneri</i>	Subunit; bioconjugate vaccine alone or in combination with adjuvant (aluminium hydroxide). Covers O-Ag polysaccharides from <i>S. flexneri</i> 2a, 3a and 6.	Prophylactic	Parenteral	GlycoVaxyn; LimmaTech Biologics; GSK	Private sector	United Kingdom; Switzerland	1	NCT02388009
Multivalent <i>Shigella</i> GMMA	<i>S. flexneri</i> , <i>S. sonnei</i>	Subunit; GMMA	Prophylactic	Parenteral	GVGH	Private sector	Italy	1 / 2	NCT05073003

GMMA: generalized modules for membrane antigens; GVGH: GSK Vaccine Institute for Global Health; O-Ag: O-antigen; OMP: outer membrane protein; TT: tetanus toxoid; virG: *Shigella* outer membrane protein essential for bacterial spreading.

Table 35. **Clinical development pipeline** for vaccine candidates no longer under active development against *Shigella* spp.

Candidates no longer under active development or discontinued							
Candidate vaccine	Approach	Prophylactic/ therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
Flexyn2a	Bioconjugate vaccine alone or in combination with adjuvant (aluminium hydroxide). Covers O-Ag polysaccharides from <i>Shigella sonnei</i> , <i>S. flexneri</i> 2a, 3a and 6.	Prophylactic	Parenteral	GlycoVaxyn; LimmaTech Biologics; GSK	Private sector	United Kingdom; Switzerland	2b NCT02646371
WRSS1	Live, attenuated vaccine; virG-based	Prophylactic	Oral	WRAIR; PATH	Other	USA	2 NCT01813071
CVD 1208S, CVD 1208 (92)	Whole pathogen; live attenuated. guaBA based.	Prophylactic	Oral	University of Maryland	Academic	USA	2 NCT00866242 NCT00866476
Sf2aWC + dmLT (94)	Whole pathogen; inactivated <i>S. flexneri</i> 2a killed vaccine	Prophylactic	Oral	PATH	Other	USA	2 NCT03038243
1790GAHB, GSK3902986A/ GSK3536852A (99)	Subunit; GMMMA. <i>S. sonnei</i> O-Ag.	Prophylactic	Parenteral	GVGH	Private sector	Italy	2 NCT03527173 NCT02676895
O-SPC/BRU	Subunit; conjugate	Prophylactic	Intramuscular	Eunice Kennedy Shriver NICHD; NIHCC	Academic	USA	1 NCT01369927 NCT01399424
GVXN SD133	Subunit; conjugate. <i>S. dysenteriae</i> bioconjugate alone or in combination with aluminium hydroxide	Prophylactic	Parenteral	GlycoVaxyn; LimmaTech Biologics	Private sector	Switzerland	1 NCT01069471

dmLT: double-mutant heat-labile; O-Ag: O-antigen; GMMMA: generalized modules for membrane molecules; GVGH: GSK Vaccine Institute for Global Health; virG: *Shigella* outer membrane protein essential for bacterial spreading; NICHD: National Institute of Child Health and Human Development; NIHCC: National Institutes of Health Clinical Center.

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

Acinetobacter baumannii

Vaccines in development	Preclinical: 5; Phase 1: 0; Phase 2: 0; Phase 3: 0
Potential target population	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
Biological feasibility	Low
Product development feasibility	Medium
Access and implementation feasibility	Low

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*.

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

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*.

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

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*.

Candidate vaccine	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Name of developer	Phase clinical trial registration number	Activity status
VLA43 (IC43)	<i>Pseudomonas aeruginosa</i>	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-OprF190-342-OprI21-83).	Prophylactic	Oral or nasal	Valneva	2/3 NCT01563263	Discontinued

OMP: outer membrane protein.

Candidates actively undergoing clinical trials: None

Enterobacter spp.

Vaccines in development	Preclinical: 0; Phase 1: 0; Phase 2: 0; Phase 3: 0
Potential target population	NA*
Biological feasibility	NA*
Product development feasibility	NA*
Access and implementation feasibility	NA*

*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

Vaccines in development	Preclinical: 0; Phase 1: 0; Phase 2: 0; Phase 3: 0
Potential target population	Patients in intensive care, immunocompromised individuals, patients with comorbidities and patients with foreign bodies
Biological feasibility	Low
Product development feasibility	Medium
Access and implementation feasibility	Low

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

Vaccines in development	Preclinical: 14; Phase 1: 1; Phase 2: 1; Phase 3: 0
Potential target population	Infants 6–59 months old, those over 60 years of age, immunocompromised patients and/or suffering from comorbidities, hospital patients undergoing elective surgery or other invasive procedures with high risk of <i>S. aureus</i> infection. Those with recurrent skin and soft tissue infections are also a possible target population.
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 of 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 39. Preclinical development pipeline for *Staphylococcus aureus*.

Candidate vaccine	Target pathogen(s)	Approach	Developer	Sponsor type	Country of sponsor	Activity status
Paragon Novel Vaccine	<i>Staphylococcus aureus</i> , ETEC, ExPEC	Subunit. Peptide-based candidate vaccine, elicits bacterial GAPDH-specific blocking antibodies to protect the host from infection.	Immunethep; Merck	Private sector	Portugal; USA	Active
IBT-V02	<i>S. aureus</i>	Subunit; toxoid. Five-component toxin-based vaccine: Hla, LukS, LukF, rTBA (fusion of TSST-1, SEB and SEA).	Integrated BioTherapeutics	Private sector	USA	Active
<i>S. aureus</i> vaccine	<i>S. aureus</i>	Subunit; alloy platform	Syntiron	Private sector	USA	Active
MRSA vaccine project	<i>S. aureus</i>	Unknown	VLP Biotech	Private sector	USA	Unknown
<i>S. aureus</i> vaccine	<i>S. aureus</i>	Targeting colonization	Abcombi Biosciences	Private sector	USA	Active
<i>S. aureus</i> vaccine program	<i>S. aureus</i>	Unknown	Astrogenetix	Private sector	USA	Active
<i>S. aureus</i> vaccine project	<i>S. aureus</i>	Subunit; MAPS platform	Affinivax	Private sector	USA	Active
SAG (<i>S. aureus</i> Ghosts)	<i>S. aureus</i>	Whole pathogen; ghost cells	Pan Chai University	Academic	China	Unknown
EVX-B1	<i>S. aureus</i>	Subunit; recombinant. Adjuvanted.	Evaxion Biotech	Private sector	USA	Active
ABN-701	<i>S. aureus</i>	Indicated for SEB (superantigen toxin)	Abion	Private sector	Republic of Korea	Active
CTI-005	<i>S. aureus</i>	Subunit; RBC nanosponge	Cellics Therapeutics	Private sector	USA	Active
CTI-036	<i>S. aureus</i>	Subunit; RBC nanosponge	Cellics Therapeutics	Private sector	USA	Active
<i>S. aureus</i> vaccine	<i>S. aureus</i>	Subunit. Antigens: CgoX (coproporphyrinogen oxidase), TPI (triosephosphate isomerase) and Pephyl (peptidoglycan hydrolase).	University of Cologne	Academic	Germany	Active
<i>S. aureus</i> vaccine	<i>S. aureus</i>	Subunit vaccine	Janssen Vaccines & Prevention	Private sector	Netherlands	Active

ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; MAPS: multiple antigen presenting system; MRSA: methicillin-resistant *S. aureus*; RBC: red blood cell; SEB: staphylococcal enterotoxin B.

Table 40. **Clinical development pipeline** for vaccine candidates actively undergoing clinical trials against *Staphylococcus aureus*.

Candidates actively undergoing clinical trials							
Vaccine candidate	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
rTSST-1 variant vaccine (ORG28077)	Subunit; recombinant. Detoxified toxic shock syndrome toxin-1 variant.	Prophylactic	Parenteral	Biomedizinische Forschungsgmbh; Medical University of Vienna	Private sector	Austria, USA	2 NCT02814708
GSK3878858A	Subunit; recombinant. Sa-5Ag with/without adjuvant.	Prophylactic	Parenteral	GSK	Private sector	United Kingdom	1/2 NCT04420221

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*.

Candidates no longer under active development or discontinued								
Vaccine candidate	Target pathogen(s)	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
V710 IsdB	<i>Staphylococcus aureus</i>	Subunit; recombinant. Contains the highly conserved <i>S. aureus</i> 0657nl iron surface determinant B.	Prophylactic	Parenteral	Merck Sharp & Dohme	Private sector	USA	3 NCT00518687
SA4Ag (<i>S. aureus</i> 4-antigen vaccine) PF-06290510/SA4Ag	<i>S. aureus</i>	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.	Prophylactic	Parenteral	Pfizer	Private sector	USA	2b NCT02388165
NDV-3A (formerly NDV3) (108)	<i>S. aureus</i>	Subunit; recombinant. Recombinant candidal surface glycoprotein antigen Als3p.	Prophylactic	Parenteral	NovaDigm Therapeutics	Private sector	USA	2 NCT03455309
AV0328	<i>S. aureus</i> ; <i>Streptococcus pneumoniae</i>	Subunit; conjugate. dPNAG conjugated to TT.	Prophylactic	Parenteral	Alopexx Vaccine	Private sector	USA	1/2 NCT02853617
rAT and rLukS-PV	<i>S. aureus</i>	Subunit; toxoid. Two <i>S. aureus</i> toxoids, rAT and rLukS-PV, as monovalent and bivalent components.	Prophylactic	Parenteral	Nabi Biopharmaceuticals	Private sector	USA	1/2 NCT01011335

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

4C-Staph	<i>S. aureus</i>	Subunit; toxoid. Contains five conserved antigens known to have different roles in <i>S. aureus</i> pathogenesis: the secreted factors α -haemolysin (Hla), ess extracellular A (EsxA) and ess extracellular B (EsxB), and the two surface proteins ferric hydroxamate uptake D2 and conserved staphylococcal antigen 1A, with a novel TLR7-dependent adjuvant.	Prophylactic	Unknown	GSK	Private sector	United Kingdom	1 NCT01160172
STEBVax (IBT-V01)	<i>S. aureus</i>	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).	Prophylactic	Parenteral	Integrated BioTherapeutics	Private sector	USA	1 NCT00974935
SA75	<i>S. aureus</i>	Whole pathogen	Prophylactic	Unknown	Vaccine Research International	Academic	United Kingdom	1
Recombinant <i>S. aureus</i> vaccine (114)	<i>S. aureus</i>	Subunit; recombinant. Hla, IsdB-N2 SpA5, mSEB, and MntC recombinant proteins and aluminium phosphate adjuvants.	Unknown	Unknown	Chengdu Olymvax Biopharmaceuticals	Private sector	China	1 NCT02804711

CP: capsular polysaccharide; dPNAG: deacylated poly-N-b-(1-6)-acetyl-L-glucosamine; SEB: staphylococcal enterotoxin B; TLR: toll-like receptor; TT: tetanus toxoid.

Helicobacter pylori

Vaccines in development	Preclinical: 6; Phase 1: 0; Phase 2: 0; Phase 3: 0
Potential target population	<ol style="list-style-type: none"> 1. A prophylactic vaccine given to children before <i>H. pylori</i> 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 <i>H. pylori</i>.
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*.

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

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*.

Candidates no longer under active development or discontinued							
Vaccine candidate	Approach	Prophylactic/therapeutic	Route of administration	Developer	Sponsor type	Country of sponsor	Phase
IMX101 (121)	Subunit; recombinant. GGT vaccine.	Prophylactic/therapeutic	Unknown	ImevaX	Private sector	Germany	1 NCT03270800





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.

Pipeline Feasibility Group	Description	Pathogens	Recommendations
Very high 	AMR priority pathogens for which licensed vaccines already exist	<ul style="list-style-type: none"> • <i>Salmonella enterica</i> ser. Typhi • <i>Streptococcus pneumoniae</i> • <i>Haemophilus influenzae</i> type b • <i>Mycobacterium tuberculosis</i> 	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	<ul style="list-style-type: none"> • Extraintestinal pathogenic <i>Escherichia coli</i> (ExPEC) • <i>Salmonella enterica</i> ser. Paratyphi A • <i>Neisseria gonorrhoeae</i> • <i>Clostridioides difficile</i> 	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	<ul style="list-style-type: none"> • Enterotoxigenic <i>Escherichia coli</i> (ETEC) • <i>Klebsiella pneumoniae</i> • Non-typhoidal <i>Salmonella</i> • <i>Campylobacter</i> spp. • <i>Shigella</i> 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	<ul style="list-style-type: none"> • <i>Acinetobacter baumannii</i> • <i>Pseudomonas aeruginosa</i> • <i>Enterobacter</i> spp. • <i>Enterococcus faecium</i> • <i>Staphylococcus aureus</i> • <i>Helicobacter pylori</i> 	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.

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

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)); Taniborbactam + 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-pGSN 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 *Chlamydomphila pneumoniae* (US FDA (8/2019) 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*.

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. tb 1 protects against active pulmonary TB; M. tb 2 protects against all forms of active TB. ETEC: enterotoxigenic *Escherichia coli*; ExPEC: extraintestinal pathogenic *E. coli*; M. tb: Mycobacterium tuberculosis; NTS: non-typhoidal *Salmonella*; spp.: species; TB: tuberculosis; UTI: urinary tract infection.

Pathogen	Advanced Candidates	Immunity from natural exposure	Understanding of immunity	Likelihood of protection against most strains	Overall Biological Feasibility	Animal models	in vitro assays	Ease of Clinical Development	Human challenge models	Overall Product Development Feasibility	Existing delivery systems	Commercial attractiveness	Clarity of licensure and policy decision	Ease of uptake	Overall Access & Implementation Feasibility
Hib	5	5	4	5	5	3	5	5	5	5	5	2	5	5	5
<i>S. Typhi</i>	5	2	3	4	4	3	5	5	5	4	5	3	5	2	4
<i>S. pneumoniae</i> 1	5	4	4	4	5	3	5	5	5	3	5	4	5	2	3
ETEC	2	4	3	3	3	4	4	3	5	4	4	3	3	3	3
ExPEC 2	2	4	4	3	3	4	5	3	5	4	3	3	4	3	3
<i>H. pylori</i>	1	1	2	NA	2	4	1	5	4	4	NA	4	4	3	4
NTS	1	3	4	3	3	4	4	3	2	3	5	3	4	3	4
<i>Shigella</i> spp.	2	4	3	4	3	4	4	3	4	4	3	3	3	2	3
<i>Campylobacter</i> spp.	1	3	2	3	2	4	3	4	5	4	4	3	3	3	3
<i>K. pneumoniae</i> 1	1	1	4	3	3	1	4	3	2	3	2	3	3	4	3
<i>M. tuberculosis</i> 2	4	3	3	4	3	3	3	2	2	2	5	4	4	4	4
<i>N. gonorrhoeae</i>	4	1	1	2	2	4	4	3	4	4	2	4	3	2	3
<i>S. Paratyphi</i>	2	3	3	4	3	3	3	2	4	3	5	1	4	2	3
ExPEC 1	1	1	3	3	2	3	3	2	5	3	3	3	3	3	3
<i>K. pneumoniae</i> 2	1	1	4	3	2	4	4	2	1	3	3	4	2	4	3
<i>M. tuberculosis</i> 1	4	3	3	4	3	3	2	2	2	2	3	3	3	3	3
<i>P. aeruginosa</i>	1	2	3	4	3	4	4	2	1	3	2	2	2	3	2
<i>S. pneumoniae</i> 2	1	4	3	5	3	3	2	2	2	2	5	4	2	3	3
<i>A. baumannii</i> 1	1	2	3	3	2	3	3	2	4	3	2	2	3	2	2
<i>A. baumannii</i> 2	1	2	3	3	2	3	3	2	4	3	2	2	3	2	2
<i>C. difficile</i>	3	2	3	3	3	4	2	2	4	2	2	2	3	3	2
<i>E. faecium</i>	1	2	3	3	2	3	4	2	3	3	2	2	3	3	2
<i>S. aureus</i>	2	1	1	1	1	3	4	3	1	3	4	3	3	3	3

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

1. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022 ([https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0), accessed 31 January 2022).
2. Drug-resistant infections: a threat to our economic future. Washington (DC): World Bank; 2017.
3. Interagency Coordination Group on Antimicrobial Resistance. No time to wait: securing the future from drug-resistant infections. Report to the Secretary-General of the United Nations. New York: United Nations; 2019.
4. Stemming the superbug tide: just a few dollars more. OECD Health Policy Studies. Paris: OECD Publishing; 2018 (<https://www.oecd.org/health/stemming-the-superbug-tide-9789264307599-en.htm>, accessed 27 July 2021).
5. New report calls for urgent action to avert antimicrobial resistance crisis. In: World Health Organization [website]. New York: Joint News Release; 2019 (<https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis>, accessed 15 February 2022).
6. How drug-resistant infections are undermining modern medicine – and why more research is needed now. London: Wellcome Trust; 2021.
7. Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017 (<https://apps.who.int/iris/handle/10665/311820>, accessed 15 February 2022).
8. Vekemans J, Hasso-Agopsowicz M, Kang G, Hausdorff WP, Fiore A, Tayler E et al. Leveraging vaccines to reduce antibiotic use and prevent antimicrobial resistance: a World Health Organization action framework. *Clin Infect Dis*. 2021;73(4):E1011–17.
9. 2020 antibacterial agents in clinical and preclinical development. Geneva: World Health Organization; 2020. (<https://apps.who.int/iris/handle/10665/340694>, accessed 15 February 2022).
10. Nontraditional products for bacterial Infections in clinical development. In: Pew Trusts/Projects [website]. Philadelphia (PA): Pew Charitable Trusts; 2021 (<https://www.pewtrusts.org/en/research-and-analysis/data-visualizations/2017/nontraditional-products-for-bacterial-infections-in-clinical-development>, accessed 15 December 2021).
11. Antimicrobial resistance benchmark 2020. Amsterdam: Access to Medicine Foundation; 2020.
12. Vaccines to tackle drug resistant infections: an evaluation of R&D opportunities. London and Boston (MA): Wellcome Trust and Boston Consulting Group; 2019 (<https://vaccinesforamr.org/read-the-report/>, accessed 27 July 2021).
13. Micoli F, Bagnoli F, Rappuoli R, Serruto D. The role of vaccines in combatting antimicrobial resistance. *Nat Rev Microbiol*. 2021;19(5):287–302.
14. Lipsitch M, Siber GR. How can vaccines contribute to solving the antimicrobial resistance problem? *MBio*. 2016;7(3):1–8.
15. Bloom DE, Black S, Salisbury D, Rappuoli R. Antimicrobial resistance and the role of vaccines. *Proc Natl Acad Sci U S A*. 2018;115(51):12868–71.
16. Jansen KU, Knirsch C, Anderson AS. The role of vaccines in preventing bacterial antimicrobial resistance. *Nat Med*. 2018;24(1):10–20.
17. Rappuoli R, Bloom DE, Black S. Deploy vaccines to fight superbugs. *Nature*. 2017;552:165–67.
18. Atkins KE, Lafferty EI, Deeny SR, Davies NG, Robotham JV, Jit M. Use of mathematical modelling to assess the impact of vaccines on antibiotic resistance. *Lancet Infect Dis*. 2017;3099(17):1–10.
19. Orenstein WA, Gellin BG, Beigi RH, Despres S, Lynfield R, Maldonado Y et al. A call for greater consideration for the role of vaccines in national strategies to combat antibiotic-resistant bacteria: recommendations from the National Vaccine Advisory Committee. *Public Health Rep*. 2016;131(1):11–16.

20. Misurski DA, Lipson DA, Changolkar AK. Inappropriate antibiotic prescribing in managed care subjects with influenza. *Am J Manag Care*. 2011;17(9):601-8.
21. Lewnard JA, Lo NC, Arinaminpathy N, Frost I, Laxminarayan R. Childhood vaccines and antibiotic use in low- and middle-income countries. *Nature*. 2020;581(7806):94-99.
22. Leveraging vaccines to reduce antibiotic use and prevent antimicrobial resistance: an action framework. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8366823/>.
23. Kennedy DA, Read AF. Why does drug resistance readily evolve but vaccine resistance does not? *Proc R Soc B Biol Sci*. 2017;284(1851).
24. Yousafzai MT, Karim S, Qureshi S, Kazi M, Memon H, Junejo A et al. Effectiveness of typhoid conjugate vaccine against culture-confirmed *Salmonella enterica* serotype Typhi in an extensively drug-resistant outbreak setting of Hyderabad, Pakistan: a cohort study. *Lancet Glob Heal*. 2021;9(8):e1154-62.
25. Klugman KP, Black S. Impact of existing vaccines in reducing antibiotic resistance: primary and secondary effects. *Proc Natl Acad Sci U S A*. 2018;115(51):12896-901.
26. Frost I, Hasso-Agopsowicz M, Giersing BK, et al. Assessments of the biological, product development and access and implementation feasibility for vaccines against pathogens of concern due to antimicrobial resistance. in prep.
27. Medise BE, Soedjatmiko S, Rengganis I, Gunardi H, Sekartini R, Koesno S et al. Six-month follow up of a randomized clinical trial-phase I study in Indonesian adults and children: safety and immunogenicity of *Salmonella typhi* polysaccharide-diphtheria toxoid (Vi-DT) conjugate vaccine. *PLoS One*. 2019;14(2):e0211784.
28. Capeding MR, Sil A, Tadesse BT, Saluja T, Teshome S, Alberto E et al. Safety and immunogenicity of Vi-DT conjugate vaccine among 6-23-month-old children: Phase II, randomized, dose-scheduling, observer-blind study. *EClinicalMedicine*. 2020;27:100540.
29. Darton TC, Jones C, Blohmke CJ, Waddington CS, Zhou L, Peters A et al. Using a human challenge model of infection to measure vaccine efficacy: a randomised, controlled trial comparing the typhoid vaccines M01ZH09 with placebo and Ty21a. *PLoS Negl Trop Dis*. 2016;10(8):e0004926.
30. Cartee RT, Thanawastien A, Griffin IV TJ, Mekalanos JJ, Bart S, Killeen KP. A phase 1 randomized safety, reactogenicity, and immunogenicity study of Typhax: a novel protein capsular matrix vaccine candidate for the prevention of typhoid fever. *PLoS Negl Trop Dis*. 2020;14(1):e0007912.
31. Typhoid vaccines: WHO position paper, March 2018 – recommendations. *Vaccine*. 2019;37(2): 214-16.
32. Giufrè M, Cardines R, Caporali MG, Accogli M, D'Ancona F, Cerquetti M. Ten years of Hib vaccination in Italy: prevalence of non-encapsulated *Haemophilus influenzae* among invasive isolates and the possible impact on antibiotic resistance. *Vaccine*. 2011;29(22):3857-62.
33. Gilsdorf JR. Hib Vaccines: Their Impact on *Haemophilus influenzae* Type b Disease. *J Infect Dis*. 2021;224(12 Suppl 2):S321-30 (<https://pubmed.ncbi.nlm.nih.gov/34590133>).
34. Kono M, Hotomi M, Hollingshead SK, Briles DE, Yamanaka N. Maternal Immunization with Pneumococcal Surface Protein A Protects against Pneumococcal Infections among Derived Offspring. *PLoS One*. 2011;6(10):e27102 (<https://doi.org/10.1371/journal.pone.0027102>).
35. Brooks WA, Chang L-J, Sheng X, Hopfer R. Safety and immunogenicity of a trivalent recombinant PcpA, PhtD, and PlyD1 pneumococcal protein vaccine in adults, toddlers, and infants: a phase I randomized controlled study. *Vaccine*. 2015;33(36):4610-17.
36. Pneumococcal conjugate vaccines in infants and children under 5 years of age: WHO position paper – February 2019. *Wkly Epidemiol Rec*. 2019;94(08):85-103.
37. Value attribution framework for the impact of vaccines on AMR. Geneva: World Health Organization; 2022. in prep.
38. Wang Y, Li J, Wang Y, Gu W, Zhu F. Effectiveness and practical uses of 23-valent pneumococcal polysaccharide vaccine in healthy and special populations. *Hum Vaccin Immunother*. 2018;14(4):1003-12 (<https://pubmed.ncbi.nlm.nih.gov/29261406>).

39. FDA. Summary Basis for Regulatory Action: Vaxneuvance. 2021 (<https://www.fda.gov/media/151201/download>).
40. von Gottberg A, de Gouveia L, Tempia S, Quan V, Meiring S, von Mollendorf C et al. Effects of vaccination on invasive pneumococcal disease in South Africa. *N Engl J Med*. 2014;371(20):1889–99.
41. WHO/UNICEF estimates of national immunization coverage (WUENIC). In: WHO/Teams/Immunization analysis and insights [website]. Geneva: World Health Organization; 2021 (<https://data.unicef.org/topic/child-health/immunization/>, accessed 15 December 2021).
42. The End TB strategy. Geneva: World Health Organization; 2015 (<https://apps.who.int/iris/bitstream/handle/10665/331326/WHO-HTM-TB-2015.19-eng.pdf?sequence=1&isAllowed=y>).
43. Fu H, Lewnard JA, Frost I, Laxminarayan R, Arinaminpathy N. Modelling the global burden of drug-resistant tuberculosis avertable by a post-exposure vaccine. *Nat Commun*. 2021;12(1):1–9.
44. Vaccines and immunization: investigational vaccine candidate M72/AS01E. In: WHO/Newsroom/Questions and answers [website]. Geneva: World Health; 2020 (<https://www.who.int/news-room/questions-and-answers/item/vaccines-and-immunization-investigational-vaccine-candidate-m72-as01e>, accessed 17 December 2021).
45. Day TA, Penn-Nicholson A, Luabeya AKK, Fiore-Gartland A, Du Plessis N, Loxton AG et al. Safety and immunogenicity of the adjunct therapeutic vaccine ID93 + GLA-SE in adults who have completed treatment for tuberculosis: a randomised, double-blind, placebo-controlled, phase 2a trial. *Lancet Respir Med*. 2021;9(4):373–86.
46. Prabowo SA, Painter H, Zelmer A, Smith SG, Seifert K, Amat M et al. RUTI Vaccination Enhances Inhibition of Mycobacterial Growth ex vivo and Induces a Shift of Monocyte Phenotype in Mice . *Front Immunol* . 2019;10 (<https://www.frontiersin.org/article/10.3389/fimmu.2019.00894>).
47. Mearns H, Geldenhuys HD, Kagina BM, Musvosvi M, Little F, Ratangee F et al. H1:IC31 vaccination is safe and induces long-lived TNF- α +IL-2+CD4 T cell responses in M. tuberculosis infected and uninfected adolescents: a randomized trial. *Vaccine*. 2017;35(1):132–41.
48. Nemes E, Geldenhuys H, Rozot V, Rutkowski KT, Ratangee F, Bilek N et al. Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination. *N Engl J Med*. 2018;379(2):138–49 (<https://doi.org/10.1056/NEJMoa1714021>).
49. Bourinbaier AS, Batbold U, Efremenko Y, Sanjagdorj M, Butov D, Damdinpurev N et al. Phase III, placebo-controlled, randomized, double-blind trial of tableted, therapeutic TB vaccine (V7) containing heat-killed M. vaccae administered daily for one month. *J Clin Tuberc Other Mycobact Dis*. 2020;18:100141.
50. Coppola M, van den Eeden SJF, Robbins N, Wilson L, Franken KLMC, Adams LB et al. Vaccines for Leprosy and Tuberculosis: Opportunities for Shared Research, Development, and Application . *Front Immunol* . 2018;9 (<https://www.frontiersin.org/article/10.3389/fimmu.2018.00308>).
51. EDCTP. Global roadmap for research and development for TB vaccines. 2021 (<http://www.edctp.org/publication/global-roadmap-for-research-and-development-of-tuberculosis-vaccines/#>).
52. Evans TG, Schragger L, Thole J. Status of vaccine research and development of vaccines for tuberculosis. *Vaccine*. 2016;34(26):2911–14.
53. Vekemans J, Brennan MJ, Hatherill M, Schragger L, Fritzell B, Rutkowski K et al. Preferred product characteristics for therapeutic vaccines to improve tuberculosis treatment outcomes: key considerations from World Health Organization consultations. *Vaccine*. 2020;38(2):135–42.
54. Franco AR, Peri F. Developing new anti-tuberculosis vaccines: focus on adjuvants. *Cells*. 2021;10(1):1–17.
55. Eldridge GR, Hughey H, Rosenberger L, Martin SM, Shapiro AM, D'Antonio E et al. Safety and immunogenicity of an adjuvanted Escherichia coli adhesin vaccine in healthy women with and without histories of recurrent urinary tract infections: results from a first-in-human phase 1 study. *Hum Vaccines Immunother*. 2021;17(5):1262–70.
56. Wade D, Cooper J, Derry F, Taylor J. Uro-Vaxom® versus placebo for the prevention of recurrent symptomatic urinary tract infections in participants with chronic neurogenic bladder dysfunction: a randomised controlled feasibility study. *Trials*. 2019;20(1):223.

57. Brodie A, El-Taji O, Jour I, Foley C, Hanbury D. A retrospective study of immunotherapy treatment with Uro-Vaxom (OM-89®) for prophylaxis of recurrent urinary tract infections. *Curr Urol.* 2020;14(3):130-34.
58. Status of vaccine research and development for paratyphoid fever. Prepared for WHO PD-VAC. In: WHO/Immunization [website]. Geneva: World Health Organization; 2014 (https://www.who.int/immunization/research/meetings_workshops/Paratyphoid_VaccineRD_Sept2014.pdf, accessed 30 January 2022).
59. Wahid R, Kotloff KL, Levine MM, Sztein MB. Cell mediated immune responses elicited in volunteers following immunization with candidate live oral *Salmonella enterica* serovar Paratyphi A attenuated vaccine strain CVD 1902. *Clin Immunol.* 2019;201(61-9):61-69.
60. Dobinson HC, Gibani MM, Jones C, Thomaidis-Brears HB, Voysey M, Darton TC et al. Evaluation of the clinical and microbiological response to *Salmonella* Paratyphi A infection in the first paratyphoid human challenge model. *Clin Infect Dis.* 2017;64(8):1066-73.
61. Vincent LR, Jerse AE. Biological feasibility and importance of a gonorrhoea vaccine for global public health. *Vaccine.* 2019;37(50):7419-26.
62. Inoue M, Yonemura T, de Solom R, Yamaji M, Aizawa M, Knirsch C et al. A phase 1 randomized study assessing safety and immunogenicity of two 3-dose regimens of a *Clostridium difficile* vaccine in healthy older Japanese adults. *Vaccine.* 2019;37(19):2600-2607.
63. Kitchin N, Remich SA, Peterson J, Peng Y, Gruber WC, Jansen KU et al. A phase 2 study evaluating the safety, tolerability, and immunogenicity of two 3-dose regimens of a *Clostridium difficile* vaccine in healthy US adults aged 65 to 85 years. *Clin Infect Dis.* 2020;70(1):1-10.
64. Bratulic A. Pfizer's *C. difficile* vaccine misses main goal of pivotal study. *FirstWordPharma.* 2022 (<https://firstwordpharma.com/story/5515307>).
65. de Bruyn G, Gordon DL, Steiner T, Tambyah P, Cosgrove C, Martens M et al. Safety, immunogenicity, and efficacy of a *Clostridioides difficile* toxoid vaccine candidate: a phase 3 multicentre, observer-blind, randomised, controlled trial. *Lancet Infect Dis.* 2021;21(2):252-62.
66. Bézay N, Ayad A, Dubischar K, Firbas C, Hochreiter R, Kiermayr S et al. Safety, immunogenicity and dose response of VLA84, a new vaccine candidate against *Clostridium difficile*, in healthy volunteers. *Vaccine.* 2016;34(23):2585-92.
67. Riley TV, Lyras D, Douce GR. Status of vaccine research and development for *Clostridium difficile*. *Vaccine.* 2019;37(50):7300-7306.
68. Pfizer. Phase 3 CLOVER Trial for Pfizer's Investigational *Clostridioides Difficile* Vaccine Indicates Strong Potential Effect in Reducing Duration and Severity of Disease Based on Secondary Endpoints [website]. 2022 (<https://investors.pfizer.com/Investors/News/news-details/2022/Phase-3-CLOVER-Trial-for-Pfizers-Investigational-Clostridioides-Difficile-Vaccine-Indicates-Strong-Potential-Effect-in-Reducing-Duration-and-Severity-of-Disease-Based-on-Secondary-Endpoints/def>, accessed 5 April 2022).
69. Qadri F, Akhtar M, Bhuiyan TR, Chowdhury MI, Ahmed T, Rafique TA et al. Safety and immunogenicity of the oral, inactivated, enterotoxigenic *Escherichia coli* vaccine ETVAX in Bangladeshi children and infants: a double-blind, randomised, placebo-controlled phase 1/2 trial. *Lancet Infect Dis.* 2020;20(2):208-19.
70. Chakraborty S, Randall A, Vickers TJ, Molina D, Harro CD, DeNearing B et al. Interrogation of a live-attenuated enterotoxigenic *Escherichia coli* vaccine highlights features unique to wild-type infection. *npj Vaccines.* 2019;4(1):1-9.
71. Darsley MJ, Chakraborty S, DeNearing B, Sack DA, Feller A, Buchwaldt C et al. The oral, live attenuated enterotoxigenic *Escherichia coli* vaccine ACE527 reduces the incidence and severity of diarrhea in a human challenge model of diarrheal disease. *Clin Vaccine Immunol.* 2012;19(12):1921-31.
72. Larocque R, Harris JB. Approach to the adult with acute diarrhea in resource-rich countries. In: Post TW, editor. *UpToDate.* Waltham (MA); 2021 (<https://www.uptodate.com/contents/approach-to-the-adult-with-acute-diarrhea-in-resource-rich-settings>, accessed 20 December 2021).
73. Wolf MK. Occurrence, distribution, and associations of O and H serogroups, colonization factor antigens, and toxins of enterotoxigenic *Escherichia coli*. *Clin Microbiol Rev.* 1997;10(4): 569-584.

74. Riddle MS, Maciel M, Porter CK, Poole ST, Gutierrez RL, Gormley R et al. A first in human clinical trial assessing the safety and immunogenicity of transcutaneously delivered enterotoxigenic *Escherichia coli* fimbrial tip adhesin with heat-labile enterotoxin with mutation R192G. *Vaccine*. 2020;38(45):7040-48.
75. Harutyunyan S, Neuhauser I, Mayer A, Aichinger M, Szijártó V, Nagy G et al. Characterization of ShigE_{TEC}, a novel live attenuated combined vaccine against Shigellae and ETEC. *Vaccines*. 2020;8(4):1-14.
76. Girardi P, Harutyunyan S, Neuhauser I, Glaninger K, Korda O, Nagy G et al. Evaluation of the Safety, Tolerability and Immunogenicity of ShigE_{TEC}, an Oral Live Attenuated Shigella-E_{TEC} Vaccine in Placebo-Controlled Randomized Phase 1 Trial. *Vaccines*. 2022;10(2).
77. Bernstein DI, Pasetti MF, Brady R, Buskirk AD, Wahid R, Dickey M et al. A phase 1 dose escalating study of double mutant heat-labile toxin LTR192G/L211A (dmLT) from enterotoxigenic *Escherichia coli* (ETEC) by sublingual or oral immunization. *Vaccine*. 2019;37(4):602-11.
78. Yang B, Foley S. Urinary tract infection vaccines - the "burning" issue. *BJU Int*. 2019;123(5):743-44.
79. Edelman R, Talor DN, Wasserman SS, McClain JB, Cross AS, Sadoff JC et al. Phase 1 trial of a 24-valent *Klebsiella* capsular polysaccharide vaccine and an eight-valent *Pseudomonas* O-polysaccharide conjugate vaccine administered simultaneously. *Vaccine*. 1994;12(14):1288-94 ([https://doi.org/10.1016/S0264-410X\(94\)80054-4](https://doi.org/10.1016/S0264-410X(94)80054-4), accessed 31 January 2022).
80. Trautmann M, Ruhnke M, Rukavina T, Held TK, Cross AS, Marre R et al. O-antigen seroepidemiology of *Klebsiella* clinical isolates and implications for immunoprophylaxis of *Klebsiella* infections. *Clin Diagn Lab Immunol*. 1997;4(5):550-55.
81. Hansen DS, Mestre F, Alberti S, Hernández-Allés S, Alvarez D, Doménech-Sánchez A et al. *Klebsiella pneumoniae* lipopolysaccharide O typing: revision of prototype strains and O-group distribution among clinical isolates from different sources and countries. *J Clin Microbiol*. 1999;37(1):56-62.
82. Choi M, Hegerle N, Nkeze J, Sen S, Jamindar S, Nasrin S et al. The diversity of lipopolysaccharide (O) and capsular polysaccharide (K) antigens of invasive *Klebsiella pneumoniae* in a multi-country collection. *Front Microbiol*. 2020;11:1249.
83. The RTSS Clinical Trials Partnership. A phase 3 trial of RTS,S/AS01 malaria vaccine in African infants. *N Engl J Med*. 2012;367(24):2284-95.
84. Stanaway JD, Parisi A, Sarkar K, Blacker BF, Reiner RC, Hay SI et al. The global burden of nontyphoidal salmonella invasive disease: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis*. 2019;19(12):1312-24.
85. Bekeredjian-Ding I. Challenges for clinical development of vaccines for prevention of hospital-acquired bacterial infections. *Front Immunol*. 2020;11(August):1-13.
86. Tennant SM, Schmidlein P, Simon R, Pasetti MF, Galen JE, Levine MM. Refined live attenuated *Salmonella enterica* serovar Typhimurium and Enteritidis vaccines mediate homologous and heterologous serogroup protection in mice. *Infect Immun*. 2015;83(12):4504-12.
87. Gil-Cruz C, Bobat S, Marshall JL, Kingsley RA, Ross EA, Henderson IR et al. The porin OmpD from nontyphoidal *Salmonella* is a key target for a protective B1b cell antibody response. *Proc Natl Acad Sci U S A*. 2009;106(24):9803-8.
88. Gibreel A, Taylor DE. Macrolide resistance in *Campylobacter jejuni* and *Campylobacter coli*. *J Antimicrob Chemother*. 2006;58(2):243-55 (<https://doi.org/10.1093/jac/dkl210>).
89. Same RG, Tamma PD. *Campylobacter* infections in children. *Pediatr Rev*. 2018;39(11):533-41.
90. Riddle MS, Kaminski RW, Di Paolo C, Porter CK, Gutierrez RL, Clarkson KA et al. Safety and immunogenicity of a candidate bioconjugate vaccine against *Shigella flexneri* 2a administered to healthy adults: a single-blind, randomized phase I study. *Clin Vaccine Immunol*. 2016;23(12):908-17.
91. Talaat KR, Alaimo C, Martin P, Bourgeois AL, Dreyer AM, Kaminski RW et al. Human challenge study with a *Shigella* bioconjugate vaccine: analyses of clinical efficacy and correlate of protection. *EBioMedicine*. 2021;66:103310.
92. Toapanta FR, Bernal PJ, Kotloff KL, Levine MM, Sztein MB. T cell mediated immunity induced by the live-attenuated *Shigella flexneri* 2a vaccine candidate CVD 1208S in humans. *J Transl Med*. 2018;16(1):61.

93. Raqib R, Sarker P, Zaman K, Alam NH, Wierzba TF, Maier N et al. A phase I trial of WRSS1, a *Shigella sonnei* live oral vaccine in Bangladeshi adults and children. *Hum Vaccin Immunother.* 2019;15(6):1326-37.
94. Chakraborty S, Harro C, DeNearing B, Bream J, Bauers N, Dally L et al. Evaluation of the safety, tolerability, and immunogenicity of an oral, inactivated whole-cell *Shigella flexneri* 2a vaccine in healthy adult subjects. *Clin Vaccine Immunol.* 2016;23(4):315-25.
95. Riddle MS, Chen WH, Kirkwood CD, MacLennan CA. Update on vaccines for enteric pathogens. *Clin Microbiol Infect.* 2018.
96. Cohen D, Atsmon J, Artaud C, Meron-Sudai S, Gougeon ML, Bialik A et al. Safety and immunogenicity of a synthetic carbohydrate conjugate vaccine against *Shigella flexneri* 2a in healthy adult volunteers: a phase 1, dose-escalating, single-blind, randomised, placebo-controlled study. *Lancet Infect Dis.* 2021;21(4):546-58.
97. Frenck RW, Baqar S, Alexander W, Dickey M, McNeal M, El-Khorazaty J et al. A phase I trial to evaluate the safety and immunogenicity of WRSS2 and WRSS3; two live oral candidate vaccines against *Shigella sonnei*. *Vaccine.* 2018;36(32):4880-89.
98. Riddle MS, Kaminski RW, Williams C, Porter C, Baqar S, Kordis A et al. Safety and immunogenicity of an intranasal *Shigella flexneri* 2a Invaplex 50 vaccine. *Vaccine.* 2011;29(40):7009-19.
99. Obiero CW, Ndiaye AGW, Sciré AS, Kaunyangi BM, Marchetti E, Gone AM et al. A phase 2a randomized study to evaluate the safety and immunogenicity of the 1790GAHB generalized modules for membrane antigen vaccine against *Shigella sonnei* administered intramuscularly to adults from a shigellosis-endemic country. *Front Immunol.* 2017;8(DEC):1884.
100. López-Siles M, Corral-Lugo A, McConnell MJ. Vaccines for multidrug resistant Gram negative bacteria: lessons from the past for guiding future success. *FEMS Microbiol Rev.* 2021;45(3):fuaa054.
101. Pachón J, McConnell M. Considerations for the development of a prophylactic vaccine for *Acinetobacter baumannii*. *Vaccine.* 2014;7(23):2534-36.
102. Zhang F, Lu YJ, Malley R. Multiple antigen-presenting system (MAPS) to induce comprehensive B-and T-cell immunity. *Proc Natl Acad Sci U S A.* 2013;110(33):13564-69.
103. Cryz SJ, Furer E, Cross AS, Wegmann A, Germanier R, Sadoff JC. Safety and immunogenicity of a *Pseudomonas aeruginosa* O-polysaccharide toxin A conjugate vaccine in humans. *J Clin Invest.* 1987;80(1):51-56.
104. Jones RJ, Roe EA, Gupta JL. Controlled trial of *Pseudomonas* immunoglobulin and vaccine in burn patients. *Lancet.* 1980;316(8207):1263-65.
105. Adlbrecht C, Wurm R, Depuydt P, Spapen H, Lorente JA, Staudinger T et al. Efficacy, immunogenicity, and safety of IC43 recombinant *Pseudomonas aeruginosa* vaccine in mechanically ventilated intensive care patients – a randomized clinical trial. *Crit Care.* 2020;24(1):1-10.
106. Kalfopoulou E, Huebner J. Advances and prospects in vaccine development against enterococci. *Cells.* 2020;9(11).
107. Sava IG, Heikens E, Huebner J. Pathogenesis and immunity in enterococcal infections. *Clin Microbiol Infect.* 2010;16(6):533-40.
108. Millar E V, Bennett JW, Barin B, Carey PM, Law NN, English CE et al. Safety, immunogenicity, and efficacy of NDV-3A against *Staphylococcus aureus* colonization: a phase 2 vaccine trial among US Army Infantry trainees. *Vaccine.* 2021;39(23):3179-88.
109. Shinefield H, Black S, Fattom A, Horwith G, Rasgon S, Ordonez J et al. Use of a *Staphylococcus aureus* conjugate vaccine in patients receiving hemodialysis. *N Engl J Med.* 2002;346(7):491-96.
110. Sakr A, Brégeon F, Mège JL, Rolain JM, Blin O. *Staphylococcus aureus* nasal colonization: an update on mechanisms, epidemiology, risk factors, and subsequent infections. *Front Microbiol.* 2018;9:2419.
111. Wertheim HFL, Melles DC, Vos MC, van Leeuwen W, van Belkum A, Verbrugh HA et al. The role of nasal carriage in *Staphylococcus aureus* infections. *Lancet Infect Dis.* 2005;5(12):751-62.

112. Fowler VG, Proctor RA. Where does a *Staphylococcus aureus* vaccine stand? *Clin Microbiol Infect.* 2014;20(S5):66-75.
113. Luna BM, Nielsen TB, Cheng B, Pantapalangkoor P, Yan J, Boyle-Vavra S et al. Vaccines targeting *Staphylococcus aureus* skin and bloodstream infections require different composition. *PLoS One.* 2019;14(6):e0217439.
114. Zeng H, Yang F, Feng Q, Zhang J, Gu J, Jing H et al. Rapid and broad immune efficacy of a recombinant five-antigen vaccine against *Staphylococcus aureus* infection in animal models. *Vaccines.* 2020;8(1).
115. Cen Q, Gao T, Ren Y, Lu X, Lei H. Immune evaluation of a *Saccharomyces cerevisiae*-based oral vaccine against *Helicobacter pylori* in mice. *Helicobacter.* 2021;26(1):e12772.
116. Wang S, Ma J, Ji Q, Liu Q. Evaluation of an attenuated *Listeria monocytogenes* as a vaccine vector to control *Helicobacter pylori* infection. *Immunol Lett.* 2021;238:68-74.
117. Chen J, Zhong Y, Liu Y, Tang C, Zhang Y, Wei B et al. Parenteral immunization with a cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) adjuvanted *Helicobacter pylori* vaccine induces protective immunity against *H. pylori* infection in mice. *Hum Vaccines Immunother.* 2020;16(11):2849-54.
118. Song Z, Li B, Zhang Y, Li R, Ruan H, Wu J et al. Outer membrane vesicles of *Helicobacter pylori* 7.13 as adjuvants promote protective efficacy against *Helicobacter pylori* infection. *Front Microbiol.* 2020;11:1340.
119. Sutton P, Boag JM. Status of vaccine research and development for *Helicobacter pylori*. *Vaccine.* 2019;37(50):7295-99.
120. Zeng M, Mao XH, Li JX, Tong W De, Wang B, Zhang YJ et al. Efficacy, safety, and immunogenicity of an oral recombinant *Helicobacter pylori* vaccine in children in China: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2015;386(10002):1457-64.
121. Oertli M, Noben M, Engler DB, Semper RP, Reuter S, Maxeiner J et al. *Helicobacter pylori* γ -glutamyl transpeptidase and vacuolating cytotoxin promote gastric persistence and immune tolerance. *Proc Natl Acad Sci U S A.* 2013;110(8):3047-52.
122. Broad J, Le Doare K, Heath PT, Hallchurch P, Whelan I, Boyd H et al. The current state of immunization against Gram-negative bacteria in children: a review of the literature. *Curr Opin Infect Dis.* 2020;33(6):517-29.
123. Rosa SS, Prazeres DMF, Azevedo AM, Marques MPC. mRNA vaccines manufacturing: challenges and bottlenecks. *Vaccine.* 2021;39(16):2190-2200 (<https://doi.org/10.1016/j.vaccine.2021.03.038>, accessed 30 January 2022).
124. Munira SL, Hendriks JT, Atmosukarto II, Friede MH, Carter LM, Butler JRG et al. A cost analysis of producing vaccines in developing countries. *Vaccine.* 2019;37(9):1245-51 (<https://doi.org/10.1016/j.vaccine.2018.11.050>, accessed 30 January 2022).
125. Sparrow E, Hasso-Agopsowicz M, Kaslow DC, Singh K, Rao R, Chibi M et al. Insights in vaccines for tropical diseases: 2022. Under review. *Front Trop Dis.*
126. Antibacterial agents in preclinical development: an open access database. Geneva: World Health Organization; 2019. (<https://apps.who.int/iris/handle/10665/330290>, accessed 15 February 2022)
127. Antibiotic resistance threats in the United States, 2019. Atlanta (GA): US Centers for Disease Control and Prevention; 2019.
128. Government of India Department of Biotechnology. Indian priority pathogen list. New Delhi: WHO Country Office for India; 2021.
129. 2020 progress report. Geneva: AMR Industry Alliance; 2020.

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