Vaccines to tackle drug resistant infections

An evaluation of R&D opportunities

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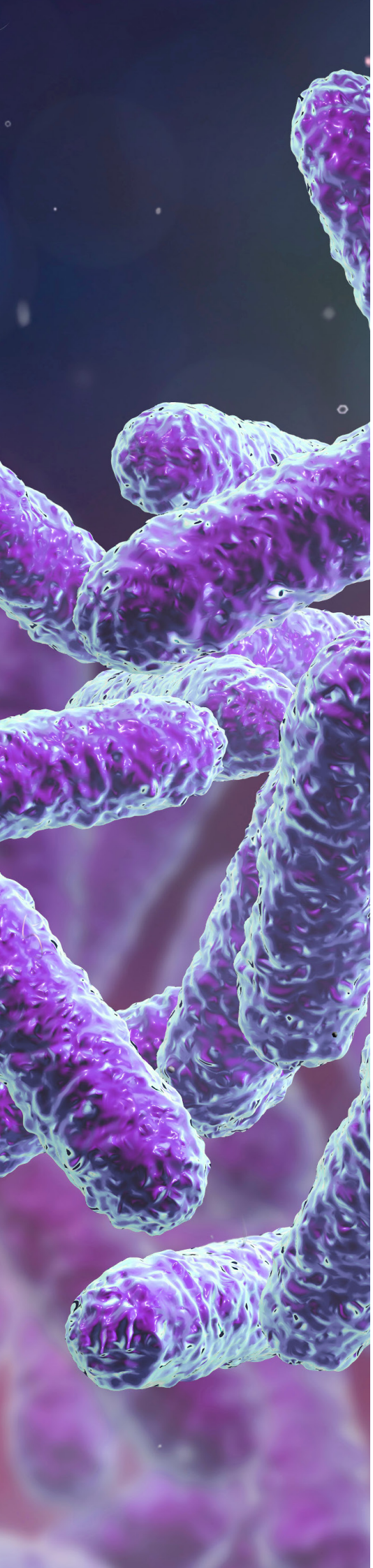


Executive Summary

The role of vaccines in combating antimicrobial resistance (AMR)

AMR is a significant and growing problem. Drug resistant infections cause 700,000 deaths per year; this number could rise to 10 million by 2050 [1] unless urgent action is taken. Furthermore, this figure does not capture the impact of being unable to safely perform high-risk medical procedures such as complex surgery or chemotherapy.

Immediate and coordinated action is required to tackle the threat posed by AMR. Vaccines alone will not be sufficient to achieve this, but they are critical tools that can play an important role when deployed alongside broader activities. A multi-faceted, One Health approach must be used because the emergence of resistance stems from behaviour across human and animal health. The development of new antibiotics and alternative therapeutics, the rational use of antibiotics in human and animal health, more effective use of diagnostics, improvements to water, sanitation and hygiene, and vaccines can all support efforts to combat AMR.

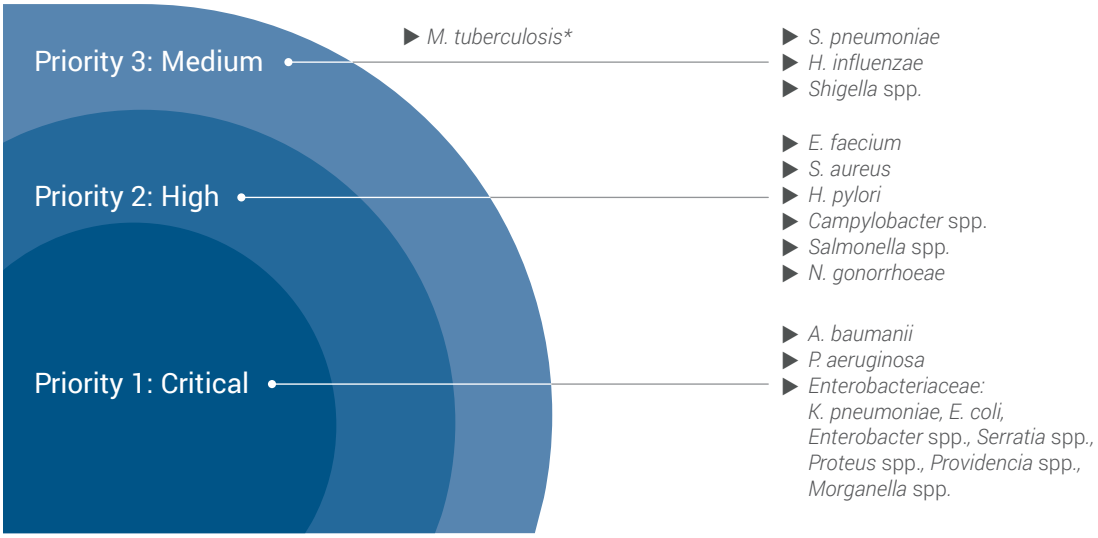
However, vaccines do have some unique advantages, and therefore bringing additional, and more effective, vaccines to market could have a huge impact on AMR. Vaccines already play a critical role, with an impressive track-record of reducing AMR [2]. Both ***H. influenzae*** b and ***S. pneumoniae*** vaccines have resulted in a dramatic reduction in disease burden and have been associated with decreased incidence of resistant strains. Additionally, both vaccines have an additional "indirect" effect on AMR by reducing antibiotic usage and therefore selection pressure on pathogens. Evidence shows that universal coverage with 13-valent ***S. pneumoniae*** vaccination could avoid 11.4 million days of antibiotic use per year in children under five [3].

Vaccines also offer a long-term sustainable approach to infection prevention, because pathogen resistance to vaccines is not common. For example, vaccines against diphtheria and pertussis have been in use for 70 years without resistance developing.

Purpose of this report

This report seeks to provide an independent, actionable assessment of the potential of vaccines to combat AMR, and encourages greater attention, focus, and funding for vaccine development against pathogens whose resistance to antimicrobial medicines was identified by WHO as posing the greatest threat to human health. By employing a carefully considered prioritisation framework to evaluate these pathogens, this report enables comprehensive comparisons across pathogens. This assessment and prioritisation provides a guide for research priorities, policy focus and investment decisions, while recognising that individuals and institutions have varied areas of focus and seek to interact at different parts of the value chain. Additionally, this report consolidates information on these pathogens, and on the development efforts against them, which is currently fragmented, providing a critical new resource to the community working to address AMR.

WHO LIST PROVIDES STARTING POINT FOR COMPARATIVELY ASSESSING VACCINES FOR PATHOGENS WITH HIGH LEVELS OF AMR



Note: WHO 2017: Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics; *M. tuberculosis was nc subjected to review for inclusion in the WHO priority list. However, it was specifically acknowledged as a globally established priority for which innovative new treatments are urgently needed. We therefore included this pathogen in our analysis.

Scope of this report

This work used the World Health Organisation (WHO) priority pathogen list as a starting point for the assessment:

It is important to note that additional pathogens, such as influenza virus, contribute to inappropriate antibiotic usage and selection for AMR, however they were not included in the assessment at this time. By setting out a robust and durable framework and methodology, this work can be taken further in the future by expanding the comparative set of pathogens and increasing the sophistication of individual metrics and indicators.

Methodology employed to assess pathogens

Each pathogen was evaluated based on the potential health impact of a vaccine against the pathogen, the probability of R&D success and the probability of vaccine uptake. The assessment evaluated the development of vaccines against all strains of each pathogen – not just those which are resistant to antibiotics.

This evaluation included the criteria and indicators summarised on the scorecard on the following page. This scorecard assessment aims to holistically capture the stages of vaccine development and establishing a vaccination programme.

Determining the health impact of a pathogen provides critical information, both for those looking to develop vaccines and those responsible for establishing and funding vaccination programmes. In the context of AMR, an understanding of the direct health impact of a pathogen needs to be assessed alongside the level of AMR threat the pathogen causes and the degree to which it drives antibiotic use.

Once a case for vaccine development is established it is important to understand how feasible the development process is likely to be. The robustness of the current pipeline provides a useful indication of the ease of advancing vaccine candidates and the level of commercial interest. A more detailed understanding of potential challenges is gained by assessing pathogen biology and the ease of pre-clinical and clinical programmes.

Assuming a vaccine is successfully brought to market, a key question remains about the likelihood of implementing a successful vaccination programme. A wide range of bodies will influence this process, including policy makers, payers and international organisations such as the WHO, Gavi and UNICEF – the relative importance of these will vary by pathogen. Finally, it is important to identify any significant barriers that could prevent uptake.

A detailed list of sources and methodology for each metric within health impact, probability of R&D success and probability of uptake can be found in the appendix.

PATHOGENS ASSESSED ACCORDING TO HEALTH IMPACT, PROBABILITY OF R&D SUCCESS AND PROBABILITY OF UPTAKE

PATHOGEN SCORECARD

Health impact:

Direct health impact

- Global mortality associated with pathogen
- Global morbidity associated with pathogen

Impact on AMR reduction

- Antibiotic use currently associated with pathogen
- Urgency of AMR threat

Secondary health impact

- Benefits of vaccination not directly related to pathogen mortality and morbidity (e.g. cross protection)

Sub-population benefits

- Benefits of particular importance to certain populations (e.g. pregnant women, children)

Alternative interventions

- List of any alternative interventions

Probability of R&D success:

Pipeline robustness

- Quantitative and qualitative assessment of pipeline strength

Pathogen biology

- Existence of natural immunity
- Knowledge of vaccine targets

Pre-clinical and clinical R&D

- Ease of pre-clinical programme
- Ease of clinical programme (incl. regulatory success)

Combination potential

- Potential to combine with other vaccines

Acceleration potential

- Identification of definitive moves to accelerate development

Major barriers to development

- Identification of scientific or other barriers

Probability of uptake:

Commercial attractiveness

- Likelihood of successful market strategy

Expected policy stance

- Strength of policy recommendations to address threat

Payer, government or Gavi support

- Likelihood of support in low-income countries, mid-income countries and high-income countries based on cost-effectiveness assessment and Gavi priorities

Barriers to uptake

- Influence of cultural factors, need for new vaccination touchpoint and new clinician behaviours

Who needs the vaccine / Potential vaccination strategy

- Identification of those who will benefit from the vaccine
- Likely vaccination strategy

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

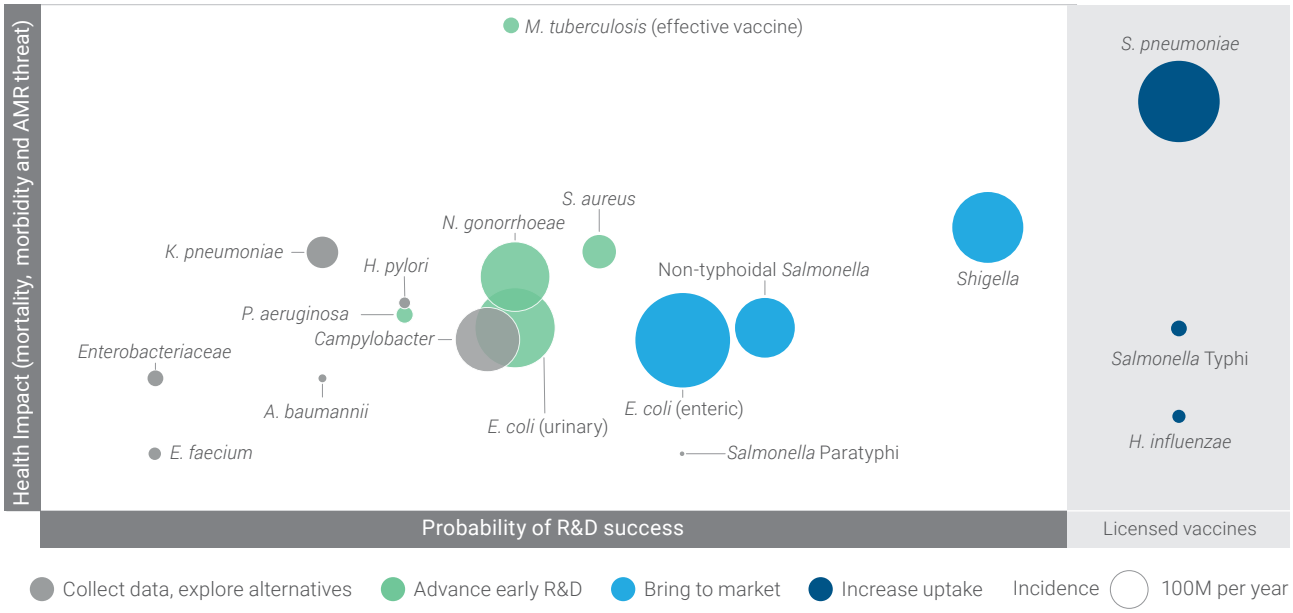
Pathogen clusters identified through this assessment

This assessment resulted in the identification of pathogen clusters that can help prioritise interventions, as illustrated in the figure below:

- The **"increase uptake" cluster** (dark blue) is composed of pathogens with effective, marketed vaccines where the key recommendation is to increase uptake
- The **"bring to market" cluster** (light blue) is composed of pathogens with significant health impact and sufficiently advanced R&D to recommend concentrating on accelerating vaccines through clinical development to market
- The **"advance early R&D" cluster** (green) is composed of pathogens with significant health impact, where more investment in early-stage R&D is needed to develop and advance a robust pipeline of vaccine candidates
- The **"collect data, explore alternatives" cluster** (grey) is composed of pathogens that are less well-suited to vaccine development, as well as pathogens where more information is needed to determine whether vaccine development should be a priority

Each pathogen falls within its cluster for a set of different reasons. It is therefore important to understand each pathogen in addition to its cluster when prioritising efforts. A summary for each pathogen is included below. A full discussion of this matrix is included in the appendix.

PATHOGEN SEGMENTATION BASED ON ASSESSMENT CREATES CLUSTERS THAT CAN HELP PRIORITISE INTERVENTIONS



Weighting used for chart

Health Impact – Mortality (50%), Morbidity (20%), AMR (30%).
Prob. of R&D success – Pathogen biology (30%), Pre-clinical and clinical R&D (30%), Pipeline robustness (40%).

Notes: Probability of R&D success (x-axis) was scored by totalling the weighted scorecard scores for each pathogen on: pathogen biology, pre-clinical and clinical R&D and pipeline robustness using the weighting listed below. The range of the combined score is 0-100.

Health impact (y-axis) was scored by totalling the weighted scorecard scores for each pathogen on: mortality, morbidity and urgency of AMR threat using the weighting listed below. The range of the combined score is 0-100.

1) Mortality and morbidity for Haemophilus influenzae B is currently low due to effective vaccine, but would be high without vaccine coverage
2) TB assessment here is of efforts to develop a highly efficacious vaccine.

Pathogen clusters

Increase uptake for existing, effective vaccines

Pathogens on the WHO list with effective vaccines include ***H. influenzae***, ***S. pneumoniae*** and ***S.*** Typhi:

- Although uptake of ***H. influenzae*** vaccine is relatively high globally at ~70%, continued efforts can be made to maintain and further expand coverage, particularly in certain geographies.
- Increasing uptake of the ***S. pneumoniae*** vaccine presents a significant opportunity; this vaccine is effective for 13 serotypes and used in high, middle and low-income countries, but currently only has ~40% coverage.
- A new, conjugated ***S.*** Typhi vaccine has recently been pre-qualified by the WHO and is supported by Gavi for introduction in 2019, following effectiveness trials. Upon completion, efforts should focus on successfully introducing a vaccination programme.

Bring to market new vaccines for pathogens where protective immunity is understood, by accelerating clinical development

Pathogens on the WHO list in this category include ***E. coli*** (enteric), non-typhoidal ***Salmonella*** and ***Shigella***:

- The high antigenic diversity of ***E. coli*** (enteric) is a challenge for vaccine development, but inclusion of LT toxoid and fimbrial antigens in a potential vaccine may help cover 70-80% of strains.
- A non-typhoidal ***Salmonella*** vaccine appears technically promising and potentially impactful, given high disease burden in Africa.
- A vaccine against ***Shigella*** would represent a major opportunity in this segment due to high incidence and significant associated mortality, particularly in low- and middle-income countries.

Advance early R&D for high impact pathogens with unclear R&D feasibility, by investing in early stage research

- Pathogens on the WHO list in this category include ***M. tuberculosis*** (due to sub-optimal effectiveness of BCG vaccine), ***N. gonorrhoeae***, ***P. aeruginosa***, ***S. aureus*** and ***E. coli*** (urinary):
- There is a strong case for vaccine development for ***M. tuberculosis*** given its health impact and AMR threat. However, current difficulties in understanding pathogen biology and translatability of pre-clinical research must be overcome.

- The case for development of a vaccine targeting ***N. gonorrhoeae*** is strong due to high incidence, high morbidity, and current circulation of resistant strains. Although significant development challenges remain, evidence of MenB vaccine cross-protection has fostered fresh optimism in the expert community.
- ***E. coli*** (urinary) has a high incidence and would be attractive for targeted vaccination in high-income countries, but antigen selection remains a challenge
- Vaccine development for ***P. aeruginosa*** is attractive for high-risk patient groups, such as cystic fibrosis patients, but vaccine development is difficult because the target population is predominantly composed of immunocompromised patients.
- Morbidity and mortality from ***S. aureus*** in high-income countries means the market for a vaccine is attractive, with significant commercially-driven activity. However, there are significant gaps in understanding disease burden and identifying vaccine targets and animal models have limited predictive capability.

Collect data and explore alternatives for those pathogens on the list less well-suited to vaccine development due to significant outstanding epidemiological questions, low incidence and associated mortality and morbidity, or preferable alternative strategies

Pathogens on the WHO list that are not currently well-suited to vaccine development: ***A. baumannii***, ***Campylobacter***, ***E. faecium***, ***Enterobacteriaceae***, ***H. pylori***, ***K. pneumoniae*** and ***S.*** Paratyphi:

- ***S.*** Paratyphi has low incidence and low associated mortality and morbidity, consequently, uptake of a standalone vaccine is unlikely. Therefore, the priority should be to explore combination vaccines with ***S.*** Typhi.
- More data is needed on ***Campylobacter*** transmission in low- and middle-income countries, particularly to understand whether transmission occurs through environmental pathways or from animal reservoirs. This will guide a determination on whether a human vaccine should be pursued or whether alternatives, such as animal vaccination, will be the preferred approach.
- A better understanding of the link between ***H. pylori*** and gastric cancer, as well as a better understanding of how AMR is likely to evolve due to relative current treatability of the pathogen, is necessary.
- ***K. pneumoniae*** has a higher burden than most other hospital-acquired infections, but more data is needed to help determine whether there are predictable sub-populations to target for clinical development and vaccine delivery. Additionally, further study is needed to more accurately estimate the disease burden.
- Due to the comparatively low incidence, morbidity, and mortality of ***Enterobacteriaceae***, ***A. baumannii*** and ***E. faecium***, they are not considered strong candidates for vaccine development. Alternatives, such as passive immunisation, should be explored. Additionally, these pathogens are Gram-negative pathogens that cause hospital-acquired infections in small, immunocompromised target populations. These characteristics present particularly challenging hurdles for vaccine development.

A detailed assessment and recommendations for each pathogen can be found in the individual pathogen chapters.

Recommendations

Based on its cluster, each pathogen has a primary, or most critical, recommendation for intervention which has been summarised in the following table. Secondary recommendations, which detail other actions that can help advance vaccine development and / or uptake for each pathogen, have also been included.

SUMMARY OF INTERVENTION RECOMMENDATIONS

Pathogen clusters			Intervention						
			Explore alternatives (e.g., monoclonals)[1]	Better understand burden/ epidemiology/ transmission	Incentivise multi-pathogen / combination vaccines	Pre-clinical research (e.g., antigen discovery & selection, animal models)	Improve translatability and/or support more first-in-human trials	Accelerate clinical development	Drive coverage and equity
	Increase uptake	*H. influenzae*		✓					✓
		S. pneumoniae				✓			✓
		S. Typhi			✓				✓
	Bring to market	*E. coli* (enteric)		✓	✓	✓		✓	
		Non-typhoidal *Salmonella*		✓	✓			✓	
		Shigella spp.			✓			✓	
	Advance early R&D	*M. tuberculosis*[2]				✓	✓		
		N. gonorrhoeae			✓	✓	✓		
		E. coli (urinary)	✓	✓		✓			
		P. aeruginosa	✓	✓		✓			
		S. aureus	✓	✓		✓	✓		
	Collect data, explore alternatives	*S.* Paratyphi			✓			✓	
		Campylobacter spp.	✓	✓	✓				
		H. pylori	✓	✓		✓			
		K. pneumoniae	✓	✓		✓			
		A. baumannii	✓	✓					
		E. faecium	✓	✓					
		Enterobac-teriaceae	✓	✓					

✓ Primary Recommendation ✓ Secondary Recommendation

1) Requires better understanding of disease biology (i.e., investments in pre-clinical research). Recommendations have focus on vaccine dev; 2) BCG vaccine is excluded here. Focus on broadly efficacious TB vaccine.

Cross-cutting activities would stimulate development of vaccines for all AMR priority pathogens

Through the process of making detailed recommendations specific to each pathogen, this report also identified knowledge gaps shared across multiple pathogens. Based upon these, several cross-cutting activities have been proposed which, if addressed in a coordinated manner, would stimulate development of vaccines for all pathogens with high levels of AMR.

Health Impact

- Promote the collection of robust epidemiological data, which is currently limited and varies greatly in quality across the pathogen set and is essential to making an investment / business case for vaccine development and for encouraging vaccine uptake.
- Model the evolution of AMR and potential health impact of interventions, potentially through a consortium of modellers, which could serve as a common resource for the global health community

Research and Development

- Target investment to new R&D platforms relevant to AMR pathogens such as DNA and RNA vaccines, viral vectors, nanoparticles, novel delivery/administration technologies, and modular manufacturing platforms. These have the potential to significantly lower vaccine manufacturing costs and to facilitate development of polyvalent vaccines.
- Collaborate for regulatory innovation, including encouraging regulatory acceptance of AMR and antibiotic usage as a measurable outcome and encouraging more regular convenings with the aim of harmonising regulatory processes where possible.

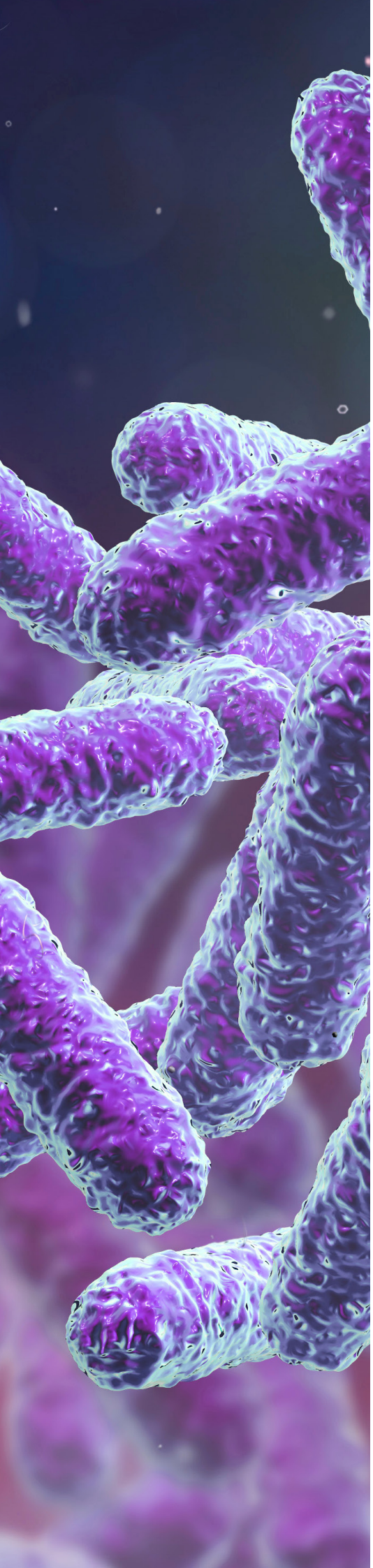
Uptake

- Continue to utilise and improve market shaping interventions where needed, with adaptation to the unique requirements of AMR priority pathogens.
- Develop the health economic case for vaccination which includes the value of a vaccine in combatting AMR, as this is critical to policy and payer recommendations.

These recommendations are discussed in more detail in the cross-cutting activities section of this report.

Action is needed today to harness these potent tools to tackle AMR

Developing a new vaccine can take decades of intensive R&D without any guarantee of success. Bringing the 13-valent pneumococcal conjugate vaccine to market required 13 clinical trials in nine countries – clearly a considerable undertaking despite decades of knowledge from developing and marketing a 7-valent vaccine [4]. Even with significant investment, only ~11% of vaccines being actively developed in 1995 were on the market by 2011[5]. With all these challenges, action is required today to ensure a robust pipeline of candidates is developed to target high priority pathogens. Failure to take decisive action now will deprive the global community of a potent tool for tackling AMR.



About this project

This report was commissioned by the Wellcome Trust and completed by The Boston Consulting Group, and seeks to provide an actionable assessment that encourages more attention, focus, and funding for vaccine development against pathogens with high levels of antimicrobial resistance (AMR).

The Wellcome Trust has identified drug-resistant infections and vaccines as two of their key priority areas for investment and lead many national and international efforts in this area.

The Boston Consulting Group has extensive international experience across healthcare and international development encompassing both the private and public sectors. The Boston Consulting Group supports private sector biopharmaceutical in topics such as R&D strategy and operations, and large international philanthropic foundations and NGOs, such as Gavi and the Bill and Melinda Gates Foundation, in topics such as vaccine portfolio assessment and strategy development.

Purpose of this report

This report evaluates development potential of vaccines against pathogens with high levels of AMR included on the WHO list of 'priority pathogens for R&D of new antibiotics'. By using a carefully considered, consistent prioritisation framework to assess these pathogens, this report enables comprehensive comparisons across pathogens. This assessment and prioritisation provides a guide for research priorities, policy focus and investment decisions, while recognising that individuals and institutions have varied areas of focus and seek to interact at different parts of the value chain. Additionally, this report consolidates information on these pathogens, and on the development efforts against them, which is currently fragmented, providing a critical new resource to the community working to address AMR.

Summary of methodology

Scope

The scope of this report was defined by the list of pathogens in the WHO 'priority pathogens list for R&D of new antibiotics' [6]. ***M. tuberculosis*** was also included due to acknowledgement of high impact in the WHO list. Whilst many other pathogens are considered important when tackling AMR, this list provides a common starting point for assessment. The scorecard is designed to be durable across a range of additional pathogens that could be assessed in the future. A full discussion of scope is included in the methodology appendix.

Sub-division of pathogens

E. coli and ***K. pneumoniae*** were split out and scored separately from the ***Enterobacteriaceae*** group to reflect their clinical importance. Pathogens were further subdivided where subtypes showed distinct clinical and epidemiological profiles:

- ***E. coli*** was subdivided into enteric and urinary subtypes
- ***Salmonella*** was divided into ***S.*** Typhi, ***S.*** Paratyphi and non-typhoidal ***Salmonella*** (NTS)

A full discussion of the rationale for subdivision of pathogens is included in the methodology appendix.

Approach to data collection

Data collection for this report focused on two goals: collecting high-quality, robust assessments, and making consistent assessments across pathogens. To achieve these goals, wherever possible the report uses data from recognised global datasets such as the Institute for Health Metrics and Evaluation (IHME), WHO, Evaluate Pharma, and similar sources, which ensures a standard quality and some level of consistency between pathogens. Where global datasets were not available, information is taken from large multi-pathogen review articles and meta-analyses, if available. Only when data was not available from these sources was data taken from individual articles in the research literature.

Additionally, the pipeline assessment employs a standard methodology to ensure consistency across pathogens. Vaccine candidates for all pathogens were collated from commercial databases (Evaluate Pharma, PharmaProjects) on 01 August 2018, and any duplicates were removed manually. Any changes in the pipeline beyond this point in time are not captured in this report. Where there was divergence in development stage between both databases, candidates were manually assessed. This list was also updated to include vaccine candidates that were listed in recent publicly available literature reviews (published from 2013 onwards) on vaccine development activities against pathogens in scope of the project. Candidates were filtered and only included in the dataset when ongoing development activities were confirmed (e.g. by the existence of scientific articles on these candidates published 2013 or later). This methodology ensures a comprehensive view on the current pipeline; however, it is not entirely exhaustive given that the literature review was extensive, but not completely exhaustive.

Similarly, when conducting the initial round of expert interviews, several measures were taken to ensure high quality and consistency. All experts were provided with the same information at the start of the interview and a structured interview guide was used to ensure consistency in questioning.

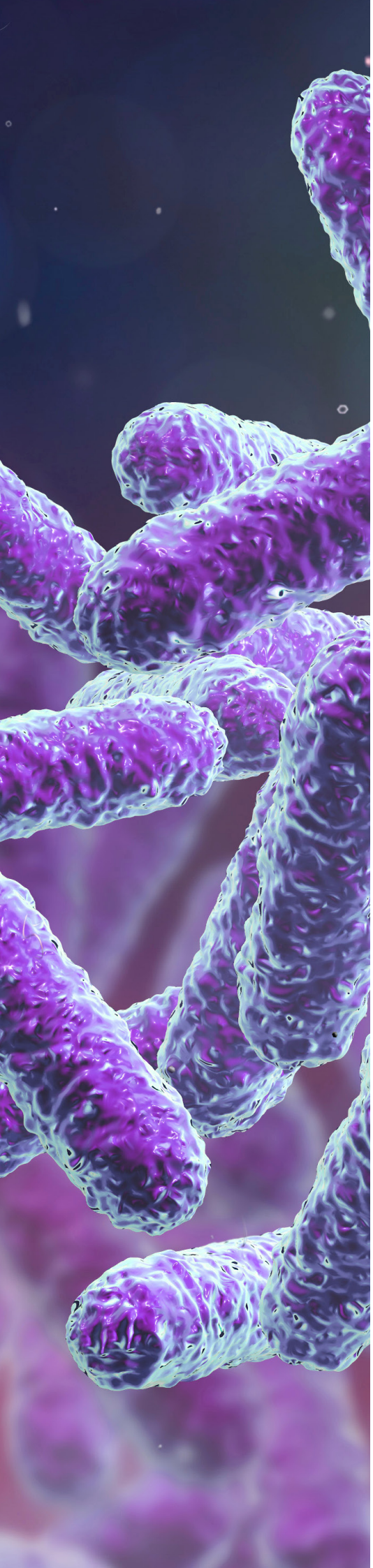
Expert interviews were conducted in three discrete rounds. The first round involved structured interviews with a wide range of experts spanning the global health community – including organisations such as the WHO and The Gates Foundation, regulatory bodies such as the European Medicines Agency (EMA), large pharmaceutical companies such as Pfizer and GlaxoSmithKline (GSK), and a number of smaller biotechnology companies. The second round included more detailed interviews with pathogen experts to confirm the outcomes of the assessments and the preliminary recommendations for each pathogen. The third round was focused on validating preliminary findings with interviewees and collecting feedback on findings and insights.

A full list of interviewees is available in the appendix.

The scorecard

To facilitate cross-pathogen comparisons, a standard scorecard was utilised which includes assessment of health impact, probability of R&D success and probability of uptake:

A detailed description of the methodology for each indicator is provided in the appendix.



Background and context

Context of AMR threat

The introduction of penicillin in the 1940s allowed for the effective treatment of previously fatal infections. However, within the same decade the first cases of resistance to penicillin had already been reported [7]. The pattern of antibiotic resistance developing soon after introduction into clinical practice has been repeated for other pathogens and is observed globally [2]. This is because resistance is easily transferred between bacteria, and that multiple resistance genes can be transferred on a single plasmid, making it possible for currently non-resistant strains to acquire extensive drug resistance in a single step [8].

With this ability to acquire genetic resistance rapidly, AMR is now a major clinical concern world-wide with treatment of some pathogens such as ***M. tuberculosis***, ***N. gonorrhoeae*** and the ***Enterobacteriaceae*** family becoming increasingly challenging. Compounding this challenge is the dearth of new antibiotics – whilst new antibiotics were regularly developed from the 1950s-1980s, no truly novel broad-spectrum agents have been approved in the last 30 years [8].

AMR is already exerting a considerable toll on populations around the globe – causing at least 700,000 deaths per year. This includes 200,000 deaths per year from resistant strains of ***M. tuberculosis*** alone. Other studies have suggested as many as 60,000 neonatal sepsis deaths just in India [1]. In addition to their impact on human health, these infections impose significant economic costs – in the United States alone, resistance to first-line therapies is estimated to have resulted in $20 billion additional healthcare costs [1].

Modelling of rising rates of resistance suggests that without effective action, it is estimated that AMR could cause over 10 million deaths per year by 2050 – and this figure does not include the deaths and ill-health caused if the ability to perform high risk medical interventions such as organ transplantation, immunosuppression, complex surgeries and Intensive Care Unit (ICU) treatments, [1] is lost. The economic impact could be enormous - amounting to $100 trillion globally[1]. With these substantial human and economic costs on the horizon, doing nothing is not an option.

Examples of the current landscape of AMR actions

AMR is a global threat that requires a concerted and coordinated global response, supported by strong political will to act from national leaders. The drivers of AMR span human and animal health and the environment, and therefore soutions must be multi-sectoral. The WHO 'Global Action Plan on AMR' provides the blueprint for the global response, but achieving the progress that is necessary to contain AMR will rely on effective national action, which will be governed by National Action Plans. There is a broad range of interventions that are needed, however current efforts primarily focus on reducing the demand for antibiotics and developing new antibiotics to treat AMR pathogens.

Reducing the demand for antibiotics is complex and difficult, requiring action to achieve the following goals:

Decreasing inappropriate prescriptions: Public awareness campaigns are needed to inform populations about the dangers of AMR. For example, the WHO coordinates World Antibiotic Awareness Week, and Public Health England lead the "Keep Antibiotics Working" campaign. Behaviour change interventions are also necessary to alter both patient and clinician behaviours in relation to the prescription and use of antibiotics, and stewardship programmes are crucial to improve the rational use of antibiotics.

Improving diagnostics to prevent inappropriate prescriptions: The lack of rapid, accurate diagnostics results in antibiotics being prescribed to treat viral infections and unnecessarily broad-spectrum agents being given when a more targeted agent would be sufficient. The National Institutes of Health (NIH) now administer a $20 million prize competition to develop rapid point of care tests that can help tackle AMR. The competition selected 10 semi-finalists in the first phase, with the next phase of awards currently underway.

Reducing the use of antibiotics in agriculture: In the US, as well as in many other countries, large percentages of antibiotics sold are for animal use – often as growth promoters. However, in 2017 the Food and Drug Administration (FDA) completed implementation of guidance that prevents antibiotics important for human health from being used as growth promoters. These agents can now only be used to treat animal illness under the supervision of a licensed veterinarian [9].

Improving hygiene to prevent the spread of infections: Effective water, sanitation and hygiene (WASH) measures can have a major impact on infection prevention, particularly in low and middle income countries.

Finally, vaccines play an important role in reducing the demand for antibiotics – this will be discussed in detail in the next section.

Developing new antibiotics is extremely commercially and scientifically challenging. Investment in antibiotic R&D has seen a long-term decline, and the pipeline of new antibiotics under development is widely regarded as inadequate to meet the future challenge of drug resistance [10]. Technical challenges in developing new antibiotics include difficulty recruiting patients to trials as hospitals must act rapidly to treat acutely ill patients, and difficulty proving clinical superiority against existing effective agents. Commercially, the expectation of active antibiotic stewardship programmes to limit the consumption of "last line" novel antibiotics, and the difficulty of predicting future patterns of demand for antibiotics, mean that predicted returns on investment are often too low to support sustained commercial R&D [10].

However, the international community is responding to the market failure to create novel antibiotics with plans to invest over $1 billion in early stage R&D between 2014 and 2021 [10]. There has been less progress in creating an attractive sales market for new antibiotics, and implementing novel reimbursement mechanisms that de-link the return on investment from the volume of antibiotics sold. Greater progress in implementing new market models of this type is seen by some as essential to securing an adequate pipeline of antibiotics over the long term.

Vaccines can clearly play a role in reducing the dependence on antibiotics, and thus mitigate the risks posed by the inadequacy of the current pipeline. However, in practical terms, increased vaccine development cannot and should not be seen as an outright substitute for reinvigorated antibiotic development; and it should be noted that improved vaccine uptake could in fact exacerbate some of the commercial challenges currently faced by antibiotic developers, by suppressing the predictable demand for novel antibiotics still further.

Vaccines as a tool for tackling AMR

Vaccines have a proven track-record of tackling AMR [2]:

Since the 1980s, the ***H. influenzae*** b vaccination has resulted in a dramatic reduction in incidence – nearly eliminating ***H. influenzae*** b disease in young children. Decreased nasopharyngeal carriage also resulted in extended population-wide protection through herd protection effects, which may represent approximately two thirds of prevented infections [11]. This reduction in ***H. influenzae*** b incidence was associated with a significant decrease in the prevalence of the beta-lactamase producing strains that are resistant to many common broad-spectrum antibiotics. Similarly, the 13-valent pneumococcal conjugate vaccine (PCV) has been proven to significantly reduce the prevalence of resistant strains of ***S. pneumoniae***.

Both vaccines have an additional "indirect" effect of reducing antibiotic use and therefore selection pressure on pathogens, which drives the development of drug resistance. Universal coverage with 13-valent ***S. pneumoniae*** vaccination could avoid approximately 11.4 million days of antibiotic use per year in children

under five [3] and ***H. influenzae*** b vaccination significantly reduces outpatient antibiotic use [12].

Pathogens are unlikely to develop resistance to a vaccine[13]:

Vaccines also offer a long-term sustainable approach to infection prevention, because pathogen resistance to vaccines is not common. For example, vaccines against diphtheria and pertussis have been in use for 70 years without resistance developing. Most vaccines act by preventing infection, which means that bacteria do not have the chance to replicate and form a large population size in which resistance is more likely to develop. Moreover, vaccines typically target multiple antigens on the pathogen which makes the development of resistance more challenging.

As a tool for tackling AMR vaccines face a number of challenges:

Uptake can be challenging even for effective vaccines. For example, global uptake of PCV is only ~40% [2]. This can be driven by multiple factors including high price-points, multiple-dose regimens and a lack of medical infrastructure to deliver a vaccination programme effectively.

Moreover, not all infections are well suited to vaccination – particularly pathogens where predicting infection is challenging or the target populations are immune-compromised. This is particularly true for many Gram-negative hospital-acquired infections where the urgency of the AMR threat is the most severe.

Developing a new vaccine is also an enormous, and expensive, undertaking. There is limited evidence on vaccine development costs, however these are likely roughly comparable to those of developing a new drug. Recent estimates suggest a $2.6 billion cost for developing a new drug, taking into account the cost of failures and opportunity cost of capital [14]. Additionally, after development, establishing a new vaccine manufacturing site can represent up to an additional $700 million investment depending on the complexity of the product [15].

The development of vaccines is unpredictable, and carries similar risks to other pharmaceutical agents – only 11% of vaccines in active development in 1995 had succeeded after 16 years [5]. In addition to the large cost and risk involved, this process takes a very long time – on average 14.3 years [5]. Bringing the 13-valent pneumococcal conjugate vaccine to market required 13 clinical trials in nine countries – clearly a considerable undertaking despite decades of knowledge from developing and marketing a 7-valent vaccine [4].

Action is needed today to harness these potent tools to tackle AMR

With all these challenges, action is required today to ensure a robust pipeline of candidates is developed to target high priority pathogens. Failure to take decisive action now will deprive the global community of a potent tool for tackling AMR.

Pathogen comparison

Each pathogen was evaluated based on health impact, the probability of vaccine R&D success, and the probability of vaccine uptake using the criteria included on the scorecard overleaf.

A detailed description of the methodology for each indicator is provided in the appendix.

The scorecard used in the assessment was adapted from the evaluation framework used by Gavi in its 'Vaccine Investment Strategy' and customised to accommodate the unique characteristics of the AMR-priority pathogens listed by the WHO. By utilising a similar methodology to Gavi, the assessment will be familiar to the global health community.

Throughout the scorecard it is important to note that the focus of the assessment was the development of vaccines against all strains of the pathogen – not just those that display drug resistance.

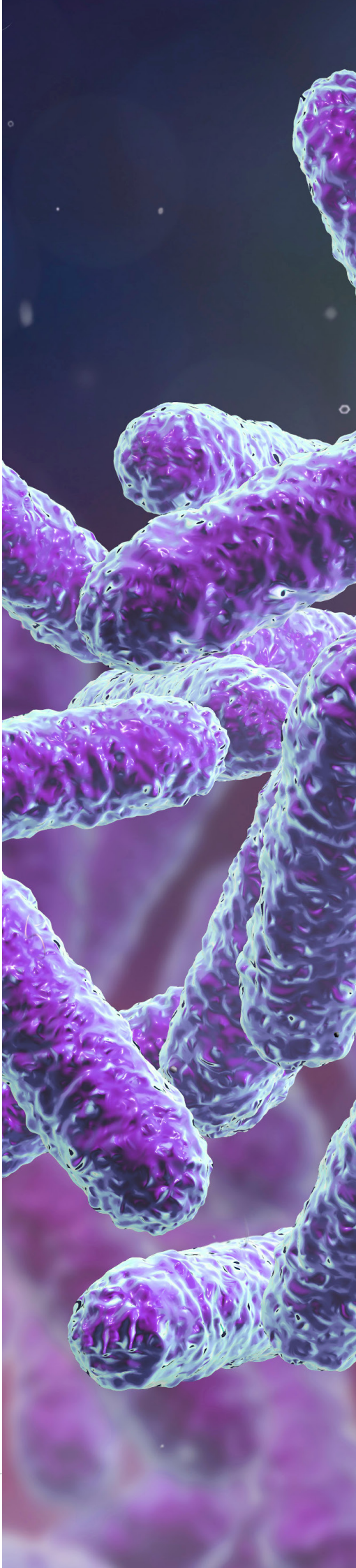
Detailed sources and methodology for each metric within health impact, probability of R&D success and probability of uptake can be found in the appendix. The opportunity exists to expand the methodology to other pathogens and increase sophistication of individual indicators over time. This is an important next step given that this list only comprises a subset of relevant pathogens, with some pathogens that drive significant antibiotic use and resistance not included.

Health impact

One of the most important metrics in determining whether a vaccine should be developed is its potential to improve global health. As a result, the assessment of health impact began with an examination of the mortality and morbidity caused by each pathogen. It is important to note that the assessment makes no assumptions about the potential efficacy or uptake of a vaccine, and thus represents the maximum possible mortality and morbidity benefit from a vaccine.

Additionally, it is critical to know the potential impact that a vaccine would have on AMR. To assess this, an evaluation of the intensity of the AMR threat was undertaken which included the pathogen's relative place on WHO priority pathogen and also its place on the Centers for Disease Control (CDC) list of most significant drug resistant threats. Initial estimates on the amount of antibiotic usage associated with the pathogen were also formulated.

To complete the evaluation, any potential secondary health impacts of a vaccine were identified – such as cross-protection against another pathogen, any sub-populations that would particularly benefit from the vaccine, and alternative interventions that could be used to address resistance in the pathogen.



PATHOGEN SCORECARD

Health impact:

Direct health impact

- Global mortality associated with pathogen
- Global morbidity associated with pathogen

Impact on AMR reduction

- Antibiotic use currently associated with pathogen
- Urgency of AMR threat

Secondary health impact

- Benefits of vaccination not directly related to pathogen mortality and morbidity (e.g. cross protection)

Sub-population benefits

- Benefits of particular importance to certain populations (e.g. pregnant women, children)

Alternative interventions

- List of any alternative interventions

Probability of R&D success:

Pipeline robustness

- Quantitative and qualitative assessment of pipeline strength

Pathogen biology

- Existence of natural immunity
- Knowledge of vaccine targets

Pre-clinical and clinical R&D

- Ease of pre-clinical programme
- Ease of clinical programme (incl. regulatory success)

Combination potential

- Potential to combine with other vaccines

Acceleration potential

- Identification of definitive moves to accelerate development

Major barriers to development

- Identification of scientific or other barriers

Probability of uptake:

Commercial attractiveness

- Likelihood of successful market strategy

Expected policy stance

- Strength of policy recommendations to address threat

Payer, government or Gavi support

- Likelihood of support in low-income countries, mid-income countries and high-income countries based on cost-effectiveness assessment and Gavi priorities

Barriers to uptake

- Influence of cultural factors, need for new vaccination touchpoint and new clinician behaviours

Who needs the vaccine / Potential vaccination strategy

- Identification of those who will benefit from the vaccine
- Likely vaccination strategy

Probability of R&D success

After evaluating each pathogen's health impact the assessment looked to determine the probability of bringing an effective vaccine to market.

A key factor in this assessment was the strength of the current R&D vaccine pipeline for each pathogen. To assess this, an array of public and proprietary sources were combined in order to analyse and score the entire current pipeline for each pathogen. A summary of this information is presented in the appendix.

The relative difficulty of developing new vaccine candidates was also assessed, by looking at each pathogen's unique biology and both pre-clinical and clinical R&D requirements.

Additionally, the potential to develop combination, multi-pathogen vaccines for these pathogens was assessed – an important consideration given an increasingly packed vaccination schedule.

To complete the evaluation, the potential to accelerate efforts and the major barriers to a development programme were identified. For many pathogens this evaluation forms an important part of the recommendations.

It is important to note, as with the other assessments in this report, that the R&D assessment represents a snapshot in time based upon the current development efforts and understanding of the pathogen. Promising candidates frequently fail in clinical trials and surprising results can breathe new life into development efforts.

Probability of uptake

As a first step to assessing the probability of vaccine uptake, the groups that would derive most benefit from the vaccine were identified and the likely vaccination strategy was defined.

It is important to note that for this assessment, the group described by the likely vaccination strategy may only be a small sub-section of the total population that could benefit from a vaccine. This reflects the different commercial routes to market for a new vaccine. For example, whilst there is a large population worldwide who could benefit from a vaccine against certain hospital-acquired infections, the likely vaccination strategy may be to concentrate, at least initially, solely on high risk patients in high resource settings.

With the likely vaccination strategy identified, the assessment then evaluated the likelihood of positive policymaker and payer support for administering vaccines to this population. In this assessment, greater emphasis was placed on the role of the WHO and Gavi for vaccines where routine immunisation in Gavi-supported countries was identified as the likely vaccination strategy. Where the likely vaccination strategy was focused on high resource settings, payer support and the role of academic guidelines were given greater emphasis.

Additionally, the likely barriers to uptake were assessed, taking into account factors such as cultural barriers and the need for new vaccination touchpoints.

To complete the evaluation, the commercial attractiveness of the vaccine was assessed. For many pathogens this evaluation forms an important part of the recommendations.

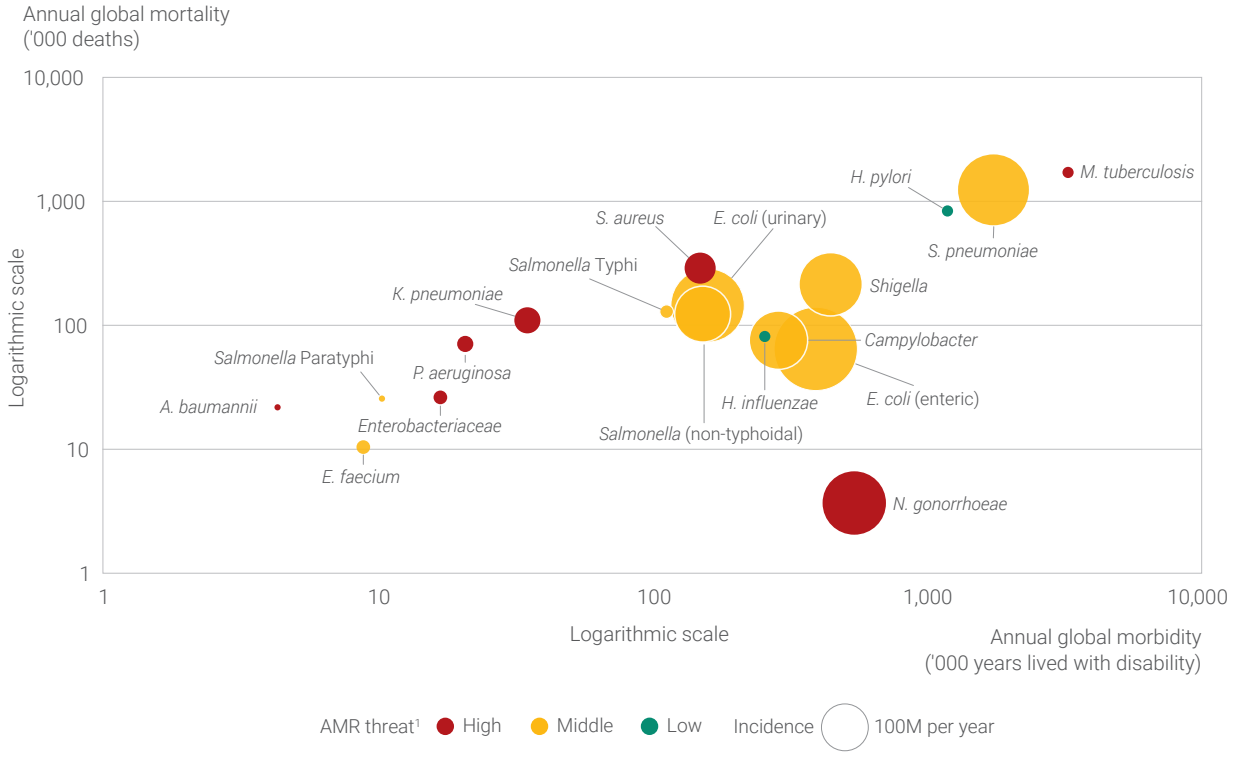
Frameworks for pathogen comparison

Based on the assessment of each pathogen, meaningful comparisons can be made across the pathogen set to better assess their relative suitability for vaccine development. With respect to health impact, the mortality and morbidity associated with each pathogen varies by orders of magnitude.

When global mortality and morbidity for each pathogen are plotted on the logarithmic scale below, these differences become apparent, creating a clear distribution of potential impact across the pathogen set. For example, mortality for ***M. tuberculosis*** at ~1.7 million deaths per year is almost three orders of magnitude greater than that for ***N. gonorrhoeae*** at ~4,000 deaths per year.

Most of these pathogens distribute on a diagonal, whereby mortality and morbidity increase in step. The clear outlier is ***N. gonorrhoeae***, for which the health impact is driven by morbidity, reflecting the high burden of chronic untreated infections.

ORDERS OF MAGNITUDE DIFFERENCES IN INCIDENCE, MORBIDITY, MORTALITY ACROSS PATHOGEN SET



1) Colour code for AMR threat different from pathogen scorecards.
Source: WHO and IHME 2016 global disease burden datasets and literature review – full source list and methodology in appendix.

Pathogens also vary greatly in their suitability for vaccine development. When examining the probability of R&D success, the pathogens range from very high feasibility – primarily capturing the licensed vaccines for ***S. pneumoniae***, ***H. influenzae*** and ***S.*** Typhi – to very low feasibility, capturing the real challenges in developing a vaccine for pathogens such as ***E. faecium***.

It is also important to note that significant technical hurdles still remain for nearly all pathogens without a licensed vaccine.

SUMMARY OF TECHNICAL HURDLES

Note: Ordered from lowest to highest in terms of hurdles for dimensions listed in columns. Does not include pipeline robustness measure.

The colour-coding reflects the pathogen's categorisation (low, medium or high) on the variables listed in the columns. Red represents significant hurdles to vaccine development, yellow represent moderate hurdles to vaccine development and green represents low hurdles to vaccine development.

1) Entire family excluding *E. coli* and *K. pneumoniae*; Source: Literature research; expert interviews; BCG analysis.

When evaluating uptake, significant differences in transmission and geographic distribution across the pathogen set drive complex uptake dynamics.

The geographic distribution of disease burden is a key factor shaping market dynamics. Support from Gavi can drive uptake if the disease burden is predominantly in low- and middle-income countries. Therefore, the extent to which a pathogen fits the Gavi funding criteria will to a large degree inform the probability of uptake. If a pathogen is also prevalent in high-income countries, the identification of a commercial market is critical to improve the probability of uptake. Where pathogens have a global prevalence, a potential dual market exists.

Uptake dynamics are particularly challenging when Gavi supported countries are the primary market for a vaccine but the pathogen causes relatively low mortality. For example, ***Campylobacter*** infections primarily impact low- and middle-income countries that are supported by Gavi, but mortality is low relative to other pathogens in this assessment at ~75,000 deaths per year. As Gavi support

ROUTE OF TRANSMISSION AND LOCATION OF DISEASE BURDEN HELP ILLUMINATE WIDE RANGE OF UPTAKE DYNAMICS

Route of transmission	Disease burden: Predominantly low- and middle-income countries	Disease burden: Both	Disease burden: Predominantly high-income countries
Hospital acquired[1]			▶ ***Acinetobacter baumannii*** ▶ ***Enterobacteriaceae*** ▶ ***Enterococcus faecium*** ▶ ***Klebsiella pnemoniae*** ▶ ***Pseudomonas aeruginosa***
Both		▶ ***Escherichia coli***	▶ ***Staphylococcus aureus***
Community acquired	▶ *Campylobacter* spp. ▶ *Mycobacterium tuberculosis* ▶ *Salmonella* spp. ▶ *Shigella* spp.	▶ ***Haemophilus influenzae*** ▶ *Helicobacter pylori* ▶ *Neisseria gonorrhoeae* ▶ ***Streptococcus pneumoniae***	

Gut commensal Non-gut commensal

1) Although hospital acquired infections are present in both low / mid and high income countries, the concentration of hospitals tilts the distribution toward high income countries, additionally data on disease burden is more available for high income countries.

Source: UpToDate, Roca et al 2012 Front Microbiol, Henriques-Normark 2010 Exp Cell Res, King 2012 Clin Transl Med.

is heavily influenced by health impact, and Gavi's criteria for support currently places significant emphasis on reducing mortality, low mortality may limit Gavi support.

The mode of transmission is also a key factor in developing vaccination strategies. Community-acquired infections usually require routine vaccination. This comes with well-understood benefits and challenges of joining the existing schedule. Hospital-acquired infections may require more targeted strategies. However, these targeted approaches are currently less well-defined, and this significantly impacts the probability of uptake.

Developing a cost-effective vaccination strategy to drive uptake is challenging for hospital-acquired infections that lack a clear, well-defined target population. For example, although ***K. pneumoniae*** is common cause of hospital-acquired infections, accurately predicting who is at risk of infection remains a significant challenge. As infections cannot be accurately predicted, a large population would have to be vaccinated. This approach would significantly reduce cost-effectiveness, and therefore impact uptake.

Finally, without compelling evidence of significant mortality and morbidity it may be particularly challenging to drive the high global uptake of a vaccine required to realise a potential impact. For example, ***H. pylori*** is associated with peptic ulcer disease, which is often not seen as a serious health condition. Although evidence suggests that ***H. pylori*** also causes gastric cancer there is little public awareness of this link, potentially limiting the appetite for vaccination.

The results of the assessment across all of the pathogens can be seen on the heatmap on the following page, which displays all the scorecard assessments side-by-side.

PATHOGEN COMPARISON TABLE

	Impact				Probability of R&D success			Probability of Uptake			
	Mortality	Morbidity	Antibiotic use	Urgency of AMR threat	Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D	Barriers to uptake	Expected policy stance	Payer, government or Gavi support	Commercial attractiveness
A. baumannii											
Campylobacter spp.											
E. coli (enteric)											
E. coli (urinary)											
E. faecium											
Enterobacteriaceae											
H. influenzae											
H. pylori											
K. pneumoniae											
M. tuberculosis											
N. gonorrhoeae											
Non-typhoidal *Salmonella*											
P. aeruginosa											
S. aureus											
S. pneumoniae											
Salmonella Paratyphi											
Salmonella Typhi											
Shigella spp.											

Favourability for vaccine development: Low Fairly low Medium Fairly high High

Note: The colour-coding reflects each pathogen's scorecard score on the variables specified in the columns. Scores range from 0-2. A score of 0 indicates low health impact, probability of R&D success or probability of uptake and is represented in dark red, reflecting low favourability for vaccine development. A score of 2 indicates high health impact, probability of R&D success or probability of uptake and is represented in dark green, reflecting high favourability for vaccine development

Pathogen clusters identified through this assessment

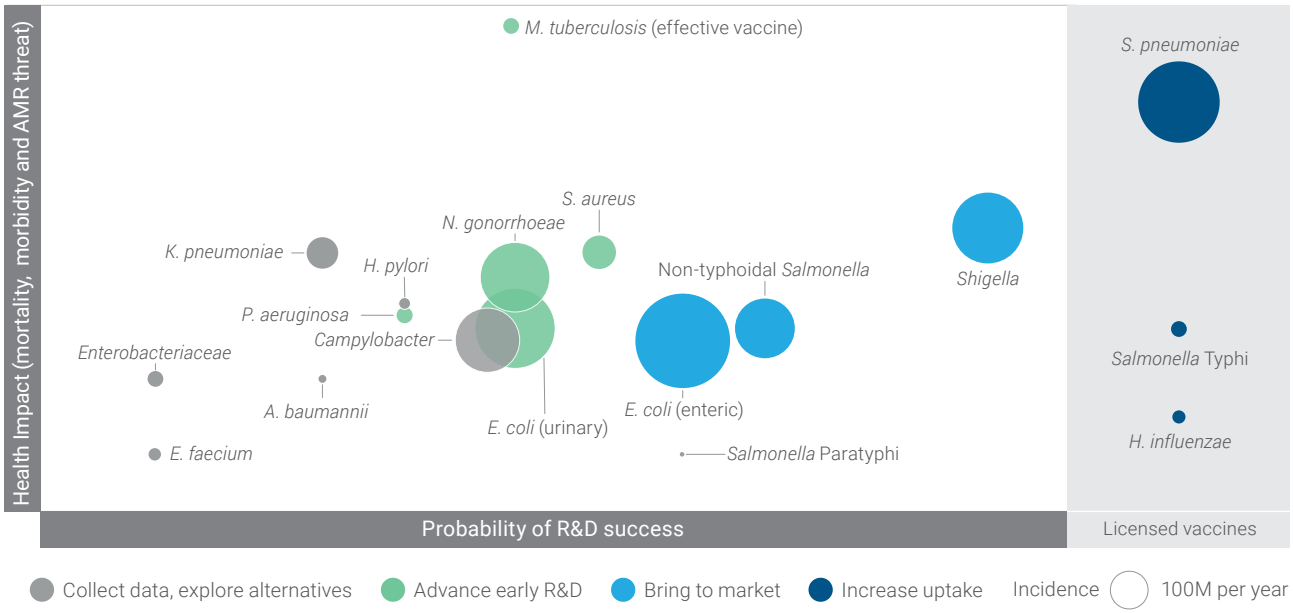
Despite significant differences across the pathogens in this report, clear clusters emerge when comparing the health impact of the pathogen and the probability of R&D success. The matrix below shows the composite health impact score on the Y-axis versus the composite probability of R&D success on the X-axis, and helps to identify relevant pathogen clusters. This matrix can then be used to guide prioritisation of vaccines for development.

This assessment resulted in the identification of pathogen clusters that can help prioritise interventions, as illustrated in the figure below:

- The **"increase uptake" cluster** (dark blue) is composed of effective, marketed vaccines where the key intervention is to increase uptake
- The **"bring to market" cluster** (light blue) is composed of pathogens with significant potential health impact where knowledge of pathogen biology and R&D is sufficiently advanced to concentrate on accelerating vaccines through clinical development to market
- The **"advance early R&D" cluster** (green) is composed of pathogens with significant health impact where more investment in early-stage R&D is needed to develop and advance a robust pipeline of vaccine candidates
- The **"collect data, explore alternatives" cluster** (grey) is composed of pathogens that are less well-suited to vaccine development, as well as pathogens where more information is needed to determine whether vaccine development should be a priority

Each pathogen falls within its cluster for a set of different reasons. It is therefore important to understand each pathogen in addition to its cluster when prioritising efforts. A summary for each pathogen is included below. A full discussion of this matrix is included in the appendix.

PATHOGEN SEGMENTATION BASED ON ASSESSMENT CREATES CLUSTERS THAT CAN HELP PRIORITISE INTERVENTIONS



Weighting used for chart

Health Impact – Mortality (50%), Morbidity (20%), AMR (30%).
Prob. of R&D success – Pathogen biology (30%), Pre-clinical and clinical R&D (30%), Pipeline robustness (40%).

Notes: Probability of R&D success (x-axis) was scored by totalling the weighted scorecard scores for each pathogen on: pathogen biology, pre-clinical and clinical R&D and pipeline robustness using the weighting listed below. The range of the combined score is 0-100.

Health impact (y-axis) was scored by totalling the weighted scorecard scores for each pathogen on: mortality, morbidity and urgency of AMR threat using the weighting listed below. The range of the combined score is 0-100.

1) Mortality and morbidity for Haemophilus influenzae B is currently low due to effective vaccine, but would be high without vaccine coverage
2) TB assessment here is of efforts to develop a highly efficacious vaccine.

Pathogen clusters

Increase uptake for existing, effective vaccines

Pathogens on the WHO list with effective vaccines include *H. influenzae*, *S. pneumoniae* and *S.* Typhi:

- Although uptake of ***H. influenzae*** vaccine is relatively high globally at ~70%, continued efforts can be made to maintain and further expand coverage, particularly in certain geographies.
- Increasing uptake of the ***S. pneumoniae*** vaccine presents a significant opportunity; this vaccine is effective for 13 serotypes and used in high, middle and low-income countries, but currently only has ~40% coverage.
- A new, conjugated ***S.*** Typhi vaccine has recently been pre-qualified by the WHO and is supported by Gavi for introduction in 2019, following effectiveness trials. Upon completion, efforts should focus on successfully introducing a vaccination programme.

Bring to market new vaccines where protective immunity to the pathogen is understood by accelerating clinical develoment

Pathogens on the WHO list in this category include *E. coli* (enteric), non-typhoidal *Salmonella* and *Shigella*:

- The high antigenic diversity of ***E. coli*** (enteric) is a challenge for vaccine development, but inclusion of LT toxoid and fimbrial antigens in a potential vaccine may help cover 70-80% of strains.
- A non-typhoidal ***Salmonella*** vaccine appears technically promising and potentially impactful, given high disease burden in Africa.
- A vaccine against ***Shigella*** would represent a major opportunity in this segment due to high incidence and significant associated mortality, particularly in low- and middle-income countries.

Advance early R&D for high impact pathogens with unclear R&D feasibility, by investing in early stage research

Pathogens on the WHO list in this category include *M. tuberculosis* (due to sub-optimal effectiveness of BCG vaccine), *N. gonorrhoeae*, *P. aeruginosa*, *S. aureus* and *E. coli* (urinary):

- There is a strong case for vaccine development for ***M. tuberculosis*** given its health impact and AMR threat. However, current difficulties in understanding pathogen biology and translatability of pre-clinical research must be overcome.
- The case for development of a vaccine targeting ***N. gonorrhoeae*** is strong due to high incidence, high morbidity, and current circulation of resistant strains. Although significant development challenges remain, evidence of MenB vaccine cross-protection has fostered fresh optimism in the expert community.
- ***E. coli*** (urinary) has a high incidence and would be attractive for targeted vaccination in high-income countries, but antigen selection remains a challenge
- Vaccine development for ***P. aeruginosa*** is attractive for high-risk patient groups, such as cystic fibrosis patients, but vaccine development is difficult because the target population is predominantly composed of immunocompromised patients.
- Morbidity and mortality from ***S. aureus*** in high-income countries means the market for a vaccine is attractive, with significant commercially-driven activity. However, there are significant gaps in understanding disease burden and identifying vaccine targets and animal models have limited predictive capability.

Collect data and explore alternatives for those pathogens on the list less well-suited to vaccine development due to significant outstanding epidemiological questions, low incidence and associated mortality and morbidity, or preferable alternative strategies

Pathogens on the WHO list that are not currently well-suited to vaccine development include: *A. baumannii*, *Campylobacter*, *E. faecium*, *Enterobacteriaceae*, *H. pylori*, *K. pneumoniae* and *S.* Paratyphi:

- ***S.*** Paratyphi has low incidence and low associated mortality and morbidity, consequently, uptake of a standalone vaccine is unlikely. Therefore, the priority should be to explore combination vaccines with *S.* Typhi.
- More data is needed on ***Campylobacter*** transmission in low- and middle-income countries, particularly to understand whether transmission occurs through environmental pathways or from animal reservoirs. This will guide a determination on whether a human vaccine should be pursued or whether alternatives, such as animal vaccination, will be the preferred approach.
- A better understanding of the link between ***H. pylori*** and gastric cancer, as well as a better understanding of how AMR is likely to evolve due to current treatability of the pathogen, is necessary.
- ***K. pneumoniae*** has a higher burden than most other hospital-acquired infections, but more data is needed to help determine whether there are predictable sub-populations to target for clinical development and vaccine delivery. Additionally, further study is needed to more accurately estimate the disease burden.

- Due to the comparatively low incidence, morbidity, and mortality of ***Enterobacteriaceae***, ***A. baumannii*** and ***E. faecium***, they are not considered strong candidates for vaccine development. Alternatives, such as passive immunisation, should be explored. Additionally, these pathogens are Gram-negative pathogens that cause hospital-acquired infections in small, immunocompromised target populations. These characteristics present particularly challenging hurdles for vaccine development.

A detailed assessment and recommendations for each pathogen can be found in the individual pathogen chapters.

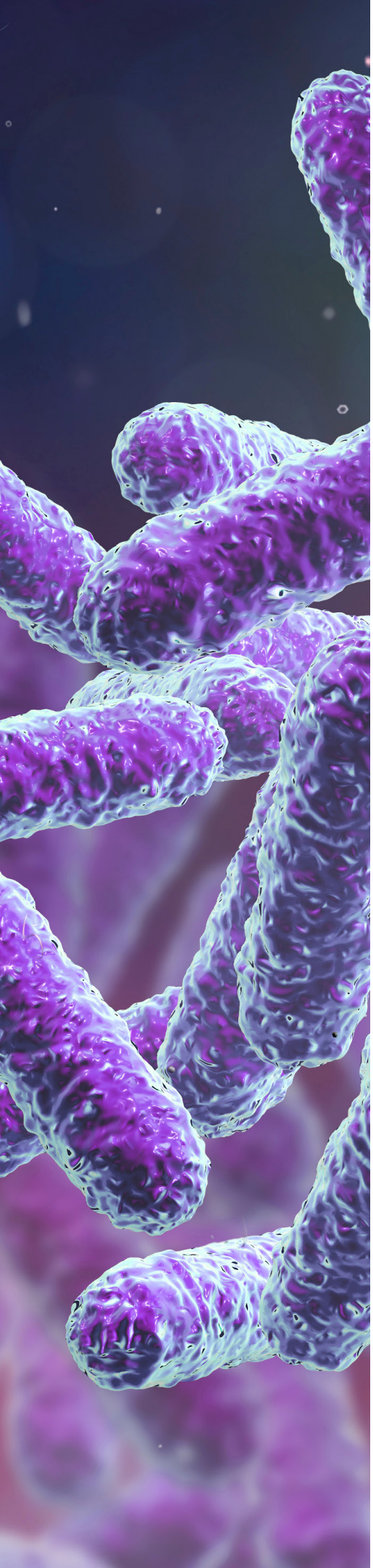
Based on its cluster, each pathogen has a primary, or most critical, recommendation for intervention which has been summarised in the following table. Secondary recommendations, which detail other actions that can help advance vaccine development or uptake for each pathogen, have also been included.

SUMMARY OF INTERVENTION RECOMMENDATIONS

			Intervention						
			Explore alternatives (e.g., monoclonals)[1]	Better understand burden/ epidemiology/ transmission	Incentivise multi-pathogen / combination vaccines	Pre-clinical research (e.g., antigen discovery & selection, animal models)	Improve translatability and/or support more first-in-human trials	Accelerate clinical development	Drive coverage and equity
Pathogen clusters	Increase uptake	*H. influenzae*		✓					✓
		S. pneumoniae				✓			✓
		S. Typhi			✓				✓
	Bring to market	*E. coli* (enteric)		✓	✓	✓		✓	
		Non-typhoidal *Salmonella*		✓	✓			✓	
		Shigella spp.			✓			✓	
	Advance early R&D	*M. tuberculosis*[2]				✓	✓		
		N. gonorrhoeae			✓	✓	✓		
		E. coli (urinary)	✓	✓		✓			
		P. aeruginosa	✓	✓		✓			
		S. aureus	✓	✓		✓	✓		
	Collect data, explore alternatives	*S.* Paratyphi			✓			✓	
		Campylobacter spp.	✓	✓	✓				
		H. pylori	✓	✓		✓			
		K. pneumoniae	✓	✓		✓			
		A. baumannii	✓	✓					
		E. faecium	✓	✓					
		Enterobac-teriaceae	✓	✓					

✓ Primary Recommendation ✓ Secondary Recommendation

1) Requires better understanding of disease biology (i.e., investments in pre-clinical research). Recommendations have focus on vaccine dev; 2) BCG vaccine is excluded here. Focus on broadly efficacious TB vaccine.



Cross-cutting activities

Through the process of making detailed recommendations specific to each pathogen, this report also identified knowledge gaps shared across multiple pathogens. Based upon these, several cross-cutting activities have been proposed which, if implemented, would stimulate development of vaccines for all pathogens with high levels of AMR. The focus of this chapter is limited to activities specific to the pathogens in this report. It does not cover recommendations that apply more widely to the vaccine industry.

The cross-cutting activities are summarised according to the three main categories on the pathogen scorecards. They span the entire process of vaccine development – from understanding health impacts and accelerating R&D to reducing R&D costs and ensuring widespread uptake for marketed vaccines. These interventions may accelerate development across many, or all, of the AMR priority pathogens, and could represent particular areas of interest for individuals and institutions interested in impact across multiple pathogens.

Health impact

Developing a detailed understanding of the direct and indirect health impacts of a vaccine is critical to making a compelling public health investment case. In this report, the potential health impact of vaccines was assessed based upon the global burden of disease associated with the relevant pathogen. To drive positive policy changes, funding and vaccine uptake, this assessment could be enhanced by generating better data on the burden of some pathogens and employing more sophisticated dynamic modelling techniques.

Promote the collection of robust epidemiological data: In the process of compiling this report, a paucity of global burden of disease data was noted for many pathogens. Estimates were produced to fill these gaps and a detailed explanation of the methodology is included in the appendix. Going forward, the global health community would benefit from collaborative, concerted efforts to improve epidemiological knowledge. This includes knowledge for pathogens where data is already available as, at present, it represents a good estimation, but is far from exact.

The pathogens on the WHO AMR priority pathogen list are found, in differing extent, in low- middle-, and high-income countries. Collecting data on the burden of disease is especially difficult in low- and middle-income countries with poor access to healthcare and weak health surveillance infrastructure. Even in high-income countries, data quantifying the burden of disease is often limited and varies in both quality and scope. Of the pathogens included on this list, high quality data is particularly scarce for those that cause hospital-acquired infections in low and middle-income countries.

The WHO and IHME both publish regular assessments of the global burden of disease. However, this data is often provided at the level of disease (e.g., "skin infection") and does not provide granularity at a pathogen level (e.g., "*S. aureus* skin infection"). Global burden data exists for ***S. pneumoniae, M. tuberculosis, N. gonorrhoeae, Shigella, Campylobacter, Salmonella, E. coli*** (enteric) and ***H. influenzae***. Further, data on the global burden of enteric disease has been gathered through a number of well-funded, multi-country, multi-pathogen studies. These include both the Global Enteric Multicenter Study (GEMS) [16], the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the

Consequences for Child Health study (MAL-ED) [17], and the World Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in 2010 [18]. The challenging nature of gathering data of this kind has led experts to express concerns about the quality of current enteric disease burden estimates. This highlights that even where data exists, it is often imperfect and efforts to improve its quality should continue. Several outstanding questions have been highlighted including the relative importance of different transmission routes for ***Campylobacter*** and the regional burden of enteric ***E. coli*** and non-typhoidal ***Salmonella***.

However, global burden data does not exist for infections caused by ***S. aureus, H. pylori, A. baumannii, P. aeruginosa, Enterobacteriaceae, K. pneumoniae or E. faecium*** (see methodology appendix for more information on how estimations were made).

Many epidemiological studies focus on either a single pathogen or a single geography. Whilst acknowledging that expanding studies to cover more than one country can be challenging, the existing multi-country, multi-pathogen studies on enteric disease prove that this is possible. Additional multicentre studies would provide scale to research efforts and may make data more robust.

Model the evolution of AMR and potential health impact of interventions: The assessment in this report is based upon the most up-to-date available data for each pathogen and provides a good starting point for the analysis of health impact. However, AMR is a complex and constantly evolving threat. In addition, vaccine efficacy, pathogen transmission dynamics, and vaccine uptake have not been factored in to the assessment.

Whilst these simplifications still allow for a useful comparison of the pathogens within this report, a more comprehensive model, perhaps derived through a consortium effort, could allow for the evaluation of the contribution of different interventions (e.g. vaccines, sanitation, and therapeutics) to reducing the prevalence of drug resistance in individual pathogens. A first step may be to harmonise modelling strategies, methodologies and assumptions so that more useful comparisons can be drawn amongst disparate models.

More definitive pathogen models, or consortia of models, would serve as a common resource for the global health community. These models would also be useful to support policy making and funding decisions once vaccines are licensed.

In addition to the need for robust data on the global burden of disease (discussed above), there are three inputs which would be critical for the modelling process:

- Data on the antibiotic usage associated with a pathogen. This would require a significant international effort to collect suitable input data. Whilst some data exists on global antibiotic usage, going forward this data should be linked to specific pathogens, and efforts should be made to encourage others to follow the process and record data in a standardised manner.
- Data on the prevalence of resistant strains for each pathogen. The recent announcement of an "AMR project" to integrate such data as part of IHME's Global Burden of Disease dataset is a very positive step forward in these efforts [19]. The Wellcome Trust is working closely with the IHME and co-funding this work.
- Data on the impact of vaccines in reducing antibiotic usage and the prevalence of resistant strains. Limited data is available for the impact of ***S. pneumoniae*** and ***H. influenzae*** vaccines on these outcomes, but should be collected for other marketed vaccines.

Research and development

The challenges of bringing a vaccine to market are well documented and this report does not seek to directly tackle this wide-ranging topic. Rather, it aims to highlight activities that could address several of the pathogens included in this report, with a specific focus on reducing the AMR threat.

Target investment to new R&D platforms relevant to AMR pathogens: There are a range of promising new technologies, platforms and pre-clinical approaches that could aid vaccine development for the pathogens listed in this report. Examples include DNA and RNA vaccines, viral vectors, nanoparticles, novel delivery/administration technologies, and modular manufacturing platforms. These platforms have the potential to both significantly lower vaccine manufacturing costs and to facilitate development of polyvalent vaccines – two key issues in R&D for many AMR priority pathogens.

Not all new platforms will be equally useful at addressing the pathogens in this report – some may have wide ranging benefits with regards to vaccine development as a whole, but have little specific utility in addressing the AMR threat. In order to maximise impact, new platforms should be assessed against the unique requirements of pathogens with high levels of AMR. For example, many of these pathogens exhibit high antigenic variation. This issue complicates vaccine development and would be well addressed by the use of new platforms that allow for multiple antigens to be targeted simultaneously at a low cost. Experts expressed optimism that vector-based

platforms, such as DNA vaccines, viral vector vaccines, and novel conjugation techniques could all provide a step-change in the ability to target multiple antigens in a single vaccine.

Collaborate for regulatory innovation: In North America and Europe, the impact of vaccines on AMR and antibiotic prescribing is not currently considered as a reportable outcome by any major regulatory body. Inclusion of AMR and antibiotic prescribing as a reportable outcome would increase the evidence-base supporting the use of vaccines to tackle AMR [20].

There has been a growing interest in the use of real-world evidence (RWE) to support pharmaceutical development [21]. Efforts in vaccine development are currently limited to proof-of-concept studies[22] but may provide a more affordable method of collecting data in the future.

Experts also expressed the opinion that additional opportunities for industry and regulators to convene would help foster closer ties. This could take the form of individual companies meeting with their individual regulator or meetings convened between industry and multiple regulatory agencies. These convenings should be international, where possible, to share expertise and harmonise processes where this is appropriate.

Uptake

Vaccines against AMR priority pathogens face particular barriers to uptake, owing either to the concentration of prevalence in low- and middle-income countries or the challenging economics of vaccinating small target populations. This is discussed in detail in the chapter on pathogen comparisons. However, across groups of pathogens there are common recommendations:

Continue to utilise and improve market shaping interventions where needed: For pathogens where there is a clear commercial vaccine market in high-income countries – for example, ***S. aureus*** – early discussion with payers and policy makers would likely improve vaccine uptake. Improving uptake is unlikely to require market shaping interventions. However, more robust burden of disease data would be beneficial, as discussed earlier in this chapter. Vaccines targeting pathogens where there is a clear Gavi market and significant public / philanthropic funding of R&D, such as for ***M. tuberculosis,*** are also unlikely to require any further market shaping interventions.

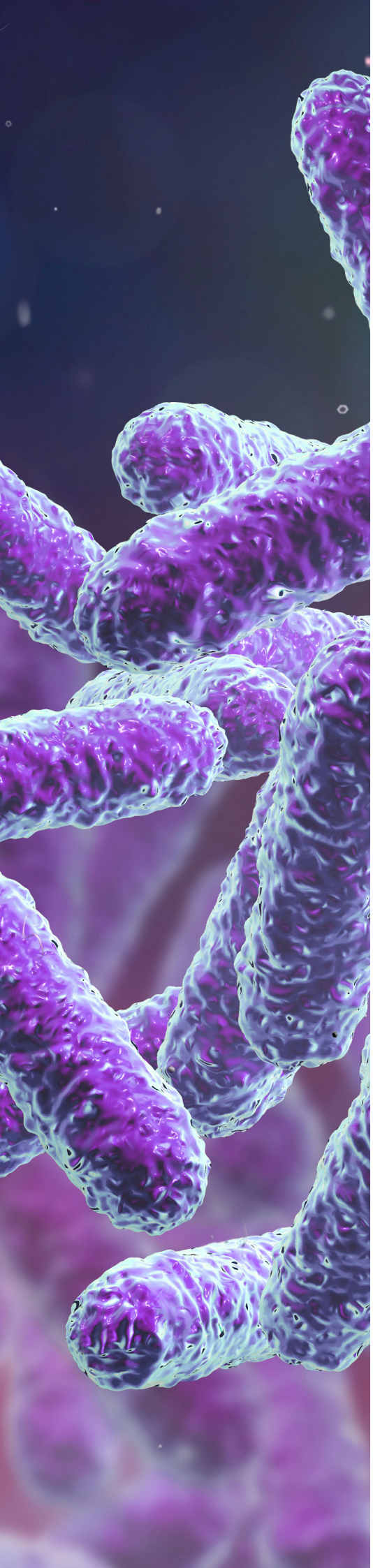
Many of the pathogens in this report predominantly impact low- and middle-income countries where Gavi support is essential for vaccination uptake. However, some potential vaccines are borderline or unlikely candidates for Gavi support. Gavi has recently incorporated impact on reducing AMR as a criteria in its Vaccine Investment Strategy (VIS) which determines the vaccines that are supported in its portfolio. Gavi's continuing shift to place more emphasis on reducing AMR will favour vaccine development for pathogens with high levels of AMR. In order to support pathogens where the pipeline is at a much earlier stage, there may be some benefit from Gavi indicating its interest in pathogens beyond the current five-year window of their VIS.

Develop the health economic case for vaccination: Gathering robust data on burden of disease is a key recommendation earlier in this chapter and is absolutely essential to making the health economic case for vaccination. This data can then be translated into both direct costs to the patient and health care system, as well as indirect costs related to the economic impact of a pathogen. These indirect costs include loss of GDP driven by lower productivity, premature deaths, and the costs of informal care (e.g. individuals caring for ill relatives). Modelling these costs on a national or regional level is a significant undertaking, but is crucial to drive positive policy change.

In addition to the metrics commonly included in health economic evaluations, the assessment of vaccines for pathogens with high levels of AMR could also include consideration of the potential cost savings associated with reducing AMR in the wider population. Frameworks for incorporating this value would need to be established.

CROSS CUTTING ACTIVITIES CAN IMPROVE OUTLOOK FOR ALL AMR PRIORITY PATHOGENS IN SCOPE

Dimension		Recommendation	Description
Dimension	**Health impact**	Promote collection of robust epidemiological data	▶ Collect robust global burden and AMR data for pathogens where this is absent or incomplete ▶ Pool resources and co-ordinate study methodologies where possible for groups of pathogens to enable multi-pathogen data collection (eg hospital acquired infections)
		Model evolution of AMR threat and potential health impact of interventions	▶ Build a single model / consortium of modellers for each pathogen to project the evolution of AMR threat over time and the direct health impact of proposed interventions ▶ Collect more AMR-specific data such as resistance rates, antibiotic usage and impact of vaccines on AMR
	R&D	Target investment to new R&D platforms relevant to AMR pathogens	▶ Assess the potential of new platforms and technologies specifically in their ability to support R&D for AMR pathogens ▶ Target investment towards platforms that have the potential to accelerate development and improve probability of success of candidate vaccines for AMR pathogens
		Collaborate for regulatory innovation	▶ Engage with regulators to explore inclusion of AMR-related end points and RWE in vaccine trials ▶ Convene regular meetings between industry and regulators
	Uptake	Utilise market shaping intervention	▶ Encourage Gavi to deepen its focus on AMR and signal potential support for vaccines in earlier stages of development
		Develop the health economic case for vaccinations	▶ Use global burden data and health economic impact models to align policy and payer support towards the utility of vaccines in reducing the burden of AMR infections



Pathogen-specific information

Acinetobacter baumannii

Executive summary

Acinetobacter baumannii (***A. baumannii***) primarily causes a hospital-acquired infection affecting patients in intensive care settings, and commonly presents as pneumonia. While there is a high urgency of AMR threat, mortality and morbidity are low.

There is no current vaccine for ***A. baumannii*** and the pipeline is empty. Pathogen biology and host immunity are poorly understood, and difficulties in differentiating between colonisation and infection will likely make study design challenging. Given the limited current state of understanding and technical challenges of developing a vaccine, the likelihood of R&D success in developing a vaccine against ***A. baumannii*** is low.

Uptake for a vaccine against ***A. baumannii*** faces significant hurdles due to low incidence and difficulty developing vaccination programmes for key target populations. Intensive care patients are the most likely target population for vaccination, but it can be difficult to predict which patients will require intensive care. Neonatal patients in some geographic areas are also at risk of ***A. baumannii*** infection but vaccination of such young patients is not routinely performed. Additionally, the cost-effectiveness of vaccination for ***A. baumannii*** is questionable because low incidence of infection results in low burden of disease. Therefore, payer, government, or Gavi support is unlikely.

Recommendations

A. baumannii falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority. Due to the comparatively low incidence, morbidity and mortality caused by ***A. baumannii***, it is not currently a strong candidate for vaccine development.

The primary recommendation is to explore alternative treatments or prevention strategies, including passive immunisation strategies, which may be better suited to the timing of administration likely required for intensive care patients, and bacteriophages. The secondary recommendation is to conduct additional studies in order to better understand the global disease burden.

SCORECARD *ACINETOBACTER BAUMANNII*

Health impact:

Direct health impact

0.0	0.0
Mortality	Morbidity

Impact on AMR reduction

0.0	2.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Intensive care patients
Long-term ventilated patients
Neonates in SE Asia

Alternative interventions
Passive immunisation
Bacteriophages

Probability of R&D success:

0.0	0.5	0.5
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
Not applicable; vaccine development not recommended

Acceleration potential
Not applicable; vaccine development not recommended

Major barriers to development
Poorly defined target population

Probability of uptake:

0.0	0.0	0.0	0.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Hospitalised patients / High-risk groups such as pre-elective surgery patients

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

A. baumannii is a Gram-negative bacterium [23]. *A. baumannii* is ubiquitous and occurs mostly as a commensal pathogen on the skin but is also found in soil, water and plants. It is predominantly hospital-acquired and usually affects patients in the intensive care setting. Clinical manifestations vary by infection site and include:

- Pneumonia, manifesting as dyspnoea, fever, tachypnoea, increased or purulent secretions, haemoptysis, reduced breath sounds, or bronchospasm [24,25]. Pneumonia is usually ventilator-associated, but *A. baumannii* can also rarely cause community-acquired pneumonia [24]
- Central line associated infection, manifesting as erythema, and swelling around line or recent line insertion, pyrexia, tachycardia, tachypnoea, or malaise
- Surgical site infections, manifesting as erythema, pain, swelling, or wound dehiscence [24]
- Catheter associated urinary tract infections, manifesting as cloudy urine, leakage around catheter, pyrexia, tachycardia, tachypnoea, or malaise [24,26]

A. baumannii is transmitted through person-to-person contact such as from the hands of healthcare workers or contact with contaminated medical equipment. In addition, airborne transmission also likely occurs [27]. Populations at greatest risk of contracting *A. baumannii* infection are patients in the intensive care setting or on mechanical ventilation and neonates in India and South East Asia [28].

A. baumannii is widely distributed geographically but the type of infection varies by region. Hospital-acquired infections are reported in Europe, North America, Asia, and the Middle East. In addition, it is a rare cause of community-acquired infections in South Asia, Australia, and the Pacific Islands [24,29,30] Expert interviews suggest that the mortality rate caused by *A. baumannii* in low-income countries is likely similar to that in high-income countries.

Potential health impact

Direct health impact

Global data on disease burden is not directly available from the IHME, WHO, or research literature [31,32] However, research literature suggests ***A. baumannii*** causes 1% of lower respiratory tract infections [33]. For other clinical syndromes, there is insufficient data on disease burden caused by ***A. baumannii***, or insufficient cases to draw a conclusion about the burden of disease caused by ***A. baumannii*** [34,35]. Expert interviews suggest that mortality may be underestimated because of the lack of high-quality data regarding neonatal sepsis which is a significant contributor to overall mortality rates. One expert states "[Lack of data is] something we struggle with continually… there are no good, broad studies that help you identify the disease burden" [28] and another calls out the lack of current estimates for neonatal deaths from primary sepsis as a notable inaccuracy, stating, "[the estimates do] not account for sepsis [and] neonatal deaths [from ***Acinetobacter*** infection] are primary sepsis" [28]. Experts also acknowledge that whilst the best quality data is from high-income countries, they believe the neonatal sepsis burden is highest in India [28]. Therefore, the level of confidence in these estimates is relatively low. A full methodology for these estimates is provided in the appendix.

Scoring: Based on the above analysis, mortality was categorised as low (score of 0 out of 2) and morbidity was categorised as low (score of 0 out of 2).

Sub-population benefits

Intensive care patients, patients who rely on mechanical ventilation, and neonates in South East Asia, the groups at highest risk of ***A. baumannii*** infection, would benefit the most from vaccination.

Antibiotic use

Recommended antibiotic treatment regimens differ by country, in part reflecting local resistance profiles. Regimens vary in length but a typical regimen consists of a week or more of intravenous broad-spectrum antibiotics. However, given that ***A. baumannii*** infection is rarely diagnosed and doctors prescribe treatment based on clinical presentation, it is difficult to know what percentage of cases are treated in accordance with this standard.

Scoring: Based on the above analysis, antibiotic use was categorised as low (score of 0 out of 2). This estimate is based on the relatively low annual incidence of ~three million LRTIs treated with a one week course of antibiotics.

Urgency of AMR threat

Both the WHO and CDC have expressed strong concern about antibiotic resistance developed by ***A. baumannii***. The WHO has listed ***A. baumannii*** as a critical priority for R&D regarding new antibiotics [32] and the CDC has listed ***A. baumannii*** as a serious threat in its list of greatest threats from AMR [7]. The incidence of multi-resistant and extensively resistant strains is rising [36]. Multiple untreatable pan-resistant strains have been reported in intensive care and paediatric patient groups [37–39].

Based on the above analysis, the urgency of AMR was categorised as high (score of 2 out of 2).

Probability of R&D success

Pipeline robustness

The pipeline for ***A. baumannii*** vaccine development is empty. There are no clinical or pre-clinical vaccine candidates that have been identified in the pipeline analysis, which includes candidates listed in commercial databases or in recent high impact literature reviews[40–42].

Scoring: Based on the above analysis, the pipeline robustness was categorised as low (score of 0 out of 2).

CURRENT PIPELINE *ACINETOBACTER BAUMANNII*

Pathogen biology

The low incidence of ***A. baumannii*** infection has precluded an understanding of natural immunity to date [28], and very little is known about host defence mechanisms. A mouse model suggests that mice that have recovered from a previous ***A. baumannii*** infection remain susceptible to reinfection [43].

There is somewhat promising, early pre-clinical work in mouse models on vaccine target development and several potential antigens and approaches to developing a vaccine against ***A. baumannii*** have been identified. However, it is not known how viable these targets will be in humans. These targets include:

- Formalin inactivated whole cells [44]: pre-clinical testing of inactivated whole cells generates robust antibody titres and high survival rates in experiments with mice, suggesting that these vaccines produce functional immunity
- Outer membrane vesicles [45]: ***A. baumannii*** secretes outer membrane vesicles which interact with host cells
- Protein-based vaccines including:
  - Recombinant outer membrane protein A of ***A. baumannii*** [44]: experiments with a mouse model suggests that a vaccine using OmpA would confer protection
  - Recombinant Bap [44], a subunit of a surface protein of ***A. baumannii***, has been shown to be associated with biofilm formation

Scoring: Based on the above analysis, pathogen biology was categorised as fairly low (score of 0.5 out of 2).

Pre-clinical and clinical R&D

Mouse models, including models for pneumonia and wound infection, are being used to study the pathogen, but the clinical relevance of these models is unclear [46]. Clinical development of a vaccine against ***A. baumannii*** would be difficult. The low incidence of disease would make adequately powered late-stage efficacy trials difficult to conduct. Furthermore, ***A. baumannii*** infection usually occurs in immunocompromised patients who may not mount an adequate immune response to the vaccine.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as fairly low (score of 0.5 out of 2).

Probability of uptake

Expected policy stance

Two distinct populations could benefit from vaccination – patients at high risk of intensive care admission with mechanical ventilation, and neonates. Both populations pose significant challenges for development of a vaccination strategy. Identifying patients at risk of ***A. baumannii*** infection is a major challenge due to the inherent unpredictability of urgent and emergency hospitalisation. Techniques to predict which patients may have a higher absolute risk of infection are not currently available, and although there may be a cohort of patients undergoing major elective surgery who might be at high relative risk of infection, the absolute risk remains very low, so vaccination may not be cost-effective. Vaccination at birth in areas with high rates of neonatal sepsis would be challenging as vaccines are not routinely administered this early in life and there is mixed evidence on efficacy of neonatal vaccination [47,48] Maternal vaccination may be possible as long as a live vaccine was not used [47–51].

At a meeting on vaccination in older adults convened by WHO in 2017, ***A. baumannii*** was mentioned as a pathogen for which AMR may be a reason to explore developing a vaccine. Despite this, experts did not think a routine vaccination strategy would be feasible and found it difficult to define a target population suitable for vaccination, limiting the likelihood of policy support. As one expert notes "even if the vaccine could be made, who would you give the vaccine to? We struggle to get adults to take influenza vaccine where we have 500,000 deaths every year. We can't define the population for which it would be cost-effective to give vaccine" [28].

Scoring: Based on the above analysis, expected policy stance was categorised as low (score of 0 out of 2).

Payer, government, or Gavi support

Without persuasive evidence of disease burden, it would be very difficult for payers or government to calculate the cost-effectiveness of vaccination. Therefore, support for vaccination in high-income countries is unlikely based on current data. The same is true for middle-income countries. Furthermore, based on limited current evidence, it is not likely that vaccination would meet middle-income countries' thresholds for cost-effectiveness. In low-income countries, current data on mortality is very limited, but mortality appears to be relatively low. Therefore, Gavi support is unlikely. However, the disproportionate burden on neonates in Gavi supported countries may encourage Gavi action.

Scoring: Based on the above analysis, payer, government or Gavi support was categorised as low (score of 0 out of 2).

Barriers to uptake

The difficulty in defining the target population for an ***A. baumannii*** vaccination presents a major logistical hurdle to vaccination uptake. In the most clear-cut case of vaccinating before planned surgical procedures, the vaccine would need to be incorporated into the pre-surgical care pathway for patients, which would be possible [52]. For other potential strategies, new touchpoints would need to be created.

If evidence was obtained for vaccination in new sub-populations, close engagement with guideline setting bodies and specialist societies would be required in order to ensure that licensure was translated into awareness and use of vaccine by clinicians.

Scoring: Based on the above analysis, barriers to uptake were categorised as high (score of 0 out of 2).

Commercial attractiveness

The commercial attractiveness of vaccination for ***A. baumannii*** is low. It is difficult to assess market size based on current epidemiological data and to define a well-circumscribed target population.

Scoring: Based on the above analysis, commercial attractiveness was categorised as low (score of 0 out of 2).

Recommendations

A. baumannii falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority.

Primary recommendation

The primary recommendation is to explore alternative treatments or prevention strategies for diseases caused by ***A. baumannii***. Given the low incidence of ***A. baumannii*** infections and difficulty in predicting which patients would most likely benefit from vaccination, passive immunisation with monoclonal antibodies represents an alternative strategy. Patients can receive monoclonal antibodies urgently or emergently, providing rapid protection against infection, which lasts for several weeks, making this approach potentially better-suited to patients in the intensive care setting than conventional vaccines. Initial work in mouse models of infection has demonstrated improved survival using monoclonal antibodies targeting

an ***A. baumannii*** capsular carbohydrate [53]. It is likely that development of monoclonal antibodies against ***A. baumannii*** would require further study of pathogen biology in order to identify potential targets for antibodies. Although developing a strategy for passive immunisation would face similar difficulties as developing a strategy for vaccination patients could be more easily targeted with monoclonals given the emergent and often unpredictable nature of infection risk. Bacteriophages may provide another alternative approach to treating ***A. baumannii*** infection.

There is a case report of a patient with multidrug resistant ***A. baumannii*** who improved after intravenous administration of bacteriophages. The bacteriophage was selected from a phage library after testing against an ***A. baumannii*** culture from the patient [54]. Advantages of phage therapy are that it is more specific than antibiotics, so less likely to alter the microbiome, with lower risk of drug interactions and toxicities, and retained activity in the presence of biofilms [54,55] The principal disadvantage of bacteriophage therapy is that it requires more personalisation than antibiotics, vaccination or monoclonal antibodies, increasing the expense of treatment, and decreasing scalability [54]. Other disadvantages include the risk of rapid release of endotoxin (which ***A. baumannii*** produces) from bacterial cell lysis and risk of transduction of genetic material into the microbiome [55]. Experts convey that early data on bacteriophages appeared promising but that there are outstanding issues; bacteriophages are often very strain-specific and cannot infect and lyse all strains [28]. They also cite some concern about immune reactions to bacteriophages [28].

Secondary recommendation

A better understanding of the disease burden, epidemiology, and transmission of ***A. baumannii*** is needed. Studies of hospital-acquired pneumonia and ventilator acquired pneumonia have identified variable rates of ***A. baumannii*** infection (~5%- ~20% for hospital-acquired pneumonia and ~4%-~40% for ventilator acquired pneumonia [56]). ***A. baumannii*** has also been reported to cause surgical site infections [57,58]. Estimating the global burden of disease is particularly difficult given the paucity of data from low- and middle-income countries. In light of the apparent variability in infection rates, it would be useful to further characterise disease burden through multisite studies to understand within country variability in burden and through multi-country studies to understand the global burden. However, whilst better characterisation of the burden is needed and case fatality is high, it is unlikely that incidence estimates will change enough for ***A. baumannii*** to be prioritised for vaccine development.

Campylobacter

Executive summary

Campylobacter causes a community-acquired infection that presents as acute gastrointestinal illness [59] and is often transmitted through undercooked meat, especially poultry. It is a cause of significant morbidity, with about 290,000 years lived with disability annually, but causes limited mortality, with about 75,000 fatal cases annually.

There is no current vaccine for ***Campylobacter***. Only three candidates are in pre-clinical development and one has reached Phase I clinical trials. The current understanding of pathogenesis, protective epitopes and antigenic diversity is incomplete, providing researchers with few starting points for vaccine development. Given the limited current state of understanding and technical challenges to developing a vaccine, the likelihood of R&D success in developing a vaccine against ***Campylobacter*** is low.

Uptake of a potential ***Campylobacter*** vaccine faces significant barriers because it causes limited mortality and relatively minor symptoms. A vaccine is unlikely to be deemed cost-effective by payers, governments or Gavi, and would therefore most likely be limited to use amongst travellers and military personnel in high-income countries. Due to comparatively low mortality of ***Campylobacter*** infection, and the potentially limited cost-effectiveness of vaccination, it is not currently a strong candidate for vaccine development.

Recommendations

Campylobacter falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority. The primary recommendation is to better understand the disease burden, epidemiology, and transmission of ***Campylobacter***. This will guide a determination on whether a human vaccine should be pursued or alternatives, such as animal vaccination, are the preferred approach to controlling ***Campylobacter*** infection. Secondary recommendations are to explore alternative treatments or prevention strategies, explore combination vaccines for enteric diseases and support pre-clinical research if vaccine development is recommended at a later point.

SCORECARD *CAMPYLOBACTER* SPP.

Health impact:

Direct health impact

0.5	1.0
Mortality	Morbidity

Impact on AMR reduction

1.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
Possible association to lymphoma

Sub-population benefits
Children
Individuals with HIV

Alternative interventions
Animal vaccination
Improved access to supportive therapies

Probability of R&D success:

0.0	1.0	1.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
Explore combination with other enteric vaccines if vaccine development is later recommended

Acceleration potential
Develop better view on disease transmission

Major barriers to development
Lack of understanding of disease epidemiology / transmission

Probability of uptake:

1.0	1.0	1.0	1.5
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Greatest need in low-income countries / Routine infant vaccination in low & middle-income countries; Travellers' vaccination in high-income countries

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

Campylobacter is a Gram-negative bacterium that causes community-acquired infections. ***Campylobacter*** is not a normal part of the human gut microbiome [60]. ***Campylobacter*** infection typically presents as gastroenteritis with diarrhoea, fever, abdominal pain, and vomiting [60]. However, the disease is usually mild and self-limiting. As such, maintenance of proper hydration (including electrolyte correction) should be the focus of therapy. Antibiotics are not needed for most cases of ***Campylobacter***-associated gastroenteritis but are often prescribed [60].

Typical routes of transmission vary somewhat by region. In high-income countries, ***Campylobacter*** is transmitted through undercooked meat, especially poultry [60]**.** In low-income countries, however, many aspects of transmission are not well-characterised. It is not clear from what sources, how, and where individuals contract infections. It is also not known what role, if any, domestic animals play in infection, whether faecal contamination in the environment can cause infection, and how long ***Campylobacter*** can survive in the environment outside of a host. The role of host undernourishment in susceptibility to infection is also not well understood. Finally, the relevance of transmission to neonates and younger children within households is not yet understood. The Bill and Melinda Gates foundation has recently started an initiative to elucidate the transmission dynamics of ***Campylobacter*** in low- and middle-income countries [61].

Campylobacter is globally distributed, with higher incidence of infection observed in the WHO African, South East Asian, and Western Pacific regions [18]. Incidence of ***Campylobacter*** is higher in children than adults, particularly in Africa, South East Asia, and the Middle East [62]. Immunocompromised populations, including patients with AIDS, are at risk of disseminated infection [63].

Potential health impact

Direct health impact

Data on morbidity and mortality are available from the IHME 2016 estimates [64]. This source uses a defined methodology and is used in the global health community. The data can therefore be viewed with a reasonable level of confidence. The IHME estimates mortality from ***Campylobacter*** infection at approximately 75,000 cases per year and morbidity approaching 290,000 years lived with disability annually. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was categorised as fairly low (score of 0.5 out of 2) and morbidity was categorised as medium (score of 1 out of 2).

Secondary health impact

Evidence from lymphoma patients showing improvement in their cancer after antibiotic treatment, as well as biopsy specimens from cancer patients suggest a possible link between ***Campylobacter*** and lymphoma [65,66]. Some research suggests an impact of diarrhoeal disease on growth trajectories for children, especially amongst children with multiple diarrhoeal episodes [67,68]. However, it is possible that these children experience catch-up growth and return to normal growth trajectories [69].

Sub-population benefits

Children in regions with high incidence of ***Campylobacter*** infection – particularly Africa, South East Asia, and the Middle East [70] would benefit from a vaccine since children have a higher rate of ***Campylobacter*** infection. Immunocompromised populations such as patients with AIDS who are at risk of disseminated disease would also benefit.

Antibiotic use

Recommended antibiotic treatment regimens differ by country, in part reflecting local resistance profiles. Regimens vary in length but a typical course is three days of a macrolide or fluoroquinolone antibiotic [60].

Scoring: Based on the above analysis, antibiotic use was categorised as medium (score of 1 out of 2). This estimate is based on an annual incidence of ~90 million ***Campylobacter*** infections treated with a three day course of antibiotics

Urgency of AMR threat

Both the WHO and CDC have expressed concern about antibiotic treatments for ***Campylobacter*** infections. The WHO has listed ***Campylobacter*** as a high priority for R&D regarding new antibiotics [31] and the CDC has listed ***Campylobacter*** as a "serious" threat in its list of greatest threats from AMR [7].

Campylobacter is inherently resistant to trimethoprim and beta lactams [60]. Macrolides are still usually effective even in geographies where resistant strains are more common [60]. Fluoroquinolone resistance exceeds 80% in South East Asia and is on the rise globally [60]. However, alternative antibiotic treatments remain effective, including carbapenems, and aminoglycosides[60]. ***Campylobacter*** is typically also sensitive to clindamycin, tetracyclines, and chloramphenicol, although there is no data on the clinical efficacy of these antibiotics [60].

Scoring: Based on the analysis described above, the urgency of AMR threat was categorised as medium (score of 1 out of 2).

Probability of R&D success

Pipeline robustness

Four vaccine candidates are currently in development, three are in pre-clinical studies, and one, conducted by the United States military, is in a Phase I clinical trial.

Scoring: Based on the above analysis, the pipeline was categorised as low (score of 0 out of 2).

CURRENT PIPELINE *CAMPYLOBACTER* SPP.

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	01	01	-	-	-	02
Number of **commercial** vaccines	02	-	-	-	-	02
Total number of vaccines	03	01	-	-	-	04

Pathogen biology

Data suggest acquired protection against ***Campylobacter*** develops over time and with repeated exposure. The incidence of clinical disease falls with increasing age, particularly after five years of age [71] . Furthermore, human challenge studies demonstrate that previous infection can protect against homologous strains of bacteria. Experts confirmed that natural immunity is likely [28].

The current understanding of vaccine targets for ***Campylobacter*** is incomplete. ***Campylobacter*** pathogenesis is not well understood [71]. To date, protective epitopes are not well characterised, and the degree of antigenic diversity is unclear [71]. Whole cell approaches or vaccines containing Lipo-oligosaccharides (LOS) of ***Campylobacter*** raise concerns about safety, since LOS can contain N- acetyl neuraminic acid moieties that mimic human gangliosides. Antibodies induced by a potential vaccine and directed against these could cross-react with human antigens causing typical sequelae of the disease, such as reactive arthritis, Irritable Bowel Syndrome (IBS) and/or Guillain-Barre Syndrome (GBS) [71]. ***Campylobacter*** expresses a polysaccharide capsule, which could provide a vaccine target based on similar conjugated polysaccharide vaccines. A capsular conjugate is the target chosen by the United States military for a vaccine currently in early clinical development.

Scoring: Based on the above analysis, pathogen biology was categorised as medium (score of 1 out of 2).

Pre-clinical and clinical R&D

Simple but predictive small animal or ***in vitro*** models are currently lacking for ***Campylobacter***. However, experts expect that a zinc-deficient mouse model developed for ETEC is also useful for ***Campylobacter*** [72]. Larger animal models that are also natural hosts of the disease such as chickens can serve as useful pre-clinical study models [71].

Correlates of protection have not yet been defined for disease caused by ***Campylobacter***. There is a human challenge model with a ***C. jejuni*** strain that lacks ganglioside mimicry in its LOS in place [71], but it is not yet known what degree of infection or illness increases the risk of chronic sequelae or whether colonisation alone is itself a risk. Therefore it is difficult to define the relevant endpoints for a clinical programme and whether this should be prevention of disease, prevention of infection, or prevention of colonisation (or combination of thereof) [71].

Clinical infrastructure is not likely to present issues in high resource settings [71]. In low resource settings, trials may be able to use the capacities built for rotavirus vaccine testing. Where this infrastructure is available, there should be sufficient field sites, experience, and regulatory pathways to take ***Campylobacter*** vaccine studies through clinical trials [71].

Scoring: Based on the analysis described above, pre-clinical and clinical R&D was categorised as medium (score of 1 out of 2).

Probability of uptake

Expected policy stance

Because ***Campylobacter*** is a self-limiting illness with supportive therapy in high-income settings resulting in good outcomes, the need for a vaccine is predominantly in low- and middle-income countries. A vaccination strategy in high-income countries would likely focus on a travellers' vaccine and vaccination of military personnel deployed to low- and middle-income countries for whom sick days are problematic when planning campaigns. In low- and middle-income countries, ***Campylobacter*** would be included in the routine neonatal vaccination programme.

Support among policy makers for a prophylactic vaccine against ***Campylobacter*** for use amongst the general public is unlikely [73]. As one expert explains "there may be some justification for a ***Campylobacter*** vaccine. I always thought this would be supplementary to ***Shigella*** as a combined vaccination" [28]. WHO has not voiced support for a ***Campylobacter*** vaccine, and in a status document prepared for WHO PDVAC, only a combined enteric vaccine was mentioned as feasible [71].

Scoring: Based on the above analysis, expected policy stance was categorised as medium (score of 1 out of 2).

Payer, government, or Gavi support

Payers in high-income countries are unlikely to deem a ***Campylobacter*** vaccine cost-effective if given routinely. Support for a travellers' vaccine may be feasible, but this comprises a small target population.

The incidence of ***Campylobacter*** is higher in middle-income countries than in high-income countries, but the cost-effectiveness barrier is also higher. Therefore, support from governments and payers in these countries is unlikely.

The likely route to market in low-income countries would be through Gavi support. However, given the relatively low mortality associated with ***Campylobacter*** infection, it is unlikely to be supported as a single vaccine, but could be supported as a combination vaccine with other enteric diseases [71].

Scoring: Based on the above analysis, payer, government, or Gavi support was categorised as medium (score of 1 out of 2).

Barriers to uptake

A vaccine for ***Campylobacter*** would not require a new touchpoint or new clinical practices, as it could be incorporated into existing paediatric or travellers' vaccination schedules.

Scoring: Based on the analysis described above, barriers to uptake was categorised as fairly low (score of 1.5 out of 2).

Commercial attractiveness

The largest market for a ***Campylobacter*** vaccine would be in low- and middle- income countries, but with no clear path through Gavi, it will be difficult to gain access to this market.

Scoring: Based on the analysis described above, commercial attractiveness was categorised as low (score of 0 out of 2).

Recommendations

Campylobacter falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority.

Primary recommendation

The primary recommendation is to better understand disease burden, epidemiology, and transmission. More data is needed on transmission in low- and middle-income countries, particularly to clarify whether transmission occurs through environmental pathways or from animal reservoirs before a determination can be made on whether a human vaccine should be pursued or whether alternatives, such as animal vaccination, will be the preferred approach. Furthermore, there is variability in estimates of global disease burden, for example WHO groups have produced very different incidence values through different modelling techniques, showing almost a two-fold difference in values [18,74].

Given the high levels of misdiagnosis of enteric conditions, it would be useful to have targeted studies with high quality laboratory diagnostics to establish disease burden [75]. Inclusion of studies such as MAL-ED and GEMS in the next iteration of the IHME Global Burden of Disease estimates may help to resolve this problem. Finally, wider data collection would reduce the need for imputation and help to establish a more accurate burden of disease.

Secondary recommendations

One secondary recommendation is to explore alternatives to a human vaccine. Developing vaccines to prevent ***Campylobacter*** infections in chickens could reduce transmission. Poultry is a major source of ***Campylobacter*** with chicken meat in retail being contaminated in up to 98% of cases in the United States and 60-80% of cases in Europe [76]. Given that chicken vaccination is used by the poultry industry to protect against several viral diseases, efforts to develop effective vaccines for chickens against ***Campylobacter*** are already underway and should be further supported. For instance, Kobierecka ***et al***. recently reported that ***in ovo*** vaccination resulted in significant levels of protection after challenge with heterologous ***C. jejuni*** strains [77].

Improved supportive therapies for ***Campylobacter*** infections should be explored. A polymer-based oral rehydration solution has been shown to be superior to the WHO standard low osmolarity oral rehydration solution in a Cochrane Review [78]. In a separate Cochrane Review, children in areas of where there is a high prevalence of zinc deficiency or malnutrition were shown to benefit from treatment with zinc [79]. These interventions are inexpensive, and there are low barriers to entry for production compared to vaccines.

Other secondary recommendations include exploring combination vaccines with other enteric pathogens and supporting pre-clinical research including the exploration of potential vaccine candidates using the new zinc deficient mouse model if vaccine development is later recommended [80,81].

Enterobacteriaceae

Executive summary

Bacteria of the family ***Enterobacteriaceae*** are a normal part of the gut flora, but in rare cases can cause hospital-acquired infections. Incidence of ***Enterobacteriaceae*** infections is thought to be low, at fewer than 10 million cases per year [31,33,34,82]. However, antibiotic resistance is particularly problematic, with ***Enterobacteriaceae*** scoring the highest rating on WHO and CDC scales for urgency of threat [7,32]. For the purposes of this report, the following species were evaluated as part of the ***Enterobacteriaceae*** family: ***Enterobacter*** spp., ***Serratia*** spp., ***Proteus*** spp., ***Providencia*** spp., and ***Morganella*** spp. ***K. pneumoniae*** and ***E. coli*** are assessed in separate chapters.

There are no vaccines currently available for ***Enterobacteriaceae*** [40–42] and the vaccine pipeline is empty [40–42]. Pathogen biology is generally poorly understood. Clinical studies would be difficult due to low disease incidence and the challenges of inducing protective immunity due to the compromised state of the patient's immune system. Additionally, the commensal nature of ***Enterobacteriaceae*** could cause difficulty in development.

Low incidence for each pathogen within the group means that even a targeted vaccine strategy would not be cost-effective and therefore not likely to be recommended by policy bodies for inclusion in vaccination schedules.

Recommendations:

Enterobacteriaceae falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority. Due to comparatively low incidence, morbidity and mortality of ***Enterobacteriaceae*** infections, this family is not a strong candidate for vaccine development.

The primary recommendation is to explore alternative treatments or prevention strategies, including passive immunisation strategies, which may be better suited to the timing of administration likely required for intensive care patients. The secondary recommendation is to conduct additional studies in order to better understand the global disease burden.

SCORECARD *ENTEROBACTERIACEAE* (EXCL. *E. COLI* & *KLEBSIELLA*)

Health impact:

Direct health impact

0.0	0.0
Mortality	Morbidity

Impact on AMR reduction

0.0	2.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Intensive care patients
Long-term ventilated patients
Individuals with urinary tract abnormalities

Alternative interventions
Passive immunisation

Probability of R&D success:

0.0	0.0	0.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
Not applicable; vaccine development not recommended

Acceleration potential
Not applicable; vaccine development not recommended

Major barriers to development
Poorly defined target population

Probability of uptake:

0.0	0.0	0.0	0.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Hospitalised patients / High-risk groups such as pre-elective surgery patients

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

Enterobacteriaceae are a family of Gram-negative bacteria that predominantly cause hospital-acquired infections. ***Enterobacteriaceae*** family members included on the WHO priority pathogens list and considered as a group are:

- *K. pneumoniae*
- *Escherichia coli*
- *Enterobacter* spp.
- *Serratia* spp.
- *Proteus* spp.
- *Providencia* spp.
- *Morganella* spp.

Escherichia coli (*E. coli*) and *K. pneumoniae* are considered in separate chapters because the higher burden of disease caused by each of these family members merits an individual assessment. Additionally, the ***Enterobacteriaceae*** family also includes ***Salmonella*** and ***Shigella***, but these are listed as separate pathogens on the WHO priority pathogen list and also evaluated in separate chapters. When the term ***Enterobacteriaceae*** is used in this chapter, it is used to refer to the family members above excluding *K. pneumoniae* and *E. coli*.

Enterobacteriaceae are commensals that are part of the normal gut flora [83]. Urinary tract infections are the most common clinical presentation, but there is a large diversity of clinical syndromes [84 85 86 87 88]. These syndromes are associated with the following symptoms:

- Urinary tract infections: dysuria, turbid urine, leakage around catheter, pyrexia, tachycardia, tachypnoea [26]
- Pneumonia: cough, purulent sputum, shortness of breath, pyrexia, tachypnoea, tachycardia [89]
- Surgical site infections: erythema, swelling, tenderness, wound dehiscence [90]
- Endocarditis: malaise, pyrexia, rigors, anorexia, weight loss, splinter haemorrhages, Roth spots on fundoscopy, new murmur on auscultation of the praecordium [91]
- Meningitis: headache, pyrexia, nuchal rigidity, confusion, lethargy [92]
- Septic arthritis: acutely swollen and painful joint with erythema, warmth and restricted movement [93]

Patients who are most susceptible to these infections are typically those who are severely unwell and immunocompromised, such as those in an intensive care setting, or those with other specific risk factors such anatomical abnormalities in the urinary tract. ***Enterobacteriaceae*** are transmitted through ascension from the gastrointestinal tract in the case of urinary tract infections [86], or through person-to-person transmission, especially in healthcare settings [86,94,95]. Current epidemiological data is insufficient to elucidate variations in global burden.

Potential health impact

Direct health impact

Complete global data on the disease burden of ***Enterobacteriaceae*** is not available from IHME, WHO, or the research literature [31,32]. However, a review of the literature suggests that ***Enterobacteriaceae*** causes limited disease burden. Globally, the family is responsible for 2% of urinary tract infections [82], 0.9% of lower respiratory tract infection [33], and 0.3% of neonatal sepsis [34]. Data on other clinical syndromes associated with ***Enterobacteriaceae*** were scarce. Therefore, it is challenging to assess the global burden of ***Enterobacteriaceae*** infection with confidence. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was categorised as low (score of 0 out of 2) and morbidity was categorised as low (score of 0 out of 2).

Sub-population benefits

Hospitalised patients, especially those in intensive care settings, and particularly patients on ventilators, would be most likely to benefit from a vaccine. Patients with abnormalities in urinary tract anatomy would also benefit.

Antibiotic use

Recommended antibiotic treatment regimens differ by country, in part reflecting local resistance profiles. Regimens vary in length but a typical regimen involves at least one week of a broad spectrum antibiotic [26,96].

Scoring: Based on the above analysis, antibiotic use was categorised as low (score of 0 out of 2). This estimate is based on an annual incidence of ~ seven million UTIs and ~ three million LRTIs, both treated with a seven day course of antibiotics

Urgency of AMR threat

Both the WHO and CDC have expressed strong concern about antibiotic treatments for ***Enterobacteriaceae*** infections. The family is listed as 'critical' in the WHO priority list of R&D for new antibiotics [31], carbapenem-resistant ***Enterobacteriaceae*** are listed as an 'urgent' threat in the CDC's list of biggest threats from AMR [7], and extended-spectrum beta lactamase-resistant Enterobacterioceae are listed as a 'serious' threat by the CDC [7].

Carbapenem-resistant ***Enterobacteriaceae*** have been reported across the world and carry a relatively poor prognosis [97]. The optimal treatment for these pathogens is uncertain, but these strains frequently require last-line therapies such as polymyxins or combination therapies such as ceftazidime/avibactam or meropenem-vaborbactam [97].

Based on the above analysis, the urgency of AMR threat was categorised as high (score of 2 out of 2).

Probability of R&D success

Pipeline robustness

No known candidate vaccines for ***Enterobacteriaceae*** are in pre-clinical or clinical development [40–42].

Scoring: Based on the above analysis, the pipeline was categorised as low (score of 0 out of 2).

Pathogen biology

Data regarding natural immunity for ***Enterobacteriaceae*** are scarce. The case fatality rate is high and if patients recover from infection (for example, those whose risk was due to stressors from surgery or temporary illness) it is difficult to recreate conditions that predispose patients to infection. Based on data for ***K. pneumoniae*** and urinary ***E. coli***, it appears unlikely that patients infected with these pathogens develop natural immunity to other ***Enterobacteriaceae*** family [98,99].

Proteus is the best-characterised member of the ***Enterobacteriaceae*** family included in this analysis. Over 20 outer membrane antigens have been identified in mouse models that are immunogenic and expressed ***in vivo*** [100]. However, the genus includes a variety of strains, potentially rendering vaccine development difficult [101]. Potential

CURRENT PIPELINE *ENTEROBACTERIACEAE* (EXCL. *E. COLI* & *KLEBSIELLA*)

targets have also been identified for Serratia. K-antigens and O-antigens could form the basis of antigens for vaccine development and 28 antigens belonging to these groups have been identified [102]. However, it is not yet clear from the research literature what proportion of these antigens are sufficiently conserved across strains to render them useful for vaccine development. It is also not yet clear whether these antigens would be immunogenic or whether they are expressed ***in vivo***.

Research into other members of the ***Enterobacteriaceae*** family is similarly limited, and strain variability presents a challenge for other family members. Over 30 O-antigens have been characterised for ***Providencia***, suggesting high antigenic variety [103], and a variety of strains exist, likely presenting challenges to vaccine development [101]. ***In silico*** work has suggested potential vaccine targets for one strain [104]. ***Enterobacter*** and ***Morganella*** also show high strain variety [105,106]. Some initial research has also been conducted to delineate virulence factors in ***Morganella*** using genomics [107].

Scoring: Based on the above analysis, pathogen biology was categorised as low (score of 0 out of 2).

Pre-clinical and clinical R&D

Although there are animal models of catheter associated UTI and critical care infection [108–110] these models have limitations and there has been very little research using animal models to explore these syndromes when caused by ***Enterobacteriaceae***.

Clinical studies of vaccines targeting ***Enterobacteriaceae*** would be very challenging to design and conduct. The low incidence of infections would make achieving adequate trial enrolment challenging. If a targeted vaccine strategy was chosen focusing only on high-risk populations, inducing a protective immune response would be complicated given the compromised state of the patients' immune systems. The commensal nature of ***Enterobacteriaceae*** could cause additional difficulty in development, with possible need to examine impact on patient microbiomes.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as low (score of 0 out of 2).

Probability of uptake

Expected policy stance

Patients with ICU stays who are at risk of mechanical ventilation or patients with predisposition to urinary tract infection from long term catheterisation or anatomical abnormalities [100] are the populations most likely to benefit from a vaccine targeting ***Enterobacteriaceae***. However, developing a strategy to vaccinate these populations would be extremely difficult. Identifying patients at risk of ***Enterobacteriaceae*** infection in ICUs is a major challenge. It is difficult to predict the risk of ICU admission or ventilation in the general population, meaning that a substantive number of patients could not be identified in time to vaccinate and generate a response prior to being at risk of infection. Although there may be cohorts of patients undergoing major elective surgery and with predisposition to UTIs, individual risk of infection from any of the constituent pathogens within the ***Enterobacteriaceae*** family is low, hence morbidity and mortality are low in absolute terms.

Policymakers are unlikely to support vaccination for ***Enterobacteriaceae***, primarily because incidence is low individually among pathogen family members and in aggregate. One expert states "none of these [are] of any interest for vaccines. Either target population is too small or you can't identify target population…we can't justify vaccinating everybody" [28].

Scoring: Based on the above analysis, expected policy stance was categorised as low (score of 0 out of 2).

Payer, government, or Gavi support

Due to the low incidence and morbidity, the cost-effectiveness for any individual pathogen in the ***Enterobacteriaceae*** family is likely to be low. Payers in high-income countries are unlikely to support a vaccine on this basis. Similarly, middle-income countries are unlikely to support vaccines targeting ***Enterobacteriaceae*** because their cost-effectiveness thresholds are more stringent than those in high-income countries.

Mortality in Gavi-eligible countries is unknown and unlikely to be higher than in high-income countries. Gavi is unlikely to invest in a vaccine for ***Enterobacteriaceae*** given the low absolute mortality burden, therefore, support for a vaccine in low-income countries is likely to be low.

Scoring: Based on the above analysis, payer, government, or Gavi support was categorised as low (score of 0 out of 2).

Barriers to uptake

As discussed in earlier sections, the target population for ***Enterobacteriaceae*** vaccines would be difficult to define. For certain populations – for example, those undergoing major elective surgery - vaccination would need to be added to the pre-surgery care bundle. For other populations such as those with long-term catheterisation or anatomical abnormalities elevating the risk of urinary infection, a vaccination touchpoint would have to be instituted at diagnosis or peri-procedure. Patient education would likely be required given that a novel vaccine strategy would be implemented in adults. Finally, if the vaccine is approved for use in new populations, there would be a continued need for dialogue between manufacturers, guideline-setting bodies, and specialist societies to publicise ability to treat pathogens with the vaccine in these new populations.

Scoring: Based on the above analysis, barriers to uptake was categorised as high (score of 0 out of 2).

Commercial attractiveness

The commercial attractiveness of vaccines targeting ***Enterobacteriaceae*** is low because of the low incidence of infection, the low mortality of ***Enterobacteriaceae*** infections, and the challenges defining a target population.

Scoring: Based on the above analysis, commercial attractiveness was categorised as low (score of 0 out of 2).

Recommendations

Enterobacteriaceae falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority.

Primary recommendation

The primary recommendation is to explore alternatives to vaccination. Given the low incidence of ***Enterobacteriaceae*** infections and difficulty in predicting which patients would most benefit from vaccination, passive immunisation represents an alternative strategy for the treatment of ***Enterobacteriaceae*** infections. Patients can receive monoclonal antibodies urgently or emergently, and have rapid protection against infection, which lasts for several weeks, obviating the need for preselection and risk stratification. It is likely that development of monoclonal antibodies against ***Enterobacteriaceae*** would require further study of pathogen biology in order to identify potential targets for antibodies, given that little is currently known about pathogens in this group. However, expert interviews have suggested that due to strain diversity, one monoclonal antibody may be insufficient to treat all strains of any individual pathogen within the family of ***Enterobacteriaceae***, adding complexity to development of treatments [28]. Monoclonal antibody approaches face many of the same development challenges as vaccines.

Some limited early-stage work has explored bacteriophages as a potential treatment for ***Enterobacteriaceae*** infections. ***In vitro*** work using a biofilm model shows efficacy of a phage cocktail against ***Proteus*** [111]. Phage therapy offers some potential benefits: it is more specific than antibiotics and therefore less likely to alter the microbiome, with lower risk of drug interactions and toxicities, and retained activity in the presence of biofilms [54,55]. The principal disadvantage of bacteriophage therapy is that it requires more personalisation than antibiotics, vaccination or monoclonal antibodies, increasing the expense of treatment, and decreasing scalability [54]. Other risks include rapid release of endotoxin (which some ***Enterobacteriaceae*** produce [112,113]) and risk of transduction of genetic material into the microbiome.

Secondary recommendation

Better characterisation of the disease burden in developed countries attributable to each clinical syndrome would be useful to more accurately assess burden of disease for ***Enterobacteriaceae***; however, collective opinion from expert interviews suggests that further study on global burden would be useful but unlikely to change R&D interest or policy direction. Infections caused by ***Enterobacteriaceae*** do not receive policy attention in low-income countries resulting in a lack of studies examining incidence, morbidity and mortality from these pathogens. While one study from Kilifi suggests presence of some of the ***Enterobacteriaceae*** family in low-income country settings [58], the disease burden is unlikely to be higher than in high-income countries, and consequently further study is likely to confirm that this pathogen grouping would likely not be prioritised for vaccine R&D.

Enterococcus faecium

Executive summary

Enterococcus faecium (***E. faecium***) causes a hospital-acquired infection with low incidence, morbidity, and mortality [82,114,115], most commonly presenting as a urinary tract infection or endocarditis. AMR is of intermediate concern; whilst resistance to penicillin and aminoglycosides has been widely reported, resistance to last-line therapies has not been reported to date.

No vaccine is currently available for ***E. faecium***, and no candidates are in pre-clinical or clinical development at this time. A target population for an ***E. faecium*** vaccine has yet to be defined, and a vaccine is unlikely to gain support from policy makers because the incidence of infection and disease burden are both low. Therefore, barriers to uptake of a vaccine would be significant.

A vaccine targeting ***E. faecium*** is unlikely to be cost-effective. Because ***E. faecium*** infection has not been identified as causing a high disease burden, a lack of policymaker support for a vaccine would likely create significant barriers to uptake globally.

Recommendations:

E. faecium falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority. ***E. faecium*** is not a strong candidate for vaccine development, therefore the primary recommendation is to explore alternative treatment and prevention strategies, including the prevention of biofilm formation on urinary catheters. The secondary recommendation is to better understand the impact of ***E. faecium*** infection. Additional epidemiological studies would likely clarify the impact of the disease, especially in low-income countries where information is currently scarce, but new information would be unlikely to change the recommendation for the pathogen.

SCORECARD *ENTEROCOCCUS FAECIUM*

Health impact:

Direct health impact

0.0	0.0
Mortality	Morbidity

Impact on AMR reduction

0.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Intensive care patients
Immunocompromised individuals

Alternative interventions
Passive immunisation

Probability of R&D success:

0.0	0.0	0.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
Not applicable; vaccine development not recommended

Acceleration potential
Not applicable; vaccine development not recommended

Major barriers to development
Poorly defined target population

Probability of uptake:

0.0	0.0	0.0	0.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Hospitalised patients / High-risk groups such as pre-elective surgery patients

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

E. faecium is a Gram-positive, commensal bacterium that causes hospital-acquired infections. ***E. faecium*** is commonly found in the gastrointestinal tract; it can also rarely be present in the oral cavity or the genitourinary tract [116]. Colonization with ***E. faecium*** can occur through person-to-person contact or exposure to contaminated objects [116].

The most common manifestations of infection are urinary tract infections (UTIs); however, ***E. faecium*** can cause a range of other infections including endocarditis and meningitis. Symptoms vary depending on the infection site, but can include the following:

- UTI: Frequency; urgency, dysuria, discolouration of urine (urine can appear cloudy, red, pink or cola-coloured) and pelvic pain in women
- Endocarditis: fatigue, malaise, night sweats, shortness of breath, new or changed heart murmur
- Meningitis: headache, neck stiffness, photophobia, nausea and vomiting, confusion, drowsiness, seizures

E. faecium infection has a global distribution [117] but is typically found only in specific at-risk groups. Groups at greatest risk for infection with ***E. faecium*** include immunocompromised individuals, particularly patients admitted to intensive care units [116], and patients with other concomitant conditions [28]. As one expert explains, "Enterococcus is found only in multimorbid patients, in addition to other underlying diseases".

Potential health impact

Direct health impact

Global data on the direct disease burden of ***E. faecium*** infections is not available from either the WHO or the IHME. A review of the literature suggests that ***E. faecium*** is responsible for approximately 3% of UTIs and 4% of endocarditis cases [82,114,115]. Based on the limited availability of data, it is challenging to assess the global burden of ***E. faecium*** infection with confidence. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was categorised as low (score of 0 out of 2). Morbidity was categorised as low (score of 0 out of 2).

Sub-population benefits

A vaccine for ***E. faecium*** would benefit immunocompromised patients, particularly in intensive care settings.

Antibiotic use

The course of treatment for ***E. faecium*** infection varies depending on the specific infection. A typical treatment course for a UTI is a 7-day course of antibiotics [118]. For infective endocarditis, treatment typically employs multiple agents in combination for approximately six weeks [119]. The low incidence of ***E. faecium*** infection drives low overall antibiotic use.

Scoring: Based on the above analysis, antibiotic use was categorised as low (score 0 out of 2). This estimate is based on an annual incidence of ~50,000 endocarditis cases treated with a six week course of antibiotics, and ~12 million UTIs seven day week course of antibiotics

Urgency of AMR threat

Both the WHO and CDC have expressed concern about the future of ***E. faecium*** treatment. The WHO has listed it as a 'high' priority for research and development of new antibiotics [6] and the CDC has listed it as a 'serious' AMR threat [7]. Resistance to penicillin and aminoglycosides has been widely reported [120] and some strains are also resistant to vancomycin (vancomycin resistant enterococcus [VRE]) [120]. Rates of VRE are highest in North America [116]. The United States Food and Drug Administration (FDA) has approved the use of linezolid for the treatment of VRE. Other last-line options are also available, including daptomycin [121].

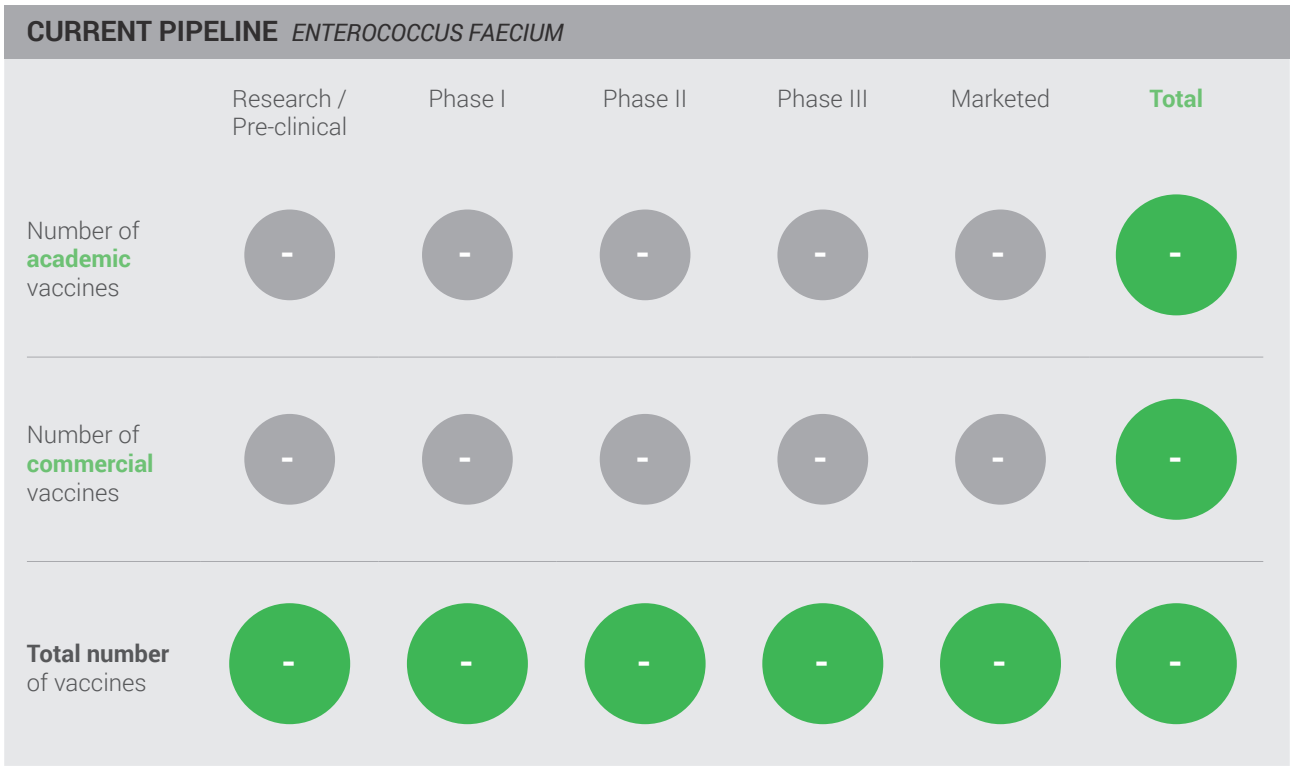
Scoring: Based on the above analysis, the urgency of AMR threat was characterised as medium (score of 1 out of 2).

Probability of R&D success

Pipeline robustness

There is currently no pipeline for vaccines against ***E. faecium***; neither commercial nor academic vaccine development programmes are underway.

Scoring: Based on the above analysis, the pipeline was categorised as low (score of 0 out of 2).



Pathogen biology

The biology of ***E. faecium*** is presently not well characterised and little is known about natural or cross-strain immunity following the commensal-to-pathogen switch [122]. Vaccine targets are also not understood in detail at this time; structural characterisation of ***E. faecium*** has been limited to the identification of teichoic acids, including lipoteichoic acid and a wall teichoic acid, and definitive structures of high molecular weight polysaccharides – for example, Pfl1-4 – have only been described recently [123].

Scoring: Based on the above analysis, pathogen biology was categorised as low (score of 0 out of 2).

Pre-clinical and clinical R&D

No pre-clinical or clinical trials of an ***E. faecium*** vaccine have been conducted to date. Mouse models and opsonophagocytic assays are currently being used to study the pathogen, but the clinical relevance of these models has not yet been determined as no vaccine candidates have reached clinical development.

The implementation of clinical programmes is also limited by the lack of knowledge about natural immunity following the commensal-to-pathogen switch and the lack of known correlates of protection that could simplify outcome measures in clinical studies. Finally, the target population for clinical studies is currently unclear.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as low (score of 0 out of 2).

Probability of uptake

Expected policy stance

It is not clear at this time how a vaccination programme for ***E. faecium*** infections would be implemented as both the target population and vaccination strategy are presently unclear. Because infection with ***E. faecium*** is limited to patients with concomitant health conditions or compromised immune systems, the healthy population is unlikely to benefit from vaccination. As one expert notes, "You are not going to develop a vaccine that you would give to the healthy population" [28]. Immunocompromised patients are most likely to benefit, but they are a complex population to effectively vaccinate. This is because whilst live attenuated vaccines are potentially pathogenic in this population, these patients may be unable to mount an adequate immune response to subunit and inactivated vaccines to ensure protection [124].

Expert interviews reflected a lack of enthusiasm to prioritise support for vaccines against ***E. faecium***. The pathogen is not well-known to policy makers and experts cited the small number of affected patients as a barrier to policy maker support, explaining "vaccines here wouldn't make a lot of sense because it wouldn't have a big impact" [28].

Scoring: Based on the above analysis, the expected policy stance was categorised as low (score of 0 out of 2).

Payer, government, or Gavi support

No expert interviews or other research indicated that ***E. faecium*** infection is a high priority for payers or governments in high-income or middle-income countries. Gavi support is also unlikely; mortality in Gavi countries is not known and is likely to be relatively low.

Scoring: Based on the above analysis, likelihood of payer, government, or Gavi support was characterised as low (score of 0 out of 2).

Barriers to uptake

The primary barrier to uptake of a vaccine for ***E. faecium*** is the difficulty in identifying a target population; as noted previously, immunocompromised patients are most likely to benefit, but formulating a strategy to vaccinate this population would likely be complex. Because ***E. faecium*** is not a well-known pathogen, extensive healthcare provider and patient education would be necessary. Implementation of a vaccination programme for ***E. faecium*** would also require changes to some clinician behaviours, and clinicians would need to understand and support incorporation of vaccination into patient pathways.

Scoring: Based on the above analysis, barriers to uptake were categorised as high (score of 0 out of 2).

Commercial attractiveness

Disease caused by ***E. faecium*** is low incidence, there is low likelihood of Gavi support and the target population is not clearly defined, therefore the commercial attractiveness of the pathogen is low.

Scoring: Based on the above analysis described above, commercial attractiveness was categorised as low (score of 0 out of 2).

Recommendations

E. faecium falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority.

Primary recommendation

The comparatively low incidence, morbidity and mortality associated with ***E. faecium*** infection, coupled with the costs of vaccine development, mean that ***E. faecium*** is not a strong candidate for vaccine development. The primary recommendation is to explore alternative treatment and prevention strategies, such as passive immunisation strategies and the prevention of biofilm formation on urinary catheters. Passive immunisation strategies are time-consuming and expensive to develop and require sufficient understanding of the pathogen biology, which is currently a hurdle for ***E. faecium***.

Secondary recommendation

The disease burden of ***E. faecium*** infection is currently not well-characterised, and additional epidemiological studies would likely provide a better understanding of disease burden, especially in low-income countries where information is currently scarce. This information will be helpful for the understanding of the pathogen but will be unlikely to change the recommendations on vaccine development.

Escherichia coli (enteric)

Executive summary

Escherichia coli (***E. coli***) is a gut commensal that is part of the ***Enterobacteriaceae*** family. It primarily causes community-acquired infections. For this report, ***E. coli*** (enteric) refers to the pathotypes associated with enteric disease (ETEC, EPEC, EHEC, and EAEC). Enteric ***E. coli*** infection causes over 60,000 deaths and almost 400,000 years lived with disability annually [31]. Anti-microbial resistance (AMR) for first-line agents is increasingly common and reports of extensively resistant strains are increasing; however, resistance to date is less common than for other ***Enterobacteriaceae*** [125–128].

There is no marketed vaccine specifically for enteric ***E. coli***. Dukoral, a cholera vaccine, has demonstrated partial short-term cross-protection effect thought to last around three months [129,130]. There are clinical candidates in the pipeline, which use relatively conserved antigens that target most enteric ***E. coli*** strains. Inclusion of LT toxoid and colonisation factor antigens (CFAs) in a potential vaccine may help cover 70-80% of strains, as it is among the most conserved antigens in ***E. coli***. As this pathogen is a gut commensal, the effect of a vaccine on gastrointestinal flora will need to be assessed and monitored in trials.

Enteric ***E. coli*** falls into a cluster of pathogens for which bringing a vaccine to market is the priority. Enteric ***E. coli*** infection has a high incidence with concentration in low- and middle-income countries. There is policy support for a standalone vaccine but funder support is likely dependent on further study regarding burden of disease.

Recommendations:

The primary recommendation is to accelerate clinical development. Secondary recommendations include developing a better understanding of pathogen epidemiology, supporting development of combined enteric vaccines, and expanding pre-clinical research.

SCORECARD *ESCHERICHIA COLI* (ENTERIC)

Health impact:

Direct health impact

0.5	1.0
Mortality	Morbidity

Impact on AMR reduction

1.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
None identified

Alternative interventions
None identified

Probability of R&D success:

0.5	1.5	1.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
Ideal to have combination with other enteric vaccines

Acceleration potential
Drive clinical development

Major barriers to development
None identified

Probability of uptake:

1.0	2.0	1.0	1.5
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Greatest need in low-income countries / Routine infant vaccination in low & middle-income countries; Travellers' vaccination in high-income countries

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

E. coli is a Gram-negative commensal that predominantly causes community-acquired infections, but can also cause hospital-acquired infections. Although ***E. coli*** is part of the ***Enterobacteriaceae*** family, it has been considered separately in this assessment because of its high incidence relative to other members of the ***Enterobacteriaceae*** family.

E. coli is part of the normal gut flora, with pathogenesis caused by several strains [131]. Most presentations from enteric ***E. coli*** are caused by Enterotoxigenic ***E. coli*** (ETEC). Other disease-causing pathotypes include Enteropathogenic ***E. coli*** (EPEC), Enterohaemorrhagic ***E. coli*** (EHEC), and Enteroaggregative ***E. coli*** (EAEC) [131]. The analysis in this chapter pertains to ETEC and EPEC. Where aggregated information on all pathotypes is included for context, it is clearly noted as such.

Enteric ***E. coli*** is transmitted through the faeco-oral route, primarily through contaminated food and water [132]. Each type of enteric ***E. coli*** can have distinct clinical features: for ETEC, these include malaise, anorexia, and abdominal cramps followed by the sudden onset of watery diarrhoea [131]; for EPEC, these include loose, watery stools, vomiting, and low grade fever [131]. Enteric ***E. coli*** affects young children with high incidence before the age of three [133]. Enteric ***E. coli*** infection is concentrated in low- and middle-income countries, affecting most of Asia, the Middle East, Africa, Mexico, and Central and South America [134].

Potential health impact

Direct health impact

Global data regarding the disease burden associated with ETEC and EPEC is available from IHME. Data from these sources suggest a relatively low mortality compared to other pathogens on the WHO priority pathogen list, at ~60,000 deaths annually. Over 50,000 of these driven by ETEC [31]. Morbidity is reported at 400,000 years lived with disability annually, also mostly driven by ETEC [18].

Data on mortality and morbidity was taken from the IHME 2016 estimates. The IHME has a defined methodology and their data is accepted in the global health community.

Scoring: Based on the above analysis, mortality was categorised as low (score of 0.5 out of 2) and morbidity was categorised as medium (score of 1 out of 2).

Secondary health impact

There is limited and conflicting data regarding the secondary health impact of enteric ***E. coli***. Some research suggests an impact of diarrhoeal disease on growth trajectories for children, especially those with multiple diarrhoeal episodes [67,68]. However, it is possible that these children return to normal growth and ultimately achieve normal milestones [69].

Sub-population benefits

Young children would benefit most from a vaccine, as enteric ***E. coli*** infection primarily affects young children with high incidence before the age of three [133].

Antibiotic use

Recommended antibiotic treatment regimens differ by country, in part reflecting local resistance profiles. A common regimen is a three-day oral course of a fluoroquinolone antibiotic [135].

Scoring: Based on the above analysis, antibiotic use was categorised as medium (score of 1 out of 2). This estimate is based on an annual incidence of ~320 million enteric E. coli cases treated with a three day course of antibiotics.

Urgency of AMR threat

While there are strong concerns from international health bodies regarding threat of antibiotic resistance from ***Enterobacteriaceae***, literature review suggests that there is less concern regarding resistant enteric ***E. coli*** strains than resistant strains in other members of the ***Enterobacteriaceae*** family.

Both the WHO and CDC have expressed strong concern about antibiotic treatments for ***Enterobacteriaceae*** (***E. coli*** is not scored separately). The WHO has listed the ***Enterobacteriaceae*** group as a 'critical' priority for R&D regarding new antibiotics [31]. The CDC has listed CRE (carbapenem-resistant ***Enterobacteriaceae***) as an 'urgent' threat in its list of greatest threats from AMR and has listed extended spectrum ***Enterobacteriaceae*** as a 'serious' threat [7].

International concerns are partly driven by reports of ***E. coli*** strains resistant to polymyxin antibiotics – a last line therapy [136]. Whilst there are reports of polymyxin resistance in enteric ***E. coli*** isolates [137,138], clinical practice remains, where indicated, to treat with fluoroquinolones or azithromycin. Despite growing resistance rates these therapies are still useful treatment options in many settings [139].

Scoring: Based on the above analysis, the urgency of AMR threat for Enteric ***E. coli*** was categorised as medium (score of 1 out of 2).

Probability of R&D success

Pipeline robustness

There is a moderate pipeline for a vaccine targeting enteric ***E. coli***, comprising a total of 18 candidates; however, all are in early stages of development, with 11 pre-clinical candidates and five clinical candidates [40–42]. All candidates currently in development target ETEC.

One candidate was reported to be in Phase III clinical trials; however, experts noted that this candidate likely does not exist.

There is also one marketed vaccine – Dukoral – that is WHO prequalified and licensed in over 60 countries, but which provides only transient benefit. Although Dukoral was developed for cholera, it provides cross-protection against ETEC arising from structural and immunological similarities between cholera toxin and the heat labile enterotoxin (LT) of ETEC. The protective effect of Dukoral is moderate, with efficacy estimated at 40-70% and only estimated to reduce up to 7% of cases of travellers' diarrhoea from all causes [140]. Additionally, this vaccine has only a short duration of protection – estimated at approximately three months [130].

Scoring: Based on the above analysis, pipeline robustness was categorised as medium (score of 1 out of 2).

Pathogen biology

Field studies and human challenge studies indicate that protective immunity to ETEC does develop [141]. Age-specific attack rates for symptomatic ETEC infection decline after three years of age; also, in human challenge studies, subjects who recovered from ETEC diarrhoea were protected against disease upon re-challenge [141]. However, ETEC strains are antigenically highly diverse, meaning that there is little cross-strain immunity [28,141].

Two key potential vaccine targets have been identified that will likely cover 70-80% of strains: the LT toxoid and colonisation factor antigens (CFAs)[28,142]. All three clinical candidates discussed in expert interviews are aimed at these targets. CFAs are good candidates since they together cover 50% of clinical isolates [141]. Although over 25 CFAs that have been identified, there are four antigens which are most frequently encountered, and which together are typically used in vaccine candidates [143]. The two ETEC enterotoxins, heat stable (ST) and LT, also represent potential vaccine targets. LT is structurally, functionally, and immunologically related to the cholera toxin, hence the cross-protection of Dukoral. LT is easier to produce in a toxoid from, enabling immunogenicity without toxicity. It has been demonstrated as suitable for development through ***in vitro*** and ***in vivo*** studies [141].

Scoring: Based on the above analysis, pathogen biology was categorised as fairly high (score of 1.5 out of 2).

CURRENT PIPELINE *ESCHERICHIA COLI* (ENTERIC)

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	03	01	01	-	-	05
Number of **commercial** vaccines	08	01	02	01[1]	01[2]	13
Total number of vaccines	11	02	03	01[1]	01[2]	18

1) Databases reported a candidate from Eubiologics in Phase III; however, experts noted that this might not exist.

2) Dukoral: WHO prequalified and licensed in over 60 countries, but which provides only transient benefit. Although Dukoral was developed for cholera, it provides cross-protection against ETEC arising from structural and immunological similarities between cholera toxin and the heat labile enterotoxin (LT) of ETEC.

Pre-clinical and clinical R&D

Pre-clinical research to develop an ETEC vaccine is limited by less than ideal animal models for ETEC and lack of correlates for protection. Historically, animal models of disease have not naturally developed diarrhoea after ETEC infection [141]. A new mouse model with zinc deficiency shows promise, displaying growth impairment, watery diarrhoea, and intestinal inflammation after ETEC infection [72]. Furthermore, rabbits, pigs and non-human primates could be used as they develop diarrhoea with infection. In summary, while current animal models are imperfect, there is promising work that may lead to better models.

Human challenge models have made clinical research easier than pre-clinical work [141]. While there has been longstanding and successful use of challenge models, there are three ways to improve their use. First, there is scope for improvement through with increased fasting time prior to challenge, which enables a lower dose that better mimics natural field exposure. Second, there is also scope to expand use of challenge models – moving beyond the strains where they have been employed. Third, establishing correlates of protection and functional assays predicting immunity would enable shorter, more efficient trials.

Trial infrastructure is likely be conducive for vaccine development, since trials for other diarrhoeal diseases such as cholera have been successful in similar settings. Vaccine candidates avoid targeting antigens expressed by commensal ***E. coli***, as toxoids are only present with pathogenic ***E. coli***, and the presence of fimbriae are correlated with pathogenicity [144] . This means that trials may be able to avoid the regulatory burden and additional expense associated with monitoring impact on commensal ***E. coli***. Route to licensure should be relatively straightforward given ETEC vaccine candidates exploit longstanding vaccine technology, such as the use of protein vaccines.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as medium (score of 1 out of 2).

Probability of uptake

Expected policy stance

A vaccination strategy for ETEC would include routine vaccination in the first year of life in low- and middle-income countries, and vaccination offered for travellers from high-income countries traveling to higher-risk areas.

Vaccination is likely to be supported by policy bodies. This is due to the high incidence of enteric ***E. coli*** [18,74] and the fact that the WHO is assessing ***E. coli*** vaccine candidates for accelerated clinical development [145]. A document prepared at the request of WHO PDVAC states "There are currently no licensed vaccines for ETEC, but studies indicate high public health impact, cost-effectiveness, and feasibility of immune protection through vaccination. ETEC vaccine development remains a World Health Organization priority" [141]. However, fluctuations in IHME estimates of mortality for ETEC have prompted desire for further data on disease burden from the policymaking community.

Scoring: Based on the above analysis, expected policy stance was categorised as high (score of 2 out of 2).

Payer, government, or Gavi support

The low mortality burden in high-income countries is likely to lead to a lack of payer support for an ETEC vaccine except as a travel vaccine. In middle-income countries, ETEC vaccination support will likely depend on the price per dose, given that particular subpopulations would benefit greatly from the vaccine. In low-income countries, the route to market would likely be through Gavi. While an analysis by the Vaccine Alliance suggested that there would be a favourable cost-effectiveness ratio of $65.00/DALY [141], the flux in mortality estimates has made cost-effectiveness more difficult to justify [141].

Scoring: Based on the above analysis, payer, government or Gavi support was categorised as medium (score of 1 out of 2).

Barriers to uptake

The logistical barriers to implementing a vaccination programme for enteric ***E. coli*** are relatively low; it would not likely require a new healthcare touchpoint and would likely be incorporated into the childhood vaccination schedule. Clinical practices would also present few barriers; as routine vaccination in infancy, an enteric ***E. coli*** vaccine would use a familiar route of delivery and no change in clinician behaviours would be required.

Scoring: Based on the above analysis, barriers to uptake were categorised as fairly low (Score 1.5 out of 2).

Commercial attractiveness

A 2011 PATH analysis suggests that a low-cost ETEC vaccine could have an estimated annual revenue potential of more than $600 million at maturity, with greatest uptake in high-income (travellers' vaccine) and mid-income countries [146]. An ETEC vaccine could compete with Dukoral as a travellers' vaccine; however, it is uncertain Gavi will support an ETEC vaccine without further evidence on disease burden.

Scoring: Based on the above analysis, commercial attractiveness was categorised as medium (score of 1 out of 2).

Recommendations

Enteric ***E. coli*** falls into a cluster of pathogens for which bringing a vaccine to market is the priority.

Primary recommendation

The primary recommendation is to accelerate clinical development of a vaccine. Increasing funding for later-stage clinical trials would likely accelerate clinical development. Key funders of enteric disease research in commercial and non-commercial spheres should be encouraged to invest in larger clinical trials for early-stage clinical research candidates, especially given that there are two Phase I candidates. Opportunities for funders to strategically coordinate efforts so they are able to pool resources and fund later-stage trials for enteric ***E. coli*** would also help accelerate clinical development.

Clinical development should also be accelerated through a focus on regulatory facilitation. A vaccine for ***Salmonella*** **Typhi** has recently been prequalified by the WHO based on evidence from human challenge models [147,148]. Similar options could be explored for enteric ***E. coli***. Human challenge models for the ETEC have been used to measure the efficacy of vaccine candidates, so use of these models could be increased for later-stage trials [141].

Secondary recommendations

One secondary recommendation is to gain a better understanding of pathogen epidemiology. IHME figures for enteric ***E. coli*** disease burden in 2015 have decreased compared to 2010 [31]. The apparent decrease in disease burden suggested by IHME has prompted some funders to leave the field [149], which increases the difficulty of implementing later stage trials. There is expert concern that the IHME numbers may underestimate the burden of disease [28,150]. In 2015, IHME moved towards using molecular methods (quantitative PCR) in burden of disease estimates. Since these methods have greater sensitivity than stool culture, there has been an increase in detection of ETEC as well as other pathogens; however, the increase in ETEC detection has not been as pronounced compared to other pathogens [150]. Not all ETEC serotypes produce the ST toxin that is detected in the assay [142]. There have also been changes in modelling methodology [142,150]. Incorporation of data from two large observational studies, MAL-ED and GEMS, into global burden of disease estimates is in process and will provide a more comprehensive picture of disease burden [150].

Further studies would develop the understanding of disease burden in two distinct directions [141,150]. First, broader datasets would help to reduce extrapolations over age ranges and imputation; second, smaller, more detailed studies would enable maximally accurate diagnostics to be used for ***E. coli*** and other infections, maximising the diagnostic yield from incident symptomatic cases, minimising misdiagnosis, and influencing how data from broader studies can be modelled.

Another secondary recommendation is to support development of combined enteric vaccines. There is a stated interest from policy bodies and funders to explore combination vaccines. There are currently combined ***Shigella***-ETEC vaccines in pre-clinical and Phase I clinical development [42].

Last, expanding pre-clinical research, including selection of animal models, is recommended. Further development of non-mouse, non-pig animal models such as rabbits or primates could provide additional data or models with improved predictive capacity for clinical development. Efforts to increase pre-clinical research should also promote development of platforms that enable manufacturing of inexpensive multivalent vaccines. Bioconjugation, for example, involves the binding of one or more antigens from a pathogen to a Toll-like receptor ligand, which enhances the immune response [149]. Multiple components can be combined in this process, resulting in an immune response to more than one pathogen or to several elements of a single pathogen [151]. This approach has been used in urinary ***E. coli*** trials, and a similar approach would likely be possible in enteric ***E. coli*** [152]. Given the commensal nature of the pathogen, pre-clinical research should also seek to better understand the potential effect of vaccines on gastrointestinal flora.

Escherichia coli (urinary)

Executive summary

Escherichia coli (***E. coli***) is a gut commensal that is part of the ***Enterobacteriaceae*** family. ***E. coli*** can cause urinary tract infections (UTIs). UTIs caused by ***E. coli*** are referred to as urinary ***E. coli***. Urinary ***E. coli*** has a high incidence and may be attractive for targeted vaccination in high-income countries, despite relatively low mortality and morbidity.

There are no current vaccines for urinary ***E. coli*** and the pipeline only has three candidates in development, the most advanced of which is in Phase II [40,41]. Antigen selection remains an ongoing challenge.

Payers in high-income countries are likely to support vaccination for specific sub-populations at high risk. This approach is likely to be cost-effective due to the high cost of UTIs.

Recommendations

Urinary ***E. coli*** falls into a cluster of pathogens for which advancing early R&D is the priority. The primary recommendation is to invest in pre-clinical research, particularly on conserved antigens and the effect of a vaccine on the microbiome. The secondary recommendations are to better understand the disease burden through pathogen level epidemiology and to explore alternative prevention strategies, such as passive immunisation.

SCORECARD *ESCHERICHIA COLI* (URINARY)

Health impact:

Direct health impact

1.0	0.0
Mortality	Morbidity

Impact on AMR reduction

2.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Individuals with recurrent urinary tract infections, urinary catheterisation, or undergoing urological procedures

Alternative interventions
Passive immunisation

Probability of R&D success:

0.5	0.5	1.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
None identified

Acceleration potential
Invest in pre-clinical research

Major barriers to development
Challenging antigen selection

Probability of uptake:

2.0	1.0	1.0	1.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Those at High-risk of urinary tract infections / High-risk groups such as pre-biopsy patients, individuals with recurrent urinary tract infections, urinary catheterisation

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

E. coli is a Gram-negative commensal bacterium that predominantly causes community-acquired infections, but also can cause hospital-acquired infections. ***E. coli*** is part of the ***Enterobacteriaceae*** family. In this assessment, ***E. coli*** is considered separately because of its high incidence relative to other ***Enterobacteriaceae*** family members.

E. coli is part of the normal gut flora, but several pathotypes cause pathogenesis [131]. Urinary symptoms are caused by uropathogenic ***E. coli*** (UPEC) [153], which belongs to a family of ***E. coli*** pathotypes that cause infection outside of the gut, known as extraintestinal pathogenic ***E. coli*** (ExPEC) [154]. A large variety of UPEC virulence genes exist andit has been suggested that there are multiple UPEC pathotypes [155]. Transmission of UPEC occurs through bowel contamination or sexual activity [153,156].

Clinical features of urinary ***E. coli*** infection include urinary frequency, dysuria, urgency, loin pain, and fever [118]. In the community setting, women are more likely to contract UTIs than men [157]. In the hospital setting, catheterised patients and patients undergoing urological procedures, including transurethral procedures and transrectal prostate biopsies, are at greatest risk of urinary ***E. coli*** infections [158]. The geographic distribution of urinary ***E. coli*** infection is poorly characterised. In particular, insufficient data from low-income countries exists to determine differences in regional burdens [159].

Potential health impact

Direct health impact

Robust global data on disease burden is not available. Urinary ***E. coli*** infections are not reported by the WHO or IHME and no publications were found in the literature that report the global burden of these infections. Some data on burden of disease exists in high-income countries, such as the United States, but data is scarce for low- and middle-income countries [159]. Experts are also uncertain as to the burden of disease [28].

A review of the literature suggests that urinary ***E. coli*** causes significant disease burden and is responsible for ~70% of UTIs globally [82]. Given limited data at a global level and uncertainty among experts regarding disease burden, confidence in this estimate is relatively low. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was scored as medium (score of 1 out of 2) and morbidity was categorised as low (score of 0 out of 2).

Sub-population benefits

UTIs disproportionately affect women, and women who experience recurrent UTIs would benefit from a vaccine. Subpopulations likely to benefit from a vaccine include patients undergoing urological procedures and patients with long term indwelling catheters [157,158].

Antibiotic use

Recommended antibiotic treatment regimens differ within and between countries, in part reflecting local resistance profiles. Regimens typically involve a seven-day oral course of an antibiotic such as nitrofurantoin or trimethoprim, or other first line agent [26,118].

Scoring: Based on the above analysis, antibiotic use was categorised as high (score of 2 out of 2). This estimate is based on an annual incidence of ~250 million urinary ***E. coli*** cases treated with a seven day course of antibiotics

Urgency of AMR threat

Both the WHO and CDC have expressed concern about antibiotic treatments for ***Enterobacteriaceae***, and ***E. coli*** falls within this family. The WHO has listed the ***Enterobacteriaceae*** group as a 'critical' priority for R&D regarding new antibiotics [32]. The CDC has listed carbapenem-resistant ***Enterobacteriaceae*** as an 'urgent' threat in its list of biggest threats from AMR and extended spectrum beta-lactamase-producing ***Enterobacteriaceae*** s as a 'serious' threat [7]. However, fluoroquinolone resistance rates for ***E. coli*** are less than 10% in much of North America and Europe, albeit with a trend of increasing resistance, notably from sequence type 131 [118,125,126,160]. Compared to other bacteria in the ***Enterobacteriaceae*** family, there is a lower frequency of AMR, and resistance is typically limited to fewer antibiotics.

Scoring: Based on the above analysis, the urgency of AMR threat was categorised as medium (score of 1 out of 2).

Probability of R&D success

Pipeline robustness

There is very little ongoing vaccine development for urinary ***E. coli***. One candidate is in pre-clinical development, and two vaccines are reported to be in clinical development.

The Phase II vaccine targets ExPEC and is known as ExPEC4V or JNJ-63871860. ExPEC4V was originally produced by GlycoVaxyn (GlaxoSmithKline) and is now being co-developed by GlycoVaxyn and Janssen. It is a bioconjugate vaccine that uses GlycoVaxyn's proprietary glycosylation platform against ***E. coli*** infection [161].

CURRENT PIPELINE *ESCHERICHIA COLI* (URINARY)

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	-	-	-	-	-	-
Number of **commercial** vaccines	01	01	01	-	-	03
Total number of vaccines	01	01	01	-	-	03

ExPEC4V targets the O-antigen of four ExPEC serotypes: O1A, O2, O6A, and O25B [162].

Data from two Phase I trials are available in the public domain. ExPEC4V was well-tolerated and elicited an immunogenic response in a Phase I trial in healthy Japanese participants [163]. Another Phase I trial was conducted in Switzerland in healthy women with a history of recurrent UTIs [161]. In this trial, ExPEC4V was safe and well-tolerated, and elicited strong, durable, and functional immune responses. Phase II trials are ongoing in adults in the United States.

Scoring: Based on the above analysis, the pipeline was categorised as fairly low (score of 0.5 out of 2).

Pathogen biology

The high incidence of recurrent and chronic UTIs suggests a lack of natural immunity [157], especially as recurrent UTIs are often caused by the same pathogen as the original UTI [164].

Experimental work suggests that the inflammatory response mounted to urinary ***E. coli*** may itself adversely affect the adaptive immune response [165,166].

Although the genomes of UPEC frequently encode many more virulence factors than commensal ***E. coli***, there is no defined core set of virulence factors that clearly differentiates UPEC from commensal ***E. coli*** [167].

Some initial efforts to develop a vaccine focused on surface polysaccharides; however, these antigens are highly diverse, making them a challenging target for a vaccine designed to achieve broad coverage. Overall, 167 O serogroup antigens have been identified, and the K serogroup is comprised of more than 80 members. However,it is likely that 10-12 O serotypes account for at least 90% of meningitis isolates and >60% of bacteraemia isolates [168]. Even with a more limited number of serotypes, designing a broadly protective UPEC vaccine against these serotypes is challenging [98]. Furthermore, these antigens are poorly immunogenic, as some are camouflaged from the adaptive immune system due to structural similarities with host antigens [98].

Other potential targets include fimbrial adhesins, toxins, and iron acquisition system-based antigens. Thus far, only a small subset of fimbrial adhesins has been evaluated for use in a UTI vaccine (P, Dr and type 1 fimbriae) [98]. Many toxins have been associated with UTI symptom severity but none seem to be required for infection [98]. Iron acquisition system-based antigens include outer membrane iron compound receptors [98] and iron-binding siderophores [98]. These molecules are required for bacterial growth in the host and could represent an appealing target for vaccine development.

Scoring: Based on the above analysis, pathogen biology was categorised as fairly low (score of 0.5 out of 2).

Pre-clinical and clinical R&D

A mouse model of experimental UTI exists and is widely used [169]. However, this model has limitations due to differences between species; for example, mouse urine has more protein and is more highly concentrated than human urine [98]. To date, no correlates of protection have been defined that could facilitate a pre-clinical programme [168]. Clinical research is also constrained by the lack of defined correlates of protection [98]. Human challenge models have not yet been established for urinary ***E. coli*** infection [98]. Trial design could present challenges because the target population is likely to include elderly people who are less capable of mounting an effective immune response than their younger counterparts [168].

The effect of vaccines on the gastrointestinal flora should be assessed in clinical trials. Whilst no substantial impact is expected, given that ***E. coli*** constitutes <1% of the intestinal flora [168], experts believe trials should verify that a vaccine does not disrupt the gut microbiome as this could cause complications. As one expert explains, "if the vaccines disrupt the commensal ***E. coli*** population – [at a] minimum we should understand what is happening" [28].

Trial infrastructure should not present barriers to clinical development [170], and the main caution regarding licensure is the need to study the impact of vaccines on the microbiome.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as medium (score of 1 out of 2).

Probability of uptake

Expected policy stance

A vaccination strategy for urinary ***E. coli*** would target high-risk populations. These populations would likely include patients undergoing pre-prostate biopsy, as well as patients with recurrent UTIs or long-term catheters.

The high incidence and significant morbidity and mortality of urinary ***E. coli*** infection in some select sub-populations suggest that a vaccine is likely to have policy support. The frequent use of antibiotics to control urinary ***E. coli*** infection also prompts interest in preventing infections, as one expert notes, "vaccination is attractive as a non-antibiotic means of controlling ***E. coli*** urinary tract infections" [28]. The existence of potentially large, defined target populations also suggests likely support, as explained by a policy expert "at least 50% of men on earth will undergo prostate biopsy at some stage so this could be a target population" [28].

However, significant challenges exist in developing vaccination strategies for key target populations (discussed in more detail section "Barriers to uptake") that could prompt some caution on the part of policy makers.

Scoring: Based on the analysis described above, expected policy stance is categorised as medium (score of 1 out of 2)

Payer, government or Gavi support

Payers in high-income countries are likely to support vaccination for specific sub-populations at high risk, given the probable cost-effectiveness of a targeted vaccination strategy. The annual cost of UTIs, including healthcare and time off work, is approximately US$3.5 billion per year in the United States [82]. One potential target population is patients prior to prostate cancer biopsy, as an alternative to antibiotic prophylaxis [171]. An estimated 1.2 million prostate biopsies are conducted per year in the United States alone [1], and rates of the procedure are similar in other high-income countries. Prophylactic antibiotic use is frequently standard practice for biopsy patients [172]. The infection rate after biopsy is ~2% and carries the risk of sepsis and mortality from infection [2]. There may also be support for vaccination amongst patients with recurrent UTIs. UTIs are common and ~25% of women experience recurrent UTI, with many experiencing recurrence despite prophylactic antibiotics [173].

In middle-income countries, the cost-effectiveness threshold for a urinary ***E. coli*** vaccine will likely be higher because of lower healthcare spending per person. Therefore, urinary ***E. coli*** vaccines may not be a priority within these health systems. In low-income countries, Gavi is unlikely to support a vaccine for urinary ***E. coli*** due to low associated mortality.

Scoring: Based on the above analysis, payer, government, or Gavi support was categorised as medium (score of 1 out of 2).

Barriers to uptake

For pre-prostate biopsy, vaccination could likely be incorporated into the pre-procedure pathway. The logistics of administration would generally allow sufficient time for maximal immune response.

Targeting patients with recurrent UTIs would require greater planning and investment. Key challenges would include the need to engage strongly with guideline setting bodies and key opinion leaders to establish thresholds for when the vaccine would be recommended.

In patients with long-term catheters, catheter associated UTIs account for ~20% of all hospital-acquired infections and ~50% of all infections in long term care facilities [174]. There are likely to be few barriers to uptake in this population as administration of a vaccine could be easily scheduled as part of the catheterisation pathway. Patients and clinicians and likely to be keen to avoid infections, which are a common complication with indwelling catheters.

Scoring: Based on the above analysis, barriers to uptake was categorised as medium (score of 1 out of 2).

Commercial attractiveness

A urinary ***E. coli*** vaccine may be commercially attractive given the potential utility in several sub-populations in high-income countries and medium likelihood of payer, government, or Gavi support. Each affected sub-population currently has a high cost of treatment from UTIs.

Scoring: Based on the above analysis, commercial attractiveness was categorised as medium (score of 1 out of 2).

Recommendations

Urinary ***E. coli*** falls into a cluster of pathogens for which advancing early R&D is the priority.

Primary recommendation

The primary recommendation is to invest in pre-clinical research. Further research into vaccine targets, especially identification of factors that differentiate urinary ***E. coli*** from ***E. coli*** found as a gut commensal, would facilitate development of a vaccine specifically targeting urinary ***E. coli***.

Substantial diversity exists within classes of UPEC virulence factors, which likely contributes to the difficulty in finding antigens that provide broad coverage against UPEC. In order to discover conserved antigens, further understanding of UPEC pathogenesis and the host mucosal immune response to infection will be necessary [98]. Identifying antigens that can be included in vaccines that target virulence factors beyond lipopolysaccharides is also likely to be useful [98].

Pre-clinical research should also seek to better understand the potential effect of vaccines on gastrointestinal flora. The gut microbiome is recognised as an important actor in a range of health outcomes, from mood to body weight [175,176] As ***E. coli*** is a key gut commensal, it is important to establish the presence of any disruption to the microbiome from a vaccine. Initial animal studies regarding the microbiome have been undertaken for Enterotoxogenic ***E. coli*** (ETEC); however, such work has yet to be pursued for UPEC [177].

Secondary recommendations

A better understanding of disease burden should be pursued through pathogen level epidemiological studies. The burden of disease and regional breakdowns provide important information for determining vaccination strategy and assessing cost-effectiveness. These decisions impact subsequent commercial decision making regarding whether to invest in vaccine development.

There is no single source of information that presents a global view of the incidence, morbidity and mortality caused by urinary ***E. coli*** infection. For urinary ***E. coli***, understanding the proportion of hospital-acquired UTIs arising post-surgery would also aid in determining the feasibility of an elective surgery vaccination strategy. There are no regional breakdowns of the urinary ***E. coli*** disease burden, and there is a particular paucity of information from low- and middle-income countries.

Alternative treatments should also be explored. An alternative prevention strategy in pre-surgical groups would be the use of monoclonal antibodies. The advantage is that if a procedure needed to be carried out urgently, monoclonal antibodies would provide rapid protection. However, monoclonal antibodies would not provide sustained protection in recurrent UTI and or long-term catheterised patients. Further, monoclonal antibody approaches face many of the same development challenges as vaccines.

Haemophilus influenzae

Executive summary

Haemophilus influenzae (***H. influenzae***) causes pneumonia, meningitis and otitis media, and has a disproportionate effect on children under five. ***H. influenzae*** serotype b (Hib) is the most virulent strain [178]. It is responsible for 95% of all invasive disease caused by ***H. influenzae*** in non-immunised populations [178–180]. As a result, the following evaluation of ***H. influenzae*** is focussed primarily on Hib.

Conjugated Hib vaccines have been on the market since the 1990s and have strong uptake, with estimated global coverage of ~70% [181]. The effectiveness of marketed vaccines is estimated to be 96% after more than one dose [182]. Current concern surrounding antimicrobial resistance (AMR) is low. Several antibiotics remain effective for Hib, and vaccination programmes have been shown to reduce the prevalence of drug resistant strains [183]. ***H. influenzae*** was included on the WHO list of priority pathogens because of the lack of availability of the vaccine in all geographies and because not all serotypes causing invasive infections are covered. Additionally, drug resistant strains of ***H. influenzae*** are increasing [184].

Recommendations

H. influenzae falls into a cluster of pathogens for which the priority is to increase vaccine uptake. Although uptake is relatively high globally, continued efforts can be made to further expand coverage of the Hib vaccine. The primary recommendation is to drive coverage and equity. The secondary recommendation is to better understand the disease burden, epidemiology, and transmission, particularly of non-Hib strains not covered by current vaccines.

H. influenzae encompasses non-typeable forms and multiple typeable forms. Research efforts into different types have not been uniform. ***H. influenzae*** type B (Hib) is the most studied type as it is the most virulent and is responsible for more than 95% of all infections in unimmunised populations. Therefore, for metrics where data was only available for Hib, this scoring is based on Hib only, as specified in the accompanying text.

SCORECARD *HAEMOPHILUS INFLUENZAE* (SCORECARD FOCUSSED ON HIB)

Health impact:

Direct health impact

0.5	1.0
Mortality	Morbidity

Impact on AMR reduction

0.0	0.0
Antibiotic use	Urgency of AMR threat

Secondary health impact

Significant evidence of herd protection since introduction of routine Hib vaccination

Sub-population benefits

Children under 5 years
The elderly
Immunocompromised individuals

Alternative interventions

None identified

Probability of R&D success:

2.0	2.0	2.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential

Not applicable; already available in combination

Acceleration potential

Not applicable; vaccines on market

Major barriers to development

Not applicable; vaccines on market

Probability of uptake:

2.0	2.0	2.0	2.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy

Global population / Routine vaccination in first year of life

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

H. influenzae is a Gram-negative bacterium that is present as a commensal organism in the nasopharynx of most healthy adults [185]. However, it can spread to cause both systemic and respiratory tract infection [185]. ***H. influenzae*** is divided into typeable and non-typeable forms based on the presence or absence of encapsulation by a polysaccharide capsule. There are six typeable serotypes of ***H. influenzae*** [186].

H. influenzae type b (Hib), a typeable form, is the most pathogenic to humans and is also the most virulent [178]. Hib is responsible for ~95% of all invasive ***H. influenzae*** infections in unimmunised populations [178]. Non-typeable strains are rare causes of serious infection among children but are a common cause of ear infections in children and bronchitis in adults [187].

H. influenzae is spread through airborne droplets and direct contact with respiratory secretions [184] and most commonly causes pneumonia [188] but can also cause meningitis, epiglottitis, septic arthritis, cellulitis, otitis media, and purulent pericarditis [189]. Symptoms vary depending on the manifestation, but can include the following:

- Pneumonia: high fever, headache, severe aches and pains, lethargy, dry cough [188]
- Meningitis: nausea and vomiting, confusion and disorientation, drowsiness or sluggishness, sensitivity to bright light, poor appetite, seizure, coma
- Epiglottitis: sore throat, fever, dyspnoea, dysphagia, drooling [190]
- Cellulitis: fever, warm skin, erythema, pain, most often located on the cheek or periorbital region [190]

Groups at high risk of ***H. influenzae*** infection include children under five years, particularly those aged between four and 18 months, with the exception of very young infants who are protected by the transfer of maternal IgG specific for polyribosyl-ribitoal -phosphate (PRP) across the placenta [191]; adults aged 65 or older [192]; and those with immune-compromising conditions such as complement deficiency, hypogammaglobulinaemia, sickle cell anaemia, functional asplenia, malignancy, and HIV [184,193].

H. influenzae has a global distribution but prevalence varies by location. Although vaccines are available and widely used in many regions, most cases occur in unvaccinated young children in low-income countries [178].

Potential health impact

Direct health impact

The following impact evaluation addresses Hib, as it is the most virulent of the ***H. influenzae*** strains and causes both the majority (95%) of ***H. influenzae***-associated invasive disease in the absence of vaccination [179,180] and the majority of H-influenzae-associated deaths [179,180]. Global data on disease burden for Hib is available from the IHME. The IHME data comprises mortality and morbidity from Hib meningitis and Hib pneumonia. This data uses a defined methodology and is used in the global health community. The data can therefore be viewed with a reasonable level of confidence. Whilst mortality from Hib meningitis is low, the IHME estimates suggest that Hib meningitis is still a significant cause of morbidity globally. Hib meningitis is estimated to be responsible for approximately 30,000 deaths and 0.25 million years lived with disability in 2016 [31]. Hib pneumonia is estimated to be responsible for approximately 48,000 deaths and 10,000 years lived with disability in 2016 [31]. Very limited data for non-Hib ***H. influenzae*** exists, and one expert explains "it is difficult to know about the disease burden because there is so little information"[28] but it is not thought to significantly contribute to the burden of invasive disease [28].

Scoring: Based on the above analysis, mortality was categorised as low (score of 0 out of 2) and morbidity was categorised as medium (score of 1 out of 2).

Secondary health impact

There is evidence of significant herd protectionfor Hib [194]. With vaccine coverage of <70%, Hib incidence was reduced dramatically in the Gambia with both vaccinated and unvaccinated children benefitting [195]. Humans are the only known reservoir of ***H. influenzae*** [186].

Sub-population benefits

Vaccination particularly benefits young children and immunocompromised individuals, the groups at greatest risk of ***H. influenzae*** infection.

Antibiotic use

A seven day course of antibiotics is a typical treatment for both meningitis and lower respiratory tract infection (LRTI), including pneumonia[196,197]. Beta-lactam agents such as amoxicillin or a second- or third-generation cephalosporin are the preferred treatment choice [184]. Alternative agents with activity against ***H. influenzae*** include fluoroquinolones, macrolides, tetracyclines, and aminoglycosides [184]. Antibiotic use associated with Hib is generally driven by LRTI as the incidence of LRTI exceeds that of meningitis.

Scoring: Based on the above analysis, antibiotic use was categorised as low (score of 0 out of 2). This estimate is based on an annual incidence of ~eight million LRTIs and ~400,000 meningitis cases, both treated with a one week course of antibiotics

Urgency of AMR threat

The WHO has expressed concern about the development of AMR in ***H. influenzae*** and has listed ampicillin-resistant ***H. influenzae*** as a 'medium' priority pathogen for R&D regarding new antibiotics [6].

However, it is not included on the CDC's list of biggest threats from AMR [7]. Beta-lactamase–negative, ampicillin-resistant ***H. influenzae*** is an emerging problem amongst both Hib and other ***H. influenzae*** strains.

Prevalence of resistance in all ***H. influenzae*** strains is currently at ~35% in Japan, ~55% in Spain, and ~3% in the United States [184]. Resistant strains therefore represent a growing threat, but ***H. influenzae*** remains susceptible to ceftriaxone [184].

Studies have shown that use of the Hib vaccine is correlated with a reduction in AMR. One 10-year study showed a 50% decrease in ampicillin-resistance and resistance to other, related antibiotics after universal introduction of the Hib vaccine in 1999 [183], and an expert states "vaccines are already playing an important role to reduce AMR in ***S. pneumoniae*** and Hib" [28]. Some experts expressed surprise that ***H. influenzae*** was on the WHO priority list, as they do not regard the AMR risk from the pathogen to be high. Furthermore, given the existence of an effective vaccine experts cite a perception that "not much more [is] needed here" [28].

Scoring: Based on the above analysis, urgency of AMR threat was categorised as low (score of 0 out of 2).

Probability of R&D success

Pipeline robustness

The ***H. influenzae*** pipeline is robust, comprising a total of 60 vaccines and including 46 licensed vaccines. Those still in development include eight in pre-clinical studies, one in Phase I, two in Phase II, and three in Phase III. Nearly all of these vaccines – 59 of 60 - are commercially developed. All licensed vaccines and the majority of vaccines in development target Hib. However, GSK is also developing a vaccine against non-typeable ***H. influenzae*** [198]. Given the focus on Hib, the remainder of the probability of R&D success section addresses Hib vaccines. More detail on the pipeline can be found in the appendix.

Scoring: Based on the above analysis, the pipeline for Hib was categorised as high (score of 2 out of 2).

Pathogen biology

Since Hib causes the majority of all ***H. influenzae*** infections, it has been the focus of most research on pathogen biology for ***H. influenzae*** to date. Natural immunity to Hib exists and is well understood.

Strain-specific immunity that is mediated by serum capsular polysaccharide specific IgG antibodies exists and has been known since the 1930s [191]. Age-specific profiles of these protective antibodies show a characteristic pattern: high levels of trans-placentally acquired anti-PRP antibodies are present at birth, then fade after birth and have a half-life of approximately 28 days [199]. Anti-PRP antibodies reach very low levels by around 6 months of age, but antibody titres rise again during the second year of life [200]. This rise in antibody levels is thought to be a response to exposure to Hib in the nasopharynx, or exposure to other organisms with cross-reactive antigens.

Vaccine targets are well-characterised as vaccines against Hib are already on the market. The Hib capsule is formed from repeating polymers of ribosyl and ribitol-phosphate and is called a PRP capsule [191]. In vaccines against Hib, PRP is conjugated to carrier proteins to induce a greater immune response. The carrier proteins are involved in T-cell activation and induce immune memory [191].

Scoring: Based on the above analysis, pathogen biology was categorised as high (score of 2 out of 2).

Pre-clinical and clinical R&D

Pre-clinical research benefits from the well-developed base of knowledge for ***H. influenzae***. Anti-PRP antibody titres are known correlates of protection [200]. Mouse, rat, guinea-pig and rabbit models are available and have been effectively used to assess the immunogenicity of ***H. influenzae*** vaccines [201].

Similarly, correlates of protection are known and used in clinical studies [202]: 0.15µg/ml anti-PRP IgG is established as the level needed to give short-term protection from invasive Hib disease [203] and field studies set a threshold of 1µg/ml, one month after completion of the primary vaccination series, as the level required to confer long-term protection from invasive Hib disease [203]. The infrastructure needed to run clinical trials is also available.

Licensed vaccines against Hib are efficacious and effective. They are marketed in multivalent combinations. The effectiveness of current vaccines against Hib meningitis is 55% after one dose, 96% after two doses, and 96% after three doses [182]. These vaccines are also effective against invasive Hib, showing 59% effectiveness

CURRENT PIPELINE *HAEMOPHILUS INFLUENZAE*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	01	-	-	-	-	01
Number of **commercial** vaccines	07	01	02	03	46	59
Total number of vaccines	08	01	02	03	46	60

after one dose and 97% after three doses. Insufficient data is available to estimate effectiveness after two doses [182]. The efficacy data do highlight the importance of ensuring target populations receive a complete vaccine series as two or more doses are required for high effectiveness [182]. Current vaccines are regarded as very safe by the WHO and CDC [204,205] and also shown to be safe and efficacious in multivalent combination vaccines (for example, pentavalent or even hexavalent DTPa-HBV-IPV/Hib).

Licensed vaccines are conjugated polysaccharide vaccines, a proven technology used to develop vaccines against a variety of pathogens. The vaccine is produced in high quantities from several manufacturers worldwide. Combination vaccines with other childhood vaccines are approved and on the market. A typical wholesale cost of a DTPw-HepB-Hib pentavalent vaccine was about 15.40 USD in 2014. Current vaccines do require refrigerated storage; Infanrix (6-valent) has a shelf life of three years and is to be stored in a refrigerator (4°C) [206] and all Hib-containing vaccines should be stored between 2 and 8 °C [203] and liquid vaccines should never be frozen.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as high (score of 2 out of 2).

Probability of uptake

Expected policy stance

Strong and established policy support for Hib vaccination already exists. The WHO recommends the inclusion of conjugate Hib vaccines in all infant immunisation programmes [203] and has taken this position since 2006. Experts concur that "Haemophilus vaccination programmes should be expanded as much as possible" [28].

Scoring: Based on the above analysis, expected policy stance was characterised as high (score of 2 out of 2).

Likelihood of payer, government, or Gavi support

More than 90% of countries provide the Hib vaccine through routine vaccination schedules [207]. By the end of 2017, 191 countries (>95% of WHO member states) had included conjugated Hib vaccines in their immunization programmes [181,203]. By the end of 2014, all Gavi-supported countries had introduced the Hib vaccine as part of the pentavalent vaccine [208].

Scoring: Based on the above analysis, likelihood of payer, government, or Gavi support was characterised as high (score of 2 out of 2).

Barriers to uptake

At a national level, uptake of the Hib vaccine is high with 191 countries including Hib in vaccination programmes by the end of 2017 [181]. Global coverage with three doses is estimated to be ~72% [181] but varies by region [181]. The highest coverage is estimated at 91% in the WHO region of the Americas and the lowest estimated at 28% in the WHO Western Pacific Region [181].

Scoring: Based on the above analysis, barriers to uptake was characterised as low (score of 2 out of 2).

Commercial attractiveness

The Hib vaccine is licensed and administration rates are high worldwide.

Scoring: Based on the above analysis, commercial attractiveness was categorised as high (score of 2 out of 2).

Recommendations

H. influenzae falls into a cluster of pathogens for which the priority is to increase vaccine uptake.

Primary recommendation

Although uptake of the Hib vaccine is relatively high globally, continued efforts can be made to further expand coverage. The primary recommendation is to drive coverage and equity. Global uptake of the Hib vaccine is estimated to be ~70% [181]. Immunisation is the most important strategy for prevention of Hib infection [209] and uptake should continue to be monitored to identify areas where intervention is needed to drive better coverage. The importance of sustained vaccination against Hib was highlighted during a Hib vaccine shortage in the United States between November 2007 and March 2008 during which outbreaks were reported in Minnesota and Pennsylvania [210].

Secondary recommendation

The secondary recommendation is to better understand disease burden, epidemiology or transmission. Epidemiological data related to non-Hib ***H. influenzae*** infections is scarce. Although studies have not comprehensively assessed global burden, estimates based on the literature suggest that there is relatively low mortality [179,180] and incidence [183,211–213] associated with these infections. Better characterisation of the burden would lead to a greater understanding of ***H. influenzae*** and would assist in evaluating the case for the development of a vaccine against non-typeable ***H. influenzae*** infections. This evaluation should include antibiotic use driven by non-Hib ***H. influenzae***.

Helicobacter pylori

Executive summary

Helicobacter pylori (***H. pylori***) is a high-incidence, low-virulence pathogen which colonises more than 50% of the world's population [214]. ***H. pylori*** colonisation is most often asymptomatic but it is the most common cause of peptic ulcers and is an important risk factor for gastric cancer [214]. Antimicrobial resistance (AMR) is a growing concern with increasing resistance to first line agents. However, several treatment options remain effective, including first-line treatment in the majority of cases.

No vaccine is currently available and the most advanced candidate vaccine is in Phase I clinical trials. Significant barriers to successful R&D include the absence of natural immunity, a lack of suitable vaccine targets, the difficultly in demonstrating efficacy without immunologic correlates and long lead time from infection to the development of outcomes of concern (gastric cancer and peptic ulcer disease). In view of these challenges, experts concur that a vaccine would be difficult to develop.

Global uptake of a vaccine is unlikely, but interest may be high in regions where gastric cancer is common. Direct mortality from ***H. pylori*** infection is relatively low compared to the high rate of colonisation, and vaccination is not currently a priority for policy bodies because it is not perceived as a serious threat. Experts do not believe a vaccine for ***H. pylori*** would have a significant impact on AMR, as resistance is not widespread and treatment options remain. However, some high- and middle-income countries could be interested in a vaccine against ***H. pylori*** to reduce rates of gastric cancer.

Recommendations:

Addressing the disease burden of ***H. pylori*** will require a better understanding of the link between ***H. pylori*** and gastric cancer, as well as a better understanding of how AMR resistance is likely to evolve in response to current antibiotic treatments.

SCORECARD *HELICOBACTER PYLORI*

Health impact:

Direct health impact

1.0 Mortality

2.0 Morbidity

Impact on AMR reduction

1.0 Antibiotic use

0.0 Urgency of AMR threat

Secondary health impact

Eradication of H. pylori could significantly reduce the incidence of gastric cancer

Sub-population benefits

Low socio-economic status
Pregnant women

Alternative interventions

Proton pump inhibitors and other acid reducing therapies
Bismuth based therapies

Probability of R&D success:

0.0 Pipeline robustness

0.5 Pathogen biology

1.0 Pre-clinical and clinical R&D

Combination potential

None identified

Acceleration potential

Identify good vaccine antigens

Major barriers to development

Lack of understanding of disease epidemiology

Probability of uptake:

2.0 Commercial attractiveness

1.0 Expected policy stance

1.0 Payer, government or Gavi support

1.0 Barriers to uptake

Who needs the vaccine / Potential vaccination strategy

Global population / Routine vaccination in first year of life

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

H. pylori falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority. The primary recommendation is to better understand the burden, epidemiology and transmission of ***H. pylori***. Secondary recommendations are to explore alternative treatments or prevention strategies and invest in pre-clinical research.

Pathogen overview

H. pylori is a Gram-negative bacterium that has co-evolved with humans for approximately 60,000 years [215] and is the most common chronic bacterial infection in humans [216]. ***H. pylori*** commonly colonises the stomach, but other sites are also occasionally colonised [215]. It is spread person-to-person in saliva and by faecal contamination of food or water [217].

H. pylori colonisation is most often asymptomatic. However, ***H. pylori*** causes many cases of atrophic gastritis [218], peptic ulcer disease [219], and is a risk factor for gastric cancer [220]. Symptoms vary depending on the manifestation, but can include epigastric pain, bloating, lack of appetite, nausea, tar-coloured stools in patients with gastritis and peptic ulcer disease, and indigestion, bloating, heartburn, nausea, and abdominal pain in patients with gastric cancer.

Patients at high risk include pregnant women, amongst whom complications of ***H. pylori*** may include hyperemesis gravidarum, severe nausea and vomiting [221,222].

H. pylori has a global distribution but prevalence varies greatly by location and development status. Prevalence has been estimated at 51% in low-income countries versus 35% in high-income countries [223]. In one systematic review and meta-analysis of 410,879 participants from 73 countries, the highest prevalence was estimated to be in Latin America and the Caribbean (59%) and the lowest in North America (26%) [223]. By nation, the highest prevalence was in Nigeria (90%) [223]. In a separate systematic review and meta-analysis from 62 countries, the prevalence was estimated to fall between 19% in Switzerland and 88% in Nigeria [214].

Potential health impact

Direct health impact

Robust global data on disease burden is not available, and neither WHO nor IHME reports ***H. pylori*** asscoiated disease. However, a review of the literature suggests that ***H. pylori*** causes significant disease burden. Globally, it is responsible for the majority of peptic ulcer disease and gastric cancer: 70% of gastric ulcers [219] and an estimated 78% of gastric cancer cases [220] are associated with ***H. pylori***. The International Agency for Research on Cancer (IARC) classified ***H. pylori*** as a Group I carcinogen in 1994, and confirmed this classification again in 2009 [220]. An expert states, "it is not disputed that ***H. pylori*** causes gastric cancer" [28].

Whilst recent systematic reviews and meta-analyses exist estimating prevalence [214,223], there is a lack of robust data at the global level estimating ***H. pylori*** mortality and morbidity by cause. However, robust global data exists for peptic ulcer disease and gastric cancer and estimates for the percentage caused by ***H. pylori*** were found in the literature. These estimates are likely to be less precise than the IHME estimates for other diseases. A full description of the methodology used to arrive at the estimates can be found in the appendix.

Scoring: Based on the above analysis, mortality was categorised as medium (score of 1 out of 2) and morbidity was categorised as high (score of 2 out of 2).

Secondary health impact

A significant reduction of ***H. pylori*** infection would likely be a driver in the reduction of gastric cancer incidence [220].

Sub-population benefits

A vaccine against ***H. pylori*** will particularly benefit individuals of low socio-economic status and pregnant women, who are at risk of complications from ***H. pylori*** infection [222,224].

Antibiotic use

Many antibiotic regimens have been evaluated for the treatment of ***H. pylori*** but few have achieved high pathogen clearance rates in individuals [225]. A typical treatment course for ***H. pylori*** may be two weeks. In geographical regions where clarithromycin-resistance is known to be low (<15%) and the patient has no history of macrolide exposure, the American College of Gastroenterology (ACG) advises the use of proton pump inhibitors (PPI), clarithromycin, and amoxicillin or metronidazole as a first-line therapy [226]. Bismuth quadruple therapy,

consisting of a PPI, bismuth, tetracycline, and a nitroimidazole, and concomitant therapy, consisting of a PPI, clarithromycin, amoxicillin and a nitroimidazole, are also recommended options [226].

Scoring: Based on the above analysis, antibiotic use was categorised as low (score of 0 out of 2). This estimate is based on an annual incidence of ~ seven million peptic ulcer disease cases treated with a two week course of antibiotics

Urgency of AMR threat

The WHO has expressed concern about the development of AMR and has listed clarithromycin-resistant ***H. pylori*** as a 'high' priority pathogen for R&D regarding new antibiotics [6]. However, it is not listed on the CDC watch list of most significant threats from AMR [7]. Experts have mixed views about the level of threat posed by resistant ***H. pylori***; an expert who is concerned about the risk states "[AMR in H. Pylori is] a problem across countries and the fear is that it will continue to increase" [28]. However, another expert disagrees, saying "why is ***H. pylori*** on the list? This does not make sense. I see no link between ***H. pylori*** and AMR threat" [28].

Resistance rates are increasing in ***H. pylori*** [227]. Resistance to clarithromycin is developing rapidly in regions where ***H. pylori*** seropositivity is high [227]. Clarithromycin resistance is particularly prevalent in China, where it is estimated to affect half of cases [227]. Less longitudinal data is available for other antibiotics but metronidazole resistance is confirmed to be increasing in many countries [227]

However, resistance to tetracycline and amoxicillin, which are both included in American College of Gastroenterology recommended first-line treatment courses, are very low <2% [227], and treatment with first-line agents is still successful in the majority of cases (~85% of cases in the United States [228] and a lower number in Europe). An expert explains "at the moment you can generally control the infection in most people" [28].

Scoring: Based on the above analysis, the urgency of AMR threat for ***H. pylori*** was categorised as low (score of 0 out of 2).

CURRENT PIPELINE *HELICOBACTER PYLORI*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	05	-	-	-	-	05
Number of **commercial** vaccines	04	01	-	-	-	05
Total number of vaccines	09	01	-	-	-	10

Probability of R&D success

Pipeline robustness

The ***H. pylori*** pipeline is weak, with a total of 10 vaccines in development. Nine are in pre-clinical development, and one is in Phase I.

Scoring: Based on the analysis described above, the pipeline for ***H. pylori*** was categorised as low (score of 0 out of 2).

Pathogen biology

It is not yet clear if natural immunity exists; however, if it exists, it is only partially effective.

There is evidence from observational research that some children are able to spontaneously clear ***H. pylori*** [229]. However, this may be attributable to exposure to antibiotic treatment for conditions other than ***H. pylori*** infection and is not necessarily evidence of natural immunity [230]. The best evidence for natural immune-mediated protection against ***H. pylori*** infection derives from a clinical trial where volunteers were exposed to ***H. pylori*** following experimental exposure to a live vaccine [231]. The vaccine was not effective but a minority of participants cleared the ***H. pylori*** challenge via a mechanism associated with a T-helper cell response [231]. Antibody-mediated protective immunity has not been demonstrated [230].

H. pylori typically colonises a physiologically unique environment, which is both acidic and mucosal. It is still unclear whether this requires a specifically adapted immune response for effective protection. The unique colonisation environment also presents challenges for vaccine development, as one expert explains "[a vaccine] could be of interest but would require mucosal protection through oral tablet or intramuscular injection" [28].

Vaccination in mice using a range of antigens can modestly reduce ***H. pylori*** colonisation. However, translation into success in clinical trials has not been shown so far, with the exception of one trial in China [230]. The trial was a Phase III, single-centre, double-blind, placebo-controlled, randomised trial of an oral recombinant ***H. pylori*** vaccine conducted in Ganyu County, Jiangsu Province, China [232] that enrolled 4464 healthy children aged 6-15 years without past or present ***H. pylori*** infection. The trial was sponsored by Jiangsu Province Centers for Disease Control and Prevention in collaboration with National Institutes for Food and Drug Control, China, Kangwei biological technology Co., Ltd (renamed Wuhu Kangwei biological technology Co., Ltd. in 2011) and Third Military Medical University. The trial was conducted from 2005-2007 but results were not published until 2015. The vaccine tested in this trial showed evidence of protection against ***H. pylori*** infection (72% efficacy in the first year, falling to 55% after three years of follow-up). Experts cite this study as "proof of concept that a vaccine against ***H. pylori*** is possible" [28], but development of the vaccine has been discontinued for unknown reasons [28,230]. Despite the likely feasibility of a vaccine, experts do not regard currently identified targets as promising: one states "there's nothing published that I would consider a good target" [28].

Scoring: Based on the above analysis, pathogen biology was categorised as fairly low (score of 0.5 out of 2).

Pre-clinical and clinical R&D

No correlates of protection have been identified that can facilitate pre-clinical research. A number of animal models are available and have some value for initial screening of vaccine candidates. However, vaccines shown to have some efficacy in mice have not been effective in clinical trials [230]. The lack of translatability may reflect insufficient protection in mouse models before progressing to clinical trials and may also reflect poor translatability of protective immunity between mouse models and humans. Lack of investment in pre-clinical research is a major barrier to R&D [28]. Experts state that "it's pretty tough to get money" [28] and "[the] biggest obstacle is investment" [28].

The lack of identified correlates of protection also constrains clinical research, as there is limited information available to help simplify study read-outs. Some experts believe this is particularly problematic for ***H. pylori*** vaccine trials because the outcomes of interest, peptic ulcer disease and cancer, occur long after infection. An expert explains "symptom latency is so far in the future you would need a surrogate or correlate of protection to prove efficacy" [28]. However, other experts disagree that this is any more problematic for ***H. pylori*** than for other pathogens, with one stating "you don't have to prove correlates of protection against ulcers or cancer because it's so well ingrained that there's a cause…the vaccine only has to prove eradication of infection. If you can do that, your clinical path should be quite straightforward" [28]. Controlled human infection trials are possible for ***H. pylori***. A challenge strain has been developed and has proven valuable for early clinical trials [233].

The target population for an ***H. pylori*** vaccine is not yet clearly defined and could vary depending on specific vaccine technologies. A vaccine could be given prophylactically to prevent infection, or therapeutically to decrease or eliminate colonisation and prevent complications. Prophylactic vaccines would have to be administered in early life, as most adults who are infected became infected in childhood. In contrast, a therapeutic

vaccine could be given at almost any age, but research would need to establish lead times between infection and complications.

Other vaccines, primarily targeting the urease antigen [230] have reached clinical trials but have not been successful. Currently, there is one candidate vaccine in clinical trials. ImevaX's IMX 101 is currently being investigated in a Phase I trial [234]. The trial is a multi-center, randomised, double-blind and adjuvant-controlled study to evaluate the safety, tolerability, and efficacy of IMX101 in ***H. pylori***-negative and ***H. pylori***-infected healthy volunteers. The study was initiated in 2017. The primary outcome is safety and tolerability, and the secondary outcome is determination of immune responses to the vaccine [234]. IMX 101 comprises an ***H. pylori*** antigen (γ-glutamyltranspeptidase (GGT)), an outer membrane protein and a muscosal adjuvant. GGT has been chosen because of its potent immunosuppressive activity which is an important part of ***H. pylori***'s immune evasion. The vaccine aims to neutralise this defence mechanism, facilitating a more effective immune response against other components of a vaccine [230].

Scoring: Based on the analysis described above, pre-clinical and clinical R&D was categorised as medium (score of 1 out of 2).

Probability of uptake

Expected policy stance

The ideal vaccination strategy has not yet been determined. A prophylactic vaccine would likely require routine vaccination in young infants prior to exposure. A therapeutic vaccine could target older age groups but would require research to help develop a strategy and vaccination schedule best suited to preventing complications.

Experts suggest that policy support may be generated by interest in preventing cancer, rather than the risk of AMR. According to one expert "the real reason to vaccinate is stomach cancer not antibiotic use" [28]. The risk of gastric cancer is not always reduced by treatment [235]. In particular, treatment with proton pump inhibitors may increase gastric cancer risk, although this link remains uncertain [236,237]. The IARC note: "Theoretically, active immunization of young children against ***H. pylori*** would be ideal to prevent infection and its chronic consequences, including peptic ulcer disease and gastric cancer" [220], suggesting that there may be WHO support for a vaccine on these grounds. However, to date there is no specific advocacy for the development of a vaccine from policy bodies. This may be because there is a general perception that ***H. pylori*** has a good range of antibiotic treatment options and is not a serious disease, as one expert states "the disease is treatable, hence a vaccine is not interesting" [28] and another agrees, saying "I would not lose a lot of sleep on ***H. pylori***" [28].

Scoring: Based on the analysis described above expected policy stance was categorised as medium (score of 1 out of 2).

Payer, government, or Gavi support

In high- and middle-income countries, a routine, prophylactic vaccine may be cost-effective [230].

The cost-effectiveness of prophylactic vaccination strategy targeting infants was estimated to be ~$4000/QALY (quality adjusted life year) in the United States and, thus, cost-effective [238]. In areas of higher incidence, the cost-effectiveness could be expected to be larger.

Gastric cancer is likely to be a more significant cost lever than peptic ulcer disease. Whilst ***H. pylori*** prevalence is highest in Africa, the burden of gastric cancer is highest in Japan, China and Korea [214]. This may be related to the predominant ***H. pylori*** strains in these regions [214]. Because of the high burden of complications in Asia, it may be the region with greatest need for a vaccine and interest in a vaccine may be highest in areas of high gastric cancer risk such as Japan and Korea, and some large middle-income countries such as China and Russia. As one expert notes "[uptake] would depend on the risk of stomach cancer in a country or population so Japan might use this first" [28]

Direct mortality from ***H. pylori*** infection is low, so investment from Gavi in low-income countries is unlikely. However, the pathogen disproportionately impacts those in low socioeconomic groups, which is something considered in Gavi decision-making frameworks [223,229].

Scoring: Based on the analysis described above, payer, government, or Gavi support has been categorised as medium (score of 1 out of 2).

Barriers to uptake

Based on cost-effectiveness estimations and the increasing prevalence of infection with age, a prophylactic vaccine would need to be administered early in life. As one expert states, "[we] would need to vaccinate very early in life and have to add to existing routine immunisation schedule" [28]. No new touchpoints would be required for addition to the routine immunisation schedule. For a therapeutic vaccine, however, target age groups, or other defined populations, may need to be identified. Whilst a therapeutic vaccine could be integrated into existing adult touchpoints, a new touchpoint might be required depending on the target group selected.

Given the low perceived threat of ***H. pylori***, there may be issues of patient acceptance of a vaccine and a strong patient education programme would be required. The particularly low perceived threat of ***H. pylori*** would also affect clinical practices, as the benefits of vaccination would have to be clearly set out to guideline setting bodies.

Scoring: Based on the analysis described above, barriers to uptake were categorised as medium (score of 1 out of 2).

Commercial attractiveness

Commercial attractiveness was categorised as high, reflecting a potentially large target population in high- and middle-income countries. However, likelihood of approval for use in a larger population will likely be difficult, as reflected in the sections above.

Scoring: Based on the analysis described above, commercial attractiveness was categorised as high (score of 2 out of 2).

Recommendations

H. pylori falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority.

Primary recommendation

The primary recommendation is to collect more data on ***H. pylori***. A better understanding of the contribution of ***H. pylori*** to AMR is needed, including clarification of the pace at which the pathogen is developing resistance to different antibiotics and an understanding of how antibiotic use for ***H. pylori*** is contributing to the development of resistance in other pathogens. In particular, there is a need to document any cases that are resistant to all treatment.

There is also a significant need to better understand the link between ***H. pylori*** and cancer. Currently, there is uncertainty about whether it is ***H. pylori*** colonisation or manifest disease which increases the risk of cancer. It is also not yet known whether effective treatment of ***H. pylori*** alone would manage the associated cancer risk. There is some evidence that long-term exposure to proton pump inhibitors increases the incidence of ***H. pylori***-associated gastric cancer [236,237]. The association between ***H. pylori***-associated cancer risk and treatments for ***H. pylori*** and for related gastric symptoms and conditions requires better understanding.

Secondary recommendations

Alternative approaches to manage ***H. pylori*** infection should be explored, including the addition of bismuth to conventional triple therapy [239,240], which can achieve high levels of ***H. pylori*** eradication. In order to determine the best treatment options for individual infections, particularly where first-line therapies have failed, better diagnostic tests for the detection of drug resistance in ***H. pylori*** should be explored [241]. Existing methods, including agar culture, agar dilution, disk diffusion and the Etest, all have specific drawbacks and genomic techniques offer a promising potential alternative to these methods. Further, the use of stool samples, as opposed to gastric biopsy, would reduce the need for an invasive procedure to detect antimicrobial resistance and warrants further exploration [241].

Pre-clinical research to better understand ***H. pylori***'s immune evasion mechanisms and how to develop effective vaccines against pathogens that colonise the acidic, mucosal environment of the stomach, in general, would increase the likelihood of developing a successful vaccine.

Klebsiella pneumoniae

Executive summary

Klebsiella pneumoniae (***K. pneumoniae***) is primarily a hospital-acquired infection, commonly presenting as pneumonia. Incidence of ***K. pneumoniae*** is high compared to other hospital-acquired pathogens on the WHO AMR priority pathogen list. It can also cause community-acquired infections in immunocompromised individuals. While there is a high urgency of AMR threat and moderate mortality, morbidity is low.

There is no current vaccine for ***K. pneumoniae*** and the pipeline is comprised of three pre-clinical candidates. There is some understanding of pathogen biology; however, there are challenges to identifying conserved antigens. Previous clinical trials have been unsuccessful and it is difficult to identify a target population for the vaccine, making clinical trials difficult. Given the current understanding of pathogen biology and technicural challenges of developing a vaccine, the likelihood of R&D success is low.

Uptake for ***K. pneumoniae*** faces hurdles due to difficulty identifying well circumscribed populations at high risk of infection. Possible target populations include hospitalised patients, patients who are immunocompromised, for example due to HIV, diabetes or alcohol dependency, and patients who are at risk of needing mechanical ventilation. It is currently difficult to predict which patients are at highest risk of infection. The cost-effectiveness of a vaccination for ***K. pneumoniae*** is questionable because of this difficulty.

Recommendations

K. pneumoniae falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority. The primary recommendation is to collect more data on the burden of disease. It is important to collect comparative data on sub-populations at risk of ***K. pneumoniae*** in order to determine which patient groups are at highest risk and whether they can be adequately targeted for clinical development and vaccine delivery.

SCORECARD *KLEBSIELLA PNEUMONIAE*

Health impact:

Direct health impact

1.0	0.0
Mortality	Morbidity

Impact on AMR reduction

1.0	2.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Individuals with recurrent urinary tract infections, HIV, chronic lung conditions or diabetes

Alternative interventions
Passive immunisation

Probability of R&D success:

0.0	0.5	0.5
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
None identified

Acceleration potential
None identified

Major barriers to development
Lack of understanding of disease epidemiology

Probability of uptake:

1.0	0.0	1.0	1.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Hospitalised patients / High-risk groups such as those with immunocompromise e.g. HIV, risk of mechanical ventilation, COPD patients

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

K. pneumoniae is a Gram-negative bacterium found in the normal flora of the human mouth and intestine that primarily causes hospital-acquired infections, but can also cause community-acquired infections in immunocompromised patients [242]. Although ***K. pneumoniae*** is part of the ***Enterobacteriaceae*** family, it has been considered separately in this assessment because of its high incidence relative to other members of the ***Enterobacteriaceae*** family. It is transmitted on medical equipment, on the hands of healthcare workers, or from environmental reservoirs [243]. Common clinical presentations and accompanying symptoms of ***K. pneumoniae*** infection include:

- Pneumonia: fever, cough, increased sputum production, pleuritic chest pain, dyspnoea, tachypnoea, crackles on physical examination.
- Urinary tract infection (UTI): frequency, dysuria, malaise, fever, loin pain
- Liver abscess: fever, right upper quadrant abdominal pain, chills

Less common presentations include spontaneous bacterial peritonitis, endophthalmitis, skin and soft tissue infections, and brain abscess.

Populations at greatest risk of ***K. pneumoniae*** infection are immunocompromised individuals, including those with diabetes, chronic lung conditions, HIV-positive individuals, and hospitalised patients. Patients who contract ***K. pneumoniae*** pneumonia may be on ventilator support, immunocompromised or have chronic airways disease e.g. COPD [242]. Those who contract ***K. pneumoniae*** UTIs may have catheters [242]. Hospital-acquired ***K. pneumoniae*** infections occur worldwide, but incidence of community-acquired infection varies by country. For example, Taiwan and South Africa have higher incidence of community-acquired pneumonia caused by K. pneumonia than other countries [242].

Potential health Impact

Direct health impact

Global data on disease burden is not available from the IHME, WHO or in the research literature [31,32]. The global burden of UTIs and lower respiratory tract infections (LRTIs) including pneumonia from all causes are available from the IHME [31]. A review of the research literature suggests that ***K. pneumoniae*** is responsible for ~7% of UTIs [82] and ~4% of LRTIs [33]. Given the lack of direct data on the burden of ***K. pneumoniae***, it is challenging to assess the global burden precisely with confidence. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was categorised as medium (score of 1 out of 2) and morbidity was categorised as low (score of 0 out of 2).

Sub-population benefits

A vaccine would particularly benefit immunocompromised individuals, hospitalised patients (including intensive care patients and patients with invasive devices, including urinary catheters [244]), the elderly [245], and individuals with chronic conditions (including chronic lung conditions, chronic liver disease, and dialysis patients [245]).

Antibiotic use

Typical antibiotic treatment courses for LRTIs and UTIs are approximately one week in duration. An international panel of experts, convened by the Infectious Diseases Society of America (IDSA) in collaboration with the European Society for Microbiology and Infectious Diseases (ESCMID), suggests nitrofurantoin is an appropriate treatment for uncomplicated UTIs [246].

Other appropriate treatments include trimethoprim and beta-lactam/beta-lactamase combinations [118]. Treatment for lower respiratory tract infection depends upon hospitalisation status and patient exposure to antibiotics. For hospitalised patients with no risk-factors for drug resistance, piperacillin-tazobactam or cefepime may be used [96]. Given the high incidence of UTIs, ***K. pneumoniae*** associated antibiotic use is primarily driven by UTIs.

Scoring: Based on the above analysis, antibiotic usage was categorised as medium (score of 1 out of 2). This estimate is based on an annual incidence of ~25 million UTIs and ~10 million LRTIs, both treated with a seven day course of antibiotics.

Urgency of AMR threat

Both the WHO and CDC have expressed concern about ***K. pneumoniae*** developing AMR. The WHO has listed ***K. pneumoniae*** as a member of the ***Enterobacteriaceae*** group of pathogens under the 'critical' priority pathogens for R&D regarding new antibiotics [6] and the CDC has listed carbapenem-resistant ***Enterobacteriaceae*** as an urgent threat in its list of biggest threats from AMR [7]. Extended-spectrum beta-lactamase (ESBL) resistant strains have also been listed as a serious threat on the CDC list [7]. Both ESBL and carbapenemase-producing ***Enterobacteriaceae*** (CPE) ***K. pneumoniae*** strains have been reported worldwide [247,248]. CPE strains frequently also exhibit resistance to fluoroquinolones and aminoglycosides [249].

Scoring: Based on the above analysis, the urgency of the AMR threat was categorised as high (score of 2 out of 2).

Probability of R&D success

Pipeline robustness

The pipeline is almost empty. There are three vaccine candidates and all are in pre-clinical development [40–42].

Scoring: Based on the above analysis, pipeline robustness was characterised as low (score of 0 out of 2).

Pathogen biology

Vaccine targets for ***K. pneumoniae*** have been explored. O-antigens and K-antigens are potential targets but have significant limitations in ***K. pneumoniae***. These antigens have been studied in detail and to date eight O-antigens and 77 K-antigens have been identified [250]. O-antigens do not appear to be useful vaccine targets for ***K. pneumoniae*** because they cause adverse toxic reactions in active immunisation [251]. K-antigens are immunogenic and non-toxic, but a vaccine would have to include at least 24 major K-types to cover 70% of ***K. pneumoniae*** strains [251].

Mannose-resistant type 3 fimbriae are another potential target [250]. They are produced by the majority of ***K. pneumoniae*** strains and stimulate IL-6, an inflammatory cytokine, demonstrating that they do induce an immune response [99]. Targeting mannose-resistant type 3 fimbriae has produced encouraging early-stage results in mouse models in which purified fimbriae from several strains protected mice against ***K. pneumoniae*** infection [252].

Overall, however, no single conserved antigen has been identified as a candidate to accelerate for vaccine development.

The development of immunity post-infection appears unlikely and if immunity occurs it would be strain-specific due to the high number of serotypes [251].

Scoring: Based on the analysis above, pathogen biology was categorised as fairly low (score of 0.5 out of 2).

Pre-clinical and clinical R&D

Animal models exist for some ***K. pneumoniae*** infection types. Mouse models for acute pneumonia and liver abscess can be used in pre-clinical studies [252,253]. However, informative models of chronic processes, especially biofilm formation, are lacking [254]. A cutaneous wound model exists but this is not a direct model of chronic lung infection [255].

No vaccines have been approved for ***K. pneumoniae*** and none are currently in clinical [40–42]. In the past, polyvalent vaccine candidates based on the K-antigen were developed, but they did not progress beyond Phase I trials in humans [251]. Therefore, no route to licensure has been established to date. Trial infrastructure would likely be similar to other hospital-acquired infections, and recruitment for efficacy trials may be complicated as there is a need to define target populations [28]. Additionally, the emergent and unpredictable nature of emergency hospitalisation makes determining which patients would be eligible for clinical trials difficult.

CURRENT PIPELINE *KLEBSIELLA PNEUMONIAE*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	**Total**
Number of **academic** vaccines	-	-	-	-	-	-
Number of **commercial** vaccines	03	-	-	-	-	03
Total number of vaccines	03	-	-	-	-	03

Scoring: Based on the analysis described above, pre-clinical and clinical R&D for ***K. pneumoniae*** was characterised as fairly low (score of 0.5 out of 2).

Probability of uptake

Expected policy stance

A ***K. pneumoniae*** vaccination strategy is difficult to define due to the challenges in targeting those at highest risk of the infection. A strategy could potentially be to vaccinate high-risk groups such as hospitalised patients, and particularly those with compromised immune systems due to HIV infection, diabetes, alcohol dependency or other conditions; and patients with chronic lung diseases; and patients undergoing mechanical ventilation [242].

This pathogen was viewed as an unlikely candidate for vaccination by policy experts who were interviewed, has not been promoted as a vaccine candidate by WHO PDVAC, literature review does not identify evidence of support for vaccination amongst policy makers. The primary factor in favour of vaccination is that incidence of ***K. pneumoniae*** is high compared to other hospital-acquired pathogens on the WHO list. However, several factors weigh against vaccination. Identification of a target population is complex and experts do not believe the incidence is sufficient to merit a routine strategy. One expert comments "who would you vaccinate? Gastro-oesophageal reflux disease patients? All people? Elderly? The load is too low" [28].

Scoring: Based on the analysis described above, expected policy stance was categorised as low (score of 0 out of 2).

Payer, government, or Gavi support

Payers and governments in high- and middle-income countries may consider a ***K. pneumoniae*** vaccine cost-effective if high-risk target groups could be easily identified. However, as discussed previously, identification of target populations presents a significant challenge. Gavi investment in a ***K. pneumoniae*** vaccine is unlikely because direct mortality is low.

Scoring: Based on the analysis described above, payer, government, or Gavi support has been categorised as intermediate (score of 1 out of 2).

Barriers to uptake

Different vaccination touchpoints would be required depending on the target population. Whilst many high-risk groups are in frequent contact with healthcare services, vaccine administration would still need to be incorporated into the existing bundle of interventions received by patients and a new programme would need to be built for every high-risk population identified, as the vaccine may fit into patients' care pathways in different ways.

New clinical practices would need to be developed for a ***K. pneumoniae*** vaccine. To ensure timely integration into the care pathways for all relevant indications, vaccine manufacturers would need to alert guideline setting bodies and specialised societies to any expansion of the indications for vaccination as they are approved, including expansion into other target populations.

Scoring: Based on the analysis described above, barriers to uptake were categorised as intermediate (score of 1 out of 2).

Commercial attractiveness

There is a possible market for a vaccine in high-income countries, coupled with the potential for a high price point. However, there are problems in identifying a specific target population, without which payers cannot accurately evaluate cost-effectiveness, and Gavi support is unlikely given low direct mortality relative to other investment options.

Based on the above analysis, commercial attractiveness was categorised as medium (score of 1 out of 2).

Recommendations

K. pneumoniae falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority.

Primary recommendation

The primary recommendation is to gain a better understanding of the disease burden and epidemiology of the pathogen. ***K. pneumoniae*** has a higher burden than most other hospital-acquired infections, but more data is needed to help determine whether there are predictable sub-populations to target for clinical development and vaccine delivery. There is a need for research studies that assess the comparative incidence and burden of disease across clinical syndromes to determine which clinical syndromes and which care environments (e.g. intensive care patients, ventilated patients, COPD patients) are most closely associated with ***K. pneumoniae*** infection and to identify risk factors that are most closely linked to ***K. pneumoniae*** infection.

Additionally, there is a need to more precisely determine burden estimates. There are no estimates of ***K. pneumoniae*** burden produced by IHME or WHO global burden studies, and the current understanding of the disease burden in high-income countries is incomplete, and in low-income countries is poor.

Secondary recommendations

Consideration of alternatives for the prevention of ***K. pneumoniae*** infection is required. An alternative in patients who deteriorating and at risk of intensive care admission or mechanical ventilation is the use of monoclonal antibodies. The advantage of monoclonal antibodies in this target population is that if a procedure needed to be carried out urgently, monoclonal antibodies would provide rapid protection. However, monoclonal antibodies would not provide the sustained protection required in some populations, such as those requiring longer-term mechanical ventilation. Additionally, developing monoclonal antibodies requires overcoming many of the same R&D hurdles relevant to the development of vaccines, including identifying appropriate antigens, and cost.

There is a need to support pre-clinical research to better understand conserved antigens for ***K. pneumoniae***. Given the antigenic diversity between strains, finding these antigens will maximise the chances of success in vaccine development or in development of alternative prevention strategies such as monoclonal antibodies.

Mycobacterium tuberculosis

Executive summary

Tuberculosis (TB) is now the world's deadliest infectious disease [256,257]. Mortality from infection with ***Mycobacterium tuberculosis*** (***M. tuberculosis***) is high, leading to approximately 1.3 million deaths annually. As one expert notes, TB is "[the] biggest cause of death now that we can treat malaria and HIV" [28].

The current vaccine – BCG – is widely used but efficacy is variable. BCG decreases incidence of severe TB such as miliary TB and TB meningitis, and global vaccine coverage is estimated at approximately 90%. However, BCG is only about 20% effective in preventing primary infection and approximately 60% effective in preventing progression to active disease in those infected [258]. BCG efficacy also appears to be variable, ranging from substantial protection shown in the UK MRC trial to the absence of clinically important benefit in a trial conducted in South India [259].

There is a strong case for developing a vaccine against ***M. tuberculosis*** given its health impact and AMR threat. However, despite ~$1 billion spent on R&D in the last 10 years, a highly efficacious vaccine is not likely to reach the market in the next 5-10 years. Pathogen biology and host immune response to ***M. tuberculosis*** are not yet sufficiently understood. Developing a protective vaccine requires not only finding the right antigens, but also activating the right ratio of protective and suppressive immune cells against these pathogens.

Clinical trials are challenging to design and conduct due to the lack of reliable correlates of immune protection or biomarkers, the difficulty of controlled human infection studies (even though models are now being established) and difficult trial infrastructure in rural areas.

Given the high global disease burden, vaccine uptake is and will be generally high for future candidates.

SCORECARD *MYCOBACTERIUM TUBERCULOSIS* (SCORECARD FOCUSSED ON AN EFFECTIVE VACCINE)

Health impact:

Direct health impact

2.0	2.0
Mortality	Morbidity

Impact on AMR reduction

2.0	2.0
Antibiotic use	Urgency of AMR threat

Secondary health impact

BCG vaccine offers some cross protection against *Mycobacterium leprae* and possibly other non-tuberculous mycobacterial species

Sub-population benefits

IInfants and the elderly
Pregnant women
Individuals with HIV
Low socio-economic status

Alternative interventions

None identified

Probability of R&D success:

0.5	0.5	1.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential

None identified

Acceleration potential

Improve understanding of biology and host immune response

Major barriers to development

Lack of good vaccine antigens

Probability of uptake:

2.0	2.0	2.0	2.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy

Global population / Routine vaccination

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Recommendations:

M. tuberculosis falls into a cluster of pathogens for which advancing early R&D is the priority. There is a strong case for vaccine development for ***M. tuberculosis*** given its health impact and AMR threat. Morbidity and mortality are high and TB is considered the world´s deadliest infectious disease. However, current difficulties in understanding pathogen biology and translatability of pre-clinical research must be overcome.

The primary recommendation is to improve the translatability of pre-clinical research. This can be achieved in several ways, such as: developing animal models with improved predictive capacity; improving and establishing human controlled infection protocols to facilitate early clinical trials; establishing reliable correlates of protection; and testing novel approaches earlier in human trials, especially if animal models with better predictive capacity cannot be developed.

Secondary recommendations are to expand pre-clinical research, including research on vaccine targets, vaccine technologies, and host immunity.

The pathogen and vaccine development were assessed assuming a highly efficacious vaccine that prevents sustained de novo infection in infants, as well as adults. Alternative vaccine development approaches such as BCG boosters or immunotherapeutic adjuncts to drug therapy intended to reduce treatment duration were not considered.

Pathogen overview

M. tuberculosis is an aerobic, non-motile bacillus that can be acquired in community or hospital settings. Due to the high lipid content in its cell wall, ***M. tuberculosis*** does not retain any common bacteriological stain and is therefore not considered to belong to either Gram-positive or Gram-negative categories [260].

M. tuberculosis predominantly causes pulmonary disease. In immunocompromised patients, ***M. tuberculosis*** can affect multiple other systems including gastrointestinal, central nervous (CNS), and genitourinary systems, and can also affect bones [261].

The primary mode of transmission is by airborne droplet. Symptoms of TB vary by lesion location, but often include fever, night sweats and weight loss, and pulmonary infection is associated with dyspnoea and chest pain. Gastrointestinal infections cause abdominal pain, nausea, vomiting, and diarrhoea. CNS infection can cause headache, fever, neck stiffness, and neurological deficits.

Incidence of TB is estimated at nearly 10 million cases per year [31] and is particularly common in South East Asia and Africa. High-risk groups include persons who have been recently infected with ***M. tuberculosis*** and immunocompromised persons [262]. Globally, TB is also responsible for between 6% and 15% of maternal mortality [263].

The BCG vaccine is the only marketed vaccine for ***M. tuberculosis***; the vaccine is produced by at least nine pharmaceutical companies [40] and global vaccine coverage is estimated at ~90% [264]. The vaccine is approximately 20% effective in preventing primary infection but can reach up to 80% effectiveness depending on location. It is also approximately 60% effective in preventing progression to active disease in those infected. Furthermore, BCG efficacy appears to be variable, ranging from substantial protection shown in the UK MRC trial to the absence of clinically important benefit in a trial conducted in South India [259].

Potential health impact

Direct health impact

Data on morbidity was available from the IHME 2016 estimates, and data on mortality was available from the WHO estimates for 2016. Both of these data sources have a defined methodology and are used in the global health community. TB has a relatively low incidence compared to other pathogens in the evaluation set, but causes high morbidity (~3.3 million years lived with disability per year) [31] and mortality (~1.7 million deaths per year) [265] globally. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was categorised as high (score of 2 out of 2) and morbidity was categorised as high (score of 2 out of 2).

Secondary health impact

A vaccine against ***M. tuberculosis*** may provide cross-protection against Mycobacterium leprae and possibly other mycobacterial species [258].

Sub-population benefits

Infants and young children are at specific risk of developing severe, disseminated disease, often presenting as TB meningitis or miliary TB; these infections often lead to death. Extra-pulmonary TB occurs in approximately 20-30% of all cases in children [266]. An efficacious vaccine would also be of particular benefit for people with low socioeconomic status, pregnant women, and HIV-infected individuals, all of whom are at elevated risk of contracting TB.

Antibiotic use

Treatment of TB requires several antibiotic drugs given simultaneously over at least a six month course of treatment, depending on age, overall health, possible drug resistance, the form of TB, and the infection's location in the body [267]. Typical antibiotics used to treat TB include isoniazid, rifampicin, ethambutol, and pyrazinamide. In patients known or suspected to have drug-resistant ***M. tuberculosis*** infections, a combination of specific antibiotics (e.g., fluoroquinolones, amikacin, kanamycin, capreomycin) is generally used for 20-30 months.

Scoring: Based on the above analysis, antibiotic use was categorised as high (score of 2 out of 2). Estimate based on an annual incidence of ~ nine million TB cases treated with an eight month course of antibiotics (Isoniazid and Raifampicin for six months; Pyrazinamide and Ethambutol for two months).

Urgency of AMR threat

Both the WHO and CDC have expressed concern about antibiotic treatments for ***M. tuberculosis***. ***M. tuberculosis*** is listed as 'critical' in the WHO priority list of research and development for new antibiotics [31] and as a 'serious' threat in the CDC list of biggest threats from AMR [7]. ***M. tuberculosis*** resistant to all antibiotics was first reported in 2009 [1] and extensively drug-resistant ***M. tuberculosis*** (XDR-TB) was reported by 123 WHO member states by the end of 2016 [2]. Approximately 0.5 million new cases of multi-drug resistant ***M. tuberculosis*** were reported worldwide in 2016 [2].

Scoring: Based on the above analysis, AMR threat was categorised as high (score of 2 out of 2)

Probability of R&D success

In this assessment "Pathogen biology" and "Pre-clinical and clinical R&D" are scored assuming a highly efficacious vaccine for infants as well as adults that prevents sustained de novo infection. For "Pipeline robustness" all TB vaccines in development are counted, but the score is adjusted via qualitative pipeline assessment.

Pipeline robustness

The pipeline for the development of vaccines against ***M. tuberculosis*** is highly active, with a total of 52 vaccines: 25 of these are in pre-clinical development; four are in

VACCINES IN DEVELOPMENT FOR *M. TUBERCULOSIS* ARE BASED ON VARIOUS TECHNOLOGIES

	Phase I	Phase II	Phase III	Marketed	Total
(Recombinant) BCG	02	-	01	10	12
Mycobacterial (whole cell or extract)	-	03	01	02	07
Protein/ Adjuvant	-	05	-	-	05
Viral vectored	02	-	-	-	02
Other	-	-	-	01	01
Total number of vaccines	04	08	02	13	27

Phase I, eight in Phase II, two in Phase III, and 13 vaccines are marketed. However, a qualitative assessment of the pipeline is also necessary for a full understanding of pipeline robustness. Whilst BCG and mycobacterial vaccines are marketed and in clinical development, only a limited number of truly novel protein/adjuvant and viral vector vaccines are in development, and those are currently in pre-clinical and earlier stage trials. Thus, a truly novel efficacious vaccine is not yet close to fruition. One exception is a clinical candidate developed by GSK (M72) which has recently completed an efficacy trial and will read out shortly [28].

Furthermore, not all vaccines against ***M. tuberculosis*** are developed with the goal of achieving high efficacy in the prevention of sustained de novo infections; candidates may be developed with narrower goals in mind, including the prevention of TB in adolescents and adults; as a replacement for BCG for early life immunisation; as BCG boosters; for vaccination of TB patients after treatment to prevent disease recurrence; or as immunotherapeutic adjuncts to drug therapy intended to reduce treatment duration [268]. One expert noted that therapeutic adjuncts are a particularly valuable approach as "therapeutic vaccines [given together with antibiotics] make a lot of sense, as they reduce treatment time and by doing so compliance [and thereby reduce development of AMR]" [28].

Experts also consistently acknowledge the need for a vaccine that effectively prevents de novo TB infection in a broad population but are divided over the feasibility of achieving this ambitious goal [28]. One expert offered the following assessment of feasibility, explaining "In tuberculosis the potential for a vaccine is very high but we are at least a decade away from creating a vaccine other than BCG in children," [28] and another stated, "I think we are not going to see anything novel in the next 10 years other than the new BCG from Serum Institute of India. At best this will replace BCG as an early life vaccine. [And it will take] 15-20 years to know if it has [an] effect" [28]. Many experts doubt the potential for success of current vaccine candidates, explaining "BCG variants are not impressive, some subunit vaccines will report shortly but I am sceptical [about the results]" [28]. However, others remain interested in novel approaches, noting "there could be novel concepts, for example whole inactivated ***M. tuberculosis*** showed proof of concept in HIV infected people in Tanzania" [28].

Scoring: Based on the above analysis, pipeline robustness was characterised as fairly low (score of 0.5 out of 2)

CURRENT PIPELINE *MYCOBACTERIUM TUBERCULOSIS*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	05	03	05	-	-	13
Number of **commercial** vaccines	20	01	03[3]	02[3]	13[4]	39
Total number of vaccines	25	04	08	02	13	52

1) Includes vaccines developed by Aeras (Non-profit organization)

2) One candidate (Ruti®) is a therapeutic vaccine

3) One candidate (Immunitor V-7) is a therapeutic vaccine

4) One candidate (Immunitor V-5) is a tableted therapeutic bivalent vaccine comprising heat-inactivated HCV antigens from pooled blood of HBV- and HCV-infected donors that might be useful as an adjuvant therapeutic against TB. It is not developed as a vaccine against TB

Pathogen biology

Some level of natural immunity against ***M. tuberculosis*** does exist [269,270]; however, protective immunity is a subject of debate in the TB research community. Most individuals develop partial immunity post-infection and are able to control but not eliminate the pathogen. ***M. tuberculosis*** is highly prevalent, with latent ***M. tuberculosis*** infection affecting approximately 25% of the worldwide population [271]. However, only a small percentage of infected and immune-competent individuals – approximately 5-10% - develop active disease.

Despite extensive research on ***M. tuberculosis*** biology, no target antigen has been identified and proven to be protective to date. It is possible that protection may not be easily measured by a specific antibody titre or an absolute number of protective immune cells against specific antigens, but rather by the relative ratio of protective and suppressive immune cells that recognize ***M. tuberculosis*** antigens. Hence, the goal of immunisation may not only include identifying antigens that will promote an immune response, but also directing the ratio of immune cells to the most effective balance [270].

Some experts point out that ***M. tuberculosis*** might have evolved to ensure T-cell recognition [28]. Known T-cell epitopes are hyper-conserved and represent some of the most conserved regions of the ***M. tuberculosis*** genome. This may indicate that T-cell epitope conservation is critical to survival and spread of ***M. tuberculosis***. Therefore, it should be explored in detail if immunodominant epitopes are indeed the preferred choice for vaccine candidates [272].

Finally, it may be important to identify ways to induce protective immunity specifically in the lungs. Targeting lung tissues directly may require alternative approaches to application, such as delivery using inhalers or nebulisers [270].

Scoring: Based on the above analysis, pathogen biology was categorised as fairly low (score of 0.5 out of 2).

Pre-clinical and clinical R&D

The pathogenesis and progression of TB are complex [273]. Infection varies by lesion location and the manifestations of pulmonary and extra-pulmonary infection (such as bone, lymphatic, enterophthisis, and meningeal) differ significantly. The progression of TB also presents some challenges to designing pre-clinical research programmes; ***M. tuberculosis*** infection can exist as latent TB or manifest as active TB, including primary TB, blood disseminated TB, and secondary TB. Although a wide variety of animal models exist, each can only mimic one or several aspects of TB, but not all forms. To understand the complete picture of human TB, all features of TB need to be replicated in various TB models for different research purposes. Simply put, to quote one expert, "animal models for TB are lousy" [28].

Reliable correlates of human protection or biomarkers for TB have not yet been identified, further limiting pre-clinical research. Monofunctional (IFN-γ secreting) and multifunctional (secreting IFN-γ, TNF, IL-2) CD4+ T cells are currently used as markers for immune protection, but accumulating experimental evidence suggests that host resistance against ***M. tuberculosis*** is independent of IFN- γ and TNF secretion from CD4+ T cells. An expert explains that "a major issue is the lack of correlates of protection. There is some insight from epidemiology observations but the basic science is still lacking" [28].

The lack of information regarding correlates of protection or biomarkers limits clinical as well as pre-clinical research. Clinical R&D of vaccine candidates also faces difficulties, as there is currently no safe human challenge model for ***M. tuberculosis***. A recent study demonstrated the feasibility of intradermal challenge with BCG (not virulent ***M. tuberculosis***) but results remain to be validated in field efficacy trials [274].

Clinical trial infrastructure also presents barriers to the development of clinical programmes. Facilities to conduct trials are often not available, and when available, often lack sufficient infrastructure or experience. It is therefore necessary for clinical researchers to collaborate with established networks with proven trial capacity, such as networks for HIV and malaria [275], or existing networks for treating comorbid infectious diseases. One expert explains a successful approach will "utilise the extensive infrastructure that already exists to treat HIV/TB coinfection" [28].

Simple diagnostics for surveillance are currently not available. Little information has been gained thus far about the functional roles of markers related to protection from natural infection, and even less is known about markers of protection from vaccines [276]. Recently, however, a study based on transcriptomic profiles from ***M. tuberculosis*** -exposed individuals revealed that progression toward active TB can be detected up to 12 months prior to onset of active disease [276]. This finding could prove helpful for trial design and allow researchers to reduce study size and duration by focusing on high-risk individuals.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as fairly low (score of 0.5 out of 2).

Probability of uptake

Expected policy stance

Policy makers strongly endorse BCG and are therefore likely to endorse a broadly protective ***M. tuberculosis*** vaccine, too. Almost 2 billion people worldwide have TB [271], and the WHO recommends BCG in settings with high incidence of TB. Experts explain that policy maker support for TB vaccines arises from the disease burden, stating "the argument for development is driven by the number of deaths, the vast majority of which are [caused by] multi-drug resistant [***M. tuberculosis***]" [28].

Scoring: Based on the above analysis, the expected policy stance was categorised as high (score of 2 out of 2).

Payer, government, or Gavi support

Support for a ***M. tuberculosis*** vaccine is likely for countries at all income levels. In high-income countries, BCG currently has support in high-risk geographies (for example, in urban areas), but cost-effectiveness does not meet requirements for routine vaccination [277]. Cost-effectiveness considerations would most likely be revised and considered more positively if a broadly and highly efficacious ***M. tuberculosis*** vaccine were available. In middle-income countries, a new vaccine would likely replace BCG using the same strategy already in place; depending on cost-effectiveness, vaccination programmes could be expanded in these regions. Finally, Gavi does not support BCG; however, given the high prevalence, mortality, and morbidity caused by TB, a more efficacious vaccine would likely meet Gavi criteria for investment.

Scoring: Based on the above analysis, payer, government, or Gavi support was categorised as high (score of 2 out of 2).

Barriers to uptake

Few substantial barriers exist to uptake of a novel efficacious ***M. tuberculosis*** vaccine replacing BCG. No new touchpoint needs to be developed; the BCG vaccine is already part of childhood vaccination programmes and offered either routinely or in at-risk areas, depending on a country's disease burden. Where routine vaccination is in place, coverage is already at approximately 90% [264]. There are no issues of cultural acceptability to a ***M. tuberculosis*** vaccine and changes to clinical practices would not be required; BCG is already part of vaccine recommendations and any more efficacious vaccine would likely replace BCG in existing programmes and recommendations.

Scoring: Based on the above analysis, barriers to uptake was categorised as low (score of 2 out of 2).

Commercial attractiveness

Overall, a new ***M. tuberculosis*** vaccine will be commercially attractive given the high expected uptake in low- and middle-income countries where the disease burden is highest. Moreover, if a new vaccine proves to be more efficacious than the existing BCG vaccine, uptake in high-income countries would most likely increase. Some high-income countries currently do not recommend BCG as a routine vaccine because of its low efficacy and the low disease burden in high-income regions, but a more efficacious vaccine could prompt high-income countries to consider broader adoption.

Scoring: Based on the above analysis, commercial attractiveness was categorised as high (score of 2 out of 2).

Recommendations

M. tuberculosis falls into a cluster of pathogens for which advancing early R&D is the priority.

Primary recommendation

Improving translatability of pre-clinical research would accelerate development of an effective ***M. tuberculosis*** vaccine. This can be achieved in several ways including developing animal models with improved predictive capacity; improving and establishing human controlled infection protocols to facilitate early clinical trials; establishing reliable correlates of protection; and testing novel approaches earlier in human trials.

Testing novel approaches earlier in human trials would likely have multiple benefits. Existing animal models are still poor predictors of effectiveness in humans. This creates the risk of investing time and research efforts in candidates that appear promising at the pre-clinical level but ultimately generate disappointing results in clinical trials. Testing earlier in human trials would circumvent this issue, especially as human controlled infection models are becoming available that may greatly reduce the cost and duration of well-powered field studies.

Secondary recommendation

Expanding pre-clinical research to better understand ***M. tuberculosis*** infection and host responses is needed to provide critical insights to development of an effective vaccine. Furthermore, investments in novel vaccine technologies that amplify and direct the immune response would likely facilitate vaccine development. Expanding research would require broadening the investment funding envelope – experts state that TB "research is underfunded" [28] and compare the current status of TB funding to other disease states, noting "When HIV was killing less people, it was attracting 1 billion per year. Funders often undervalue the TB effort" [28]. In fact, according to the G-FINDER public search tool provided by Policy Cures Research, almost 7 times more funding was provided for the development of preventative HIV vaccines compared to TB vaccines from 2012-2016 [278].

Neisseria gonorrhoeae

Executive summary

Neisseria gonorrhoeae (***N. gonorrhoeae***) causes gonorrhoea, a common sexually transmitted infection (STI) with an annual incidence of 190 million cases globally each year. Although infection is rarely fatal with global mortality estimated at 3,000 deaths per year, ***N. gonorrhoeae*** causes a significant morbidity burden through chronic, untreated infections particularly affecting women.

The recent emergence of extensively drug-resistant strains of ***N. gonorrhoeae*** has generated significant concerns that untreatable infections could soon emerge and has been reported extensively in the global press.

No vaccine is currently available, however, recent results from a study of the MeNZB vaccination programme suggests that vaccination against ***N. meningitidis*** offers some protection against ***N. gonorrhoeae***. This has generated significant interest in the field and experts expressed optimism that vaccine development could now be accelerated. Vaccine uptake could be challenging given cultural sensitivities and a low likelihood of support from Gavi.

Recommendations

N. gonorrhoeae falls into a cluster of pathogens for which advancing early R&D is the priority. A vaccine against ***N. gonorrhoeae*** would be a useful tool to prevent untreatable ***N. gonorrhoeae*** emerging. The primary recommendation is to advance early R&D efforts by increasing the pace at which promising pre-clinical candidates enter human trials. The secondary recommendations are to further explore the protective effect of ***N. meningitidis*** vaccination and the potential to develop a combined ***N. gonorrhoeae*** and ***N. meningitidis*** vaccine.

SCORECARD *NEISSERIA GONORRHOEAE*

Health impact:

Direct health impact

0.0	2.0
Mortality	Morbidity

Impact on AMR reduction

1.0	2.0
Antibiotic use	Urgency of AMR threat

Secondary health impact

Infection linked to low birth weight and risk of premature birth
Infertility in women
Increased risk of HIV infection

Sub-population benefits

Women of reproductive age
Men who have sex with men

Alternative interventions

None identified

Probability of R&D success:

0.5	0.5	1.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential

Potential combination with meningitis vaccine; other STI vaccines

Acceleration potential

Potential combination with meningitis vaccine; other STI vaccines

Major barriers to development

Host specificity of pathogen

Probability of uptake:

1.0	1.0	1.0	1.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy

Sexually active adults / Routine vaccination before peak sexual activity

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

N. gonorrhoeae is a Gram-negative bacterium that causes sexually transmitted infections (STIs) and can affect both men and women. It can also be transmitted from mothers to children during childbirth [279]. ***N. gonorrhoeae*** infection can significantly affect reproductive health and increases the risk of HIV transmission [279,280]. The most common site of infection is the urogenital tract, but ***N. gonorrhoeae*** may also affect other areas of the body, causing anorectal or pharyngeal infection, and more rarely, conjunctival or ovarian infections [281].

Symptoms of gonorrhoea include vaginal discharge, vaginal bleeding, dyspareunia and abdominal/pelvic pain in women, and painful urination, pus-like discharge from the penis and testicular pain or swelling in men. However, ***N. gonorrhoeae*** infection is frequently asymptomatic, particularly in women, resulting in difficulties in obtaining a diagnosis. Untreated infections in women can result in pelvic inflammatory disease, ectopic pregnancies, infertility and chronic pelvic pain, and these complications can develop in the absence of symptoms.

N. gonorrhoeae is distributed throughout the world with the highest burden in low and middle-income countries. The incidence of gonorrhoea is particularly high in Africa and in the Western Pacific [282]. The risk of contracting gonorrhoea is highest among men who have sex with men and HIV-positive individuals. Repeat infections are common; natural immunity appears to confer a limited protective effect from subsequent infection [283,284]. No vaccines are currently available, but retrospective studies show some evidence of cross-protection from the MeNZB ***N. meningitidis*** vaccine [285].

Potential health impact

Direct health impact

In this analysis, disease burden is used as a proxy for the potential direct health impact of vaccination. ***N. gonorrhoeae*** infection has a substantial direct public health impact because of its high global incidence and morbidity; however, the disease has only a low impact on mortality. According to the Institute for Health Metrics and Evaluation, there were 190 million incident cases of gonorrhoea, ~500,000 years lived with disability and 3,000 deaths in 2016 [31]. This source uses a defined methodology and is used in the global health community. The data can therefore be viewed with a reasonable level of confidence.

Scoring: Based on the above analysis, mortality was categorised as low (score of 0 out of 2) and morbidity was categorised as high (score of 2 out of 2).

Secondary health impact

N. gonorrhoeae's secondary health impact is also substantial. ***N. gonorrhoeae*** is associated with infertility in women, increased susceptibility to HIV infection [286,287], and low birth weight and pre-term birth in infected mothers [282,288].

Sub-population benefits

A vaccine targeting ***N. gonorrhoeae*** would likely have significant benefits for specific sub-populations including prevention of infertility in women and lowering the rate of transmission of HIV infection in high-risk populations including men who have sex with men.

Antibiotic use

Antibiotics are currently the only treatment for gonorrhoea infections. Recommended antibiotic treatment regimens differ by country, in part reflecting local resistance profiles [289]. Many regimens consist of a one-time, dual therapy dose (for example, the CDC recommends ceftriaxone given as an intra-muscular injection in combination with oral azithromycin). The rationale for using single dose regimens is to limit overall antibiotic use to treat gonorrhoea despite high disease incidence.

Scoring: Based on the above analysis, antibiotic use was categorised as medium (score of 1 out of 2). This estimate is based on an annual incidence of ~190 million gonorrhoea infections treated with a single, one-off antibiotic dose.

Urgency of AMR threat

N. gonorrhoeae has an extensive history of developing resistance to new agents and no single, reliable monotherapy to treat ***N. gonorrhoeae*** infection remains [282]. Both the WHO and the CDC have expressed concerns about the future of gonorrhoea treatment: the WHO has listed ***N. gonorrhoeae*** as a 'high priority' for research and development of new treatments and the CDC has listed it as an 'urgent' AMR threat [6,7]. The first antibiotic resistant strains of ***N. gonorrhoeae*** developed in the 1940s when sulphonamide-resistant strains emerged [289]. By the end of the 1980s, resistance to penicillin was widespread and cephalosporins became the preferred treatment, but in 2011, a strain with high-level resistance to cephalosporin was reported [289]. Resistance to several drug classes is now widespread, including macrolides, tetracyclines, and fluoroquinolones [289]. Moreover, reports of extensively drug-resistant strains – resistant to both ceftriaxone and azithromycin – emerged in 2018 in the UK and Australia, leading to concerns that untreatable strains of ***N. gonorrhoeae*** could develop.

Scoring: Based on the above analysis, the urgency of AMR threat was characterised as high (score of 2 out of 2).

Probability of R&D success

Pipeline robustness

The pipeline for vaccines against ***N. gonorrhoeae*** is weak, with only four candidates in pre-clinical development. However, while acknowledging a lack of progress, experts are optimistic that a fully efficacious vaccine can be developed against ***N. gonorrhoeae*** – not least because of the result results of retrospective studies that show some evidence of cross-protection from the MeNZB ***N. meningitidis*** vaccine [285].

Scoring: Based on the above analysis, pipeline robustness was characterised as fairly low (score of 0.5 out of 2).

Pathogen biology

The evidence for natural immunity against ***N. gonorrhoeae*** is not compelling. Repeated exposure to ***N. gonorrhoeae*** appears to be associated with a reduced risk of salpingitis (inflammation of the fallopian tubes) but does not appear to protect against uncomplicated infections [283]. A study conducted in Nairobi suggested that women suffering repeated infections showed partial serovar-specific immunity against the prevalent circulating ***N. gonorrhoeae*** strain [290]; however, this finding was not replicated in a study of less-exposed subjects in the United States [284]. Experts' opinions were consistent with this data; according to one expert "[we are] seeing some people getting gonorrhoea 12 times a year within a very small subset of the population" [28].

Several conserved targets have been identified, some of which have shown protection in pre-clinical mouse models. These include a 2C7 mimetic given with MAP1 adjuvant, OMV given with IL-12 and rrPorB-VRP (viral replication particle vector boosted with rrPorB + Ribi 700) [282]. Additional candidates have shown the ability to induce antibodies with anti-gonococcal activity in mice, including TbpA, TbpB, AniA, and MtrE. No vaccine specifically targeting ***N. gonorrhoeae*** has been tested in humans to date.

Scoring: Based on the above analysis, pathogen biology was categorised as fairly low (score of 0.5 out of 2).

Pre-clinical and clinical R&D

A large retrospective case-control study conducted in New Zealand demonstrated that the ***N. meningitidis*** MeNZB vaccine generated some cross-protection against ***N. gonorrhoeae*** infection, providing some encouraging support for development of a vaccine. This study examined the protective effect of the ***N. meningitidis*** MeNZB vaccine in 15-30 year-old participants born between 1984 and 1998 who were eligible for the MeNZB vaccine and had been diagnosed with gonorrhoea and/or chlamydia after attending one of 11 participating sexual health clinics in New Zealand. After controlling for ethnicity, deprivation, geographical area, and sex, the MeNZB vaccine demonstrated 31% efficacy in preventing ***N. gonorrhoeae*** infection [285]. However, protection waned over time, indicating that higher titres may be needed [28]. Experts suggest that higher titres could be achieved with multiple boosters, or that an alternative vaccine could achieve better efficacy.

CURRENT PIPELINE *NEISSERIA GONORRHOEAE*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	02	-	-	-	-	02
Number of **commercial** vaccines	02	-	-	-	-	02
Total number of vaccines	04	-	-	-	-	04

Development of a vaccine against ***N. gonorrhoeae*** will require some obstacles to pre-clinical and clinical development to be addressed. As with most STIs, animal modelling in pre-clinical development is complicated by the human-specificity of the pathogen [282]. A well-characterised female mouse model of lower genital tract infection is in place; however, this model is limited by the absence of several human-specific factors involved in adherence and invasion and the avoidance of complement-mediated killing of ***N. gonorrhoeae*** in humans. These factors include human transferrin and lactoferrin, soluble negative regulators of the complement cascade (factor H, C4b binding protein), receptors for gonococcal adhesins and invasins (i.e. CEACAMs), C3R integrin, CD46, and the pilus receptor. The development of transgenic mice expressing these absent host-factors could facilitate development of a ***N. gonorrhoeae*** vaccine, and in the absence of such a model, a combined approach incorporating challenge studies in normal mice and ***in vitro*** studies in human cells may provide insights into the efficacy of ***N. gonorrhoeae*** vaccines in humans.

Clinical development of a vaccine will also face some challenges. Experimental urethral infection of male subjects is possible due to the low risk of complication (for example, in kinetics studies, understanding the host response or virulence factors and similar studies). However, this might not reliably predict vaccine efficacy in women, or against complicated infection. Because of significant biological differences in gonorrhoea infection in men and women, men are likely to be a limited model for vaccine development in women 28.

The lack of established correlates of protection also presents a challenge for clinical development of a vaccine, as it limits researchers' ability to understand what type of immune response a vaccine targeting ***N. gonorrhoeae*** needs to produce to provide protection against future infection. The observation of antibodies against gonococcal opacity proteins and absence of blocking antibodies in patients who show partial natural immunity against ***N. gonorrhoeae*** provides some insight into potential mechanisms of protection; however, the mechanisms by which ***N. gonorrhoeae*** manipulates host immune responses are not yet fully understood [282].

Trial infrastructure and design also present challenges for development of a vaccine for ***N. gonorrhoeae***. Prospective efficacy trials would require participants to engage in unprotected sex, raising ethical questions about trial design. Furthermore, it may also be important to test a candidate vaccine in the context of a ***N. gonorrhoeae***/***Chlamydia trachomatis*** (***C. trachomatis***) infection model, because ***C. trachomatis*** seems to create a more hospitable environment for ***N. gonorrhoeae***. However, it is not clear how such a model could feasibly be implemented in a clinical trial.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as medium (score of 1 out of 2).

Probability of uptake

Expected policy stance

The most likely target population for vaccination against ***N. gonorrhoeae*** is adolescents and young adults prior to peak age of sexual activity. The most likely strategy for deployment of a vaccine would involve routine vaccination of this group. This could allow for a vaccination programme where the ***N. gonorrhoeae*** vaccine is delivered with the HPV vaccine or combined with the ***N. meningitidis*** vaccine to help drive uptake. If the duration of protection is limited, a second touchpoint would be required in later adolescence.

Development of a more targeted strategy is complicated by difficulty identifying and reaching a better-defined target population. Men who have sex with men (MSM), for example, are a high-risk group but may not be a large enough target population to achieve herd protection. Furthermore, MSM are unlikely to present for vaccination in countries where MSM are not widely accepted. Adolescents and young adults who have many sexual partners are also a high-risk group. However, this group is difficult to identify and targeting individuals with multiple partners may increase the stigma associated with the vaccine.

The WHO is supportive of vaccination due to high incidence and increasing treatment failures caused by antibiotic resistance [291–293]. Similarly, the 2017 Chatham house report on vaccines supported a ***N. gonorrhoeae*** vaccine because of the poor antibiotic pipeline [294]. However, the perception that ***N. gonorrhoeae*** is a low-risk pathogen with low mortality may generate some resistance to routine vaccination of all adolescents/young adults.

Scoring: Based on the above analysis, the expected policy stance was categorised as medium (score of 1 out of 2).

Likelihood of payer, government, or Gavi support

Vaccination against ***N. gonorrhoeae*** would likely benefit from payer support in high-income countries. Antibiotic-resistant ***N. gonorrhoeae*** infection incurs high costs – estimated at $500 million annually in the United States [294] – and an increase in drug-resistant strains would raise the risk of even higher costs. Governments in middle-income countries, however, may raise some concerns about cost-effectiveness, particularly the potentially lower cost-effectiveness of a routine vaccination strategy targeting all adolescents and young adults compared with a targeted strategy focusing on specific high-risk groups. Finally, Gavi is unlikely to support a ***N. gonorrhoeae*** vaccine under current prioritisation criteria because of the low mortality from gonorrhoea relative to other investment options. In the longer-term, Gavi support may be possible if their prioritisation criteria evolves to put stronger weight on AMR [28].

Scoring: Based on the above analysis, likelihood of payer, government, or Gavi support was categorised as medium (score of 1 out of 2).

Barriers to uptake

Some cultural and logistical considerations are likely to present obstacles to implementing a ***N. gonorrhoeae*** vaccination programme. The target population – adolescents and young adults – is generally a hard-to-reach group with sporadic contact with healthcare services. This could present challenges not only in initiating vaccination, but in ensuring multiple touchpoints if the duration of vaccine protection is limited. Uptake of a ***N. gonorrhoeae*** vaccine could be increased, however, if delivery in conjunction with a second vaccine is feasible. HPV and ***N. meningitidis*** present two potential candidates for a coordinated strategy. Delivery in combination with HPV could promote adoption of a ***N. gonorrhoeae*** vaccine in girls and young women; however, experts cite some challenges constraining adoption of the HPV vaccine that are also likely to affect a ***N. gonorrhoeae*** vaccine. Creating a combination vaccine against ***N. gonorrhoeae*** and ***N. meningitidis*** may better reduce the potential stigma associated with vaccines targeting STIs and benefit from a better-established healthcare touchpoint [28].

Experts agree that there is a stigma associated with vaccination against STIs that may cause resistance to widespread uptake. These experts explain that even for HPV – an STI with potential fatal outcomes – it is difficult to encourage widespread adoption among patients and their parents or caregivers. Because gonorrhoea is not fatal, healthcare providers may face even greater challenges in driving extensive adoption of a gonorrhoea vaccine. Some experts expect this stigma will be the most significant barrier to the implementation of a successful vaccination programme.

Experts also cite a clear need for healthcare provider education as part of any ***N. gonorrhoeae*** vaccination programme, even if the vaccine is administered alongside HPV, and particularly if the two vaccines cannot be administered on an identical schedule.

Scoring: Based on the above analysis, barriers to uptake were categorised as medium (score of 1 out of 2).

Commercial attractiveness

A ***N. gonorrhoeae*** vaccine is somewhat likely to be commercially attractive in high-income markets. Incidence is high in these markets; for example, the CDC estimates more than 800,000 cases annually in the US[295]. In addition, gonorrhoea causes high morbidity, with more than 500,000 years lived with disability. Finally, some sequelae such as infertility are expensive to treat, so payers may be able to reduce the cost burden of those sequelae through vaccination.

However, the potential barriers to uptake mean that companies may be reticent to pursue development, especially given the R&D challenges. The stigma related to STIs could result in poor uptake, similar to what has been observed to date for the HPV vaccine. Vaccine developers may also harbour concerns that the public will not perceive gonorrhoea as a significant enough risk to warrant vaccination.

Interest in developing a ***N. gonorrhoeae*** vaccine has increased in high-income countries in recent years, but there is not a clear consensus among experts regarding the commercial attractiveness of a vaccine. Some experts believe ***N. gonorrhoeae*** is a "commercially interesting target" [28], whilst others suggest that it may not be "big enough for pharma" [28].

Scoring: Based on the above analysis, commercial attractiveness was categorised as medium (score 1 out of 2).

Recommendations

N. gonorrhoeae falls into a cluster of pathogens for which advancing early R&D is the priority.

Primary recommendation

Vaccine development could be accelerated by increasing the pace at which promising current and future pre-clinical candidates are moved from animal to human trials. ***N. gonorrhoeae*** infection is highly human-specific and, as such, success in pre-clinical trials may not translate to humans. Small human trials at an earlier stage are likely to provide more insight into the potential success of candidate vaccines than continued animal research.

Early clinical trials should build upon challenge trials already conducted in males. Specific areas of inquiry that merit consideration include clinical trials replacing ***N. meningitidis*** antigens with ***N. gonorrhoeae***-specific antigens [28]. Further, the findings of the New Zealand trial should be supported by additional studies detailing the protective effect of the ***N. meningitidis*** vaccine, including investigation of the duration of protective effect, the doses required for protection, and whether the vaccine protects against all strains of ***N. gonorrhoeae***.

Despite the potential of a ***N. gonorrhoeae*** vaccine to reduce morbidity and AMR, the vaccine development pipeline is weak. Strong and sustained commitment is required to strengthen this pipeline, such that it better reflects the potential impact of vaccination.

Secondary recommendations

Focus on early stage R&D and pre-clinical research is still required. In particular, better understanding of the protective effect of the ***N. meningitidis*** vaccine against ***N. gonorrhoeae*** may allow investigators to explore substituting or altering ***N. meningitidis*** vaccine antigens to enhance protection against ***N. gonorrhoeae***.

The potential for a combined vaccine with ***N. meningitidis*** should also be explored in greater detail. A combined ***N. meningitidis*** and ***N. gonorrhoeae*** vaccine would ease some of the uptake challenges, particularly around cultural acceptability, for the vaccine.

Pseudomonas aeruginosa

Executive summary

Pseudomonas aeruginosa (***P. aeruginosa***) is predominantly hospital-acquired and patients with compromised immune systems are predisposed to infection. Patients with chronic lung diseases such as cystic fibrosis and bronchiectasis are most at risk of colonisation from ***P. aeruginosa***. The burden of disease caused by ***P. aeruginosa*** is not well-defined, but WHO has ranked it as causing low morbidity and mortality relative to other pathogens on the WHO priority list. AMR is an immediate concern as ***P. aeruginosa*** is inherently drug-resistant and pan-resistant strains have been reported [1]. The WHO has listed this pathogen as being at critical risk level for antibiotic resistance [32].

Currently there are no licensed vaccines for ***P. aeruginosa***, and vaccine development faces significant challenges. Previous attempts to develop vaccines have been unsuccessful, and pathogen biology presents significant scientific and technical challenges to developing a vaccine. Host immune defects further complicate identification of vaccine candidates, and animal models are poorly predictive of patient response.

Although payer support in high-income countries is likely for high-risk groups, defining a target population beyond these groups is difficult, leading to challenges in establishing a vaccine programme. In low- and middle-income countries the disease burden is not well-defined, but the perception that ***P. aeruginosa*** infection has a low impact on mortality and morbidity may preclude support for vaccine uptake.

Recommendations

P. aeruginosa falls into a cluster of pathogens for which advancing early R&D is the priority. Vaccine development is attractive for high risk patient groups, such as cystic fibrosis patients, but few candidates have entered the pipeline to date. The primary recommendation is to

SCORECARD *PSEUDOMONAS AERUGINOSA*

Health impact:

Direct health impact

0.5	0.0
Mortality	Morbidity

Impact on AMR reduction

1.0	2.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Patients with chronic lung disease
Intensive care patients
Immunocompromised individuals
Individuals with cystic fibrosis
Burns patients

Alternative interventions
Passive immunisation

Probability of R&D success:

0.0	0.5	1.5
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
None identified

Acceleration potential
Develop better animal models

Major barriers to development
None identified

Probability of uptake:

2.0	0.0	2.0	2.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Patients with chronic lung disease / High-risk groups such as individuals with cystic fibrosis and bronchiectasis

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

increase the number of candidates in development by supporting pre-clinical research. The secondary recommendation is to explore alternative treatments or prevention strategies and to better understand pathogen-level epidemiology.

Pathogen overview

P. aeruginosa is a Gram-negative bacterium that primarily causes hospital-acquired infections. Colonisation with ***P. aeruginosa***, however, can be community-acquired or hospital-acquired.

Immunocompromised patients infected with ***P. aeruginosa*** are at risk of several clinical syndromes including pneumonia, post-burns skin infection, and post-surgical infections, such as surgical site infections and urinary tract infections [296]. Community-acquired infections associated with ***P. aeruginosa*** include folliculitis and pneumonia.

P. aeruginosa is transmitted through touch and contaminated equipment [297]. In the case of lung colonisation, the pathogen can also be transmitted through air droplets spread by patients who are already infected, or through animal reservoirs [298]. The presentation of ***P. aeruginosa*** is dependent on clinical syndrome. Clinical features of pneumonia include pyrexia, headache, malaise, and dry cough [296]. Surgical site infections can show purulent drainage, pain, swelling, erythema, heat, wound dehiscence, fever, and abscess [296].

P. aeruginosa is known to be present worldwide [299]. However, there is insufficient epidemiological information to determine the burden of disease. In some sub-populations, it is possible to determine the geographic distribution of clinical syndromes that are associated with increased incidence of ***P. aeruginosa*** infection. For example, the prevalence of cystic fibrosis is highest in Europe, North America and Australia [300].

Potential health impact

Direct health impact

Robust global data on disease burden is not available. Globally, ***P. aeruginosa*** is estimated to be responsible for approximately 3% of pneumonia cases [33], 2% of urinary tract infection cases [82], and less than 1% of neonatal meningitis cases [34]. The level of confidence in these estimates is relatively low because ***P. aeruginosa*** infections are not reported by the WHO or IHME and no publications that report the global burden of this pathogen were found. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was characterised as low (score of 0 out of 2) and morbidity was categorised as fairly low (score of 0.5 out of 2).

Sub-population benefits

Patients with chronic lung disease are at risk of ***P. aeruginosa*** colonisation [301,302,303] and would benefit from a vaccine.

Antibiotic use

Recommended antibiotic treatment regimens differ by country, in part reflecting local resistance profiles. Regimens vary in length but often involve a two-week course of a broad spectrum antibiotic for pneumonia and a five-day course of a fluoroquinolone antibiotic for urinary tract infection [304,305]. However, ***P. aeruginosa*** infection is not easy to treat. One expert notes "***P. aeruginosa*** is difficult to reach with antibiotics even if appropriate activation of the immune system [is achieved]" [28]. This is because part of the process of ***P. aeruginosa*** colonisation involves the pathogen reducing the expression of virulence factors and forming biofilms [306,307]. These actions diminish the ability of antibiotics to have bacteriostatic or bactericidal effects.

Scoring: Based on the above analysis, antibiotic use was categorised as medium (score of 1 out of 2). This estimate is based on an annual incidence of ~ nine million LRTIs treated with a two week course of antibiotics, and ~five million UTIs treated with a five day course of antibiotics.

Urgency of AMR threat

Both the WHO and CDC have expressed strong concern about antibiotic treatments for ***P. aeruginosa***. The WHO lists ***P. aeruginosa*** as 'critical' in its priority list of R&D for new antibiotics [31] and the CDC lists it as a 'serious' threat in its list of biggest threats from AMR [7]. ***P. aeruginosa*** is inherently drug-resistant for two reasons: first, it has constitutive expression of certain proteins which enable resistance to antibiotics, for example, expression of AmpC beta-lactamase and efflux pumps for penicillin resistance, and second, the outer membrane of ***P. aeruginosa*** has low permeability to antibiotics [308]. Additionally, ***P. aeruginosa*** can develop additional resistance during treatment, due to the ability to easily acquire many escape mechanisms [309,310]. Some strains are resistant to more than three classes of antibiotic and pan-drug resistant strains have been reported [310].

Scoring: Based on the above analysis, the urgency of AMR threat was categorised as high (score of 2 out of 2).

Probability of R&D success

Pipeline robustness

The pipeline for vaccines against ***P. aeruginosa*** is weak, with only four vaccines currently in pre-clinical development. Other historic clinical-stage candidates are no longer undergoing active development.

Scoring: Based on the above analysis, the pipeline was categorised as low (score of 0 out of 2).

Pathogen biology

Current research does not provide a clear understanding of natural immunity to ***P. aeruginosa***. Infection with ***P. aeruginosa*** induces an innate immune response in healthy individuals [311]. However, the adaptive immune response in cases of chronic infection can cause airway remodelling, which is maladaptive and does not result in pathogen clearance [312].

One way to infer the extent of natural immunity is to examine cross-infection of different strains of ***P. aeruginosa*** in cystic fibrosis patients. Cross-infection is known to occur with hyper-transmissible strains and between siblings with cystic fibrosis [313]. It is difficult to infer the extent of natural immunity, since once one strain of ***P. aeruginosa*** colonises a patient, it adapts to the host environment, for example through becoming less virulent, and establishing biofilms [314,315]. This prevents further strains from establishing themselves [316]. Furthermore, it is difficult to interpret data regarding reinfection from patients with chronic lung diseases, as these patients often do not readily clear a first infection and because they have a maladaptive response to colonisation which contributes to difficulty clearing pathogens. For example in individuals with cystic fibrosis, there is impaired bacterial ingestion and bacteria are able to bind more easily to viscous mucus [317]. Consequently, it is difficult to know if the subsequent infection is a new infection or a prior infection that was not completely cleared.

Vaccine targets are extensively characterised for ***P. aeruginosa*** including LPS O-antigens, outer membrane and secreted protein targets [318]. However, since ***P. aeruginosa*** has many inherent escape mechanisms, an effective vaccine will have to encompass many targets. [318]. A selection of these mechanisms include targeting opsonic antibodies, anti-toxin antibodies, anti-virulence antibodies and potentially T cell immunomodulation [318]. The need to target multiple mechanisms makes vaccine development more challenging.

Scoring: Based on the above analysis, pathogen biology was categorised as fairly low (score of 0.5 out of 2).

Pre-clinical and clinical R&D

A variety of different animal models are in place for hospital-acquired pneumonia. These include "one-hit" (single insult) acute pneumonia models in rats and mice, ventilator-associated pneumonia models in piglets, rats, and mice, and a model using agar beads to mimic the

CURRENT PIPELINE *PSEUDOMONAS AERUGINOSA*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	01	-	-	-	-	01
Number of **commercial** vaccines	03	-	-	-	-	03
Total number of vaccines	04	-	-	-	-	04

biofilm matrix of cystic fibrosis [319]. However, these have often failed to predict efficacy in humans. Animal models are inconsistent and higher infecting doses are rapidly lethal to the animals they infect, whilst lower infecting doses often resolve rapidly [255].

Other models are invasive and ethically or technically challenging to develop (for example, burn-wound infection model) [255]. The development of humanised mice that could serve as an improved animal model is ongoing and will likely address some of the limitations of existing models [319]. Despite the limitations of animal models, experts believe enough is known about the immunology of ***P. aeruginosa*** to develop a vaccine.

Clinical development of a ***P. aeruginosa*** vaccine faces some challenges. No easily accessible correlates of protection have been employed in humans [25]. There are no known serum markers of seroconversion which can be used in research or clinical practice and there do not appear to be any human controlled infection models ready to be used in clinical testing. However, trial infrastructure is in place and the target population is well-defined. The most recent Phase II/III trial of a ***P. aeruginosa*** vaccine was conducted in 800 mechanically ventilated intensive care unit patients [320,321]. This trial was unsuccessful in terms of clinical outcomes, as there was no significant difference in ***P. aeruginosa*** infection rates between trial arms.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as medium (score of 1 out of 2).

Probability of uptake

Expected policy stance

Hospitalised patients, patients with compromised immune systems, and patients with lung disease, including those with cystic fibrosis, would benefit from vaccination. A vaccination strategy would likely be based on diagnosis of conditions such as cystic fibrosis or other factors placing patients at risk of infection.

There is a paucity of policy documentation in favour of vaccination against ***P. aeruginosa***, and no current momentum for vaccination in the international policy community. At a meeting on vaccination in older adults convened by the WHO in 2018, ***P. aeruginosa*** was mentioned as a pathogen for which AMR may be a reason to consider vaccination [322], but aside from this mention, ***P. aeruginosa*** has attracted little attention. Expert opinion suggests that strategies other than targeting patients with long term colonisation would be problematic given the small size of the target population and the low incidence of post-surgical complications [28].

Scoring: Based on the above analysis, expected policy stance was categorised as low (score of 0 out of 2).

Payer, government, or Gavi support

Payers in high-income countries are likely to support vaccination against ***P. aeruginosa***. The high risk of colonisation in lung disease means that that these patients would provide a suitable target population. High ***P. aeruginosa*** colonisation rates in cystic fibrosis patients cause high morbidity [323]. There are ~70,000 cystic fibrosis patients worldwide [324] predominantly in high-income countries. This target population would likely support a high price point as high prices are tolerated for cystic fibrosis interventions, with some treatments costing over £100,000/year [325]. There are also 1-2 million bronchiectasis patients worldwide [326], and a quarter are colonised with ***P. aeruginosa*** [301], causing substantial burden in high-income countries [327]. Bronchiectasis is a potentially life-shortening, chronic disease with high morbidity. ***P. aeruginosa*** infection worsens mortality, morbidity and will result in increased hospitalisations in these patients, hence there is likely to be payer support for this population.

A ***P. aeruginosa*** vaccine would be less likely to receive support in middle-income countries given the higher thresholds needed for cost-effectiveness in order to access healthcare funding. Gavi is unlikely to support a vaccine for ***P. aeruginosa*** because of low mortality from ***P. aeruginosa*** infection.

Scoring: Based on the above analysis, payer, government, or Gavi support was categorised as high (score of 2 out of 2).

Barriers to uptake

Patients with ***P. aeruginosa*** colonisation come from sub-populations with significant disease burden and high levels of engagement and advocacy such as cystic fibrosis patients. These patient groups are likely to overcome any barriers to treatment, as they are highly motivated to take actions to modify disease course.

Although a new healthcare touchpoint would need to be created for vaccination programmes in each target population, vaccination programmes would likely be able to leverage touchpoints at diagnosis of conditions that increase the risk of ***P. aeruginosa*** colonisation. Vaccines could therefore be embedded into existing clinical pathways relatively easily.

New vaccination programmes would require engagement with specialist societies and guideline setting bodies to ensure awareness of new programmes and dissemination of guidelines.

Scoring: Based on the above analysis, barriers to uptake was categorised as low (score of 2 out of 2)

Commercial attractiveness

A vaccine targeting ***P. aeruginosa*** would likely be commercially attractive because of well-defined target populations, especially patients with chronic lung disease. While mortality and morbidity at the global level is likely low, within target populations it is high and in high-income countries there is likely to be high willingness to pay for treatment.

Scoring: Based on the above analysis, commercial attractiveness was categorised as high (score of 2 out of 2).

Recommendations

P. aeruginosa falls into a cluster of pathogens for which advancing early R&D is the priority.

Primary recommendation

The primary recommendation is to support pre-clinical research. Existing animal models have limited predictive value for clinical research and can be technically challenging for researchers. The development of humanised animal models may lead to more informative animal studies [255,319]. An alternative approach is to test ***P. aeruginosa*** vaccines in disease-specific models. For example, in cystic fibrosis, non-murine, non-rodent animal models, such as ferret and pig models, show promise in better replicating human disease [323,328]. In bronchiectasis, knowledge of disease aetiology and pathophysiology is incomplete, making development of an animal model challenging [329,330]. Given the commensal nature of the pathogen, pre-clinical research should also seek to better understand the potential effect of vaccines on gastrointestinal flora.

In addition to funders already actively investing in vaccines, working with cystic fibrosis advocacy groups may increase interest in funding vaccine development, and expand awareness amongst patients of the possibility of participating in research that contributes to vaccine development.

Secondary recommendations

Alternative treatments should be explored for ***P. aeruginosa*** infection. For example, passive immunisation should be investigated for hospital-acquired ***P. aeruginosa*** infections. However, this is a difficult and expensive alternative. Many of the challenges of vaccine development would be shared with the development of monoclonal antibodies, such as the need for good animal models. The benefits of a passive immunisation approach are that it is effective independent of the status of a patient's adaptive immune system, as antibodies are already formed. Since many patients with ***P. aeruginosa*** infections are immunocompromised and may not mount a strong immune response to a vaccine, this is a particularly attractive advantage. Passive immunisation also confers protection immediately which is advantageous because it is difficult to predict which patients will require ventilation or otherwise be at high risk of infection. The ability to give monoclonal antibodies at the time of infection obviates the need to prejudge which patients are likely to be at risk and the need to evaluate acceptable risk thresholds where vaccination is considered necessary. However, this approach also faces many of the same development challenges as vaccines. It is difficult to predict the effect passive immunisation would have on colonisation and, since the protective effects of passive immunisation might only last a few weeks, the approach may not prevent colonisation of the lungs.

Another secondary recommendation is to better understand the disease burden through better elucidating pathogen-level epidemiology. The burden of disease and regional breakdowns are important for determining vaccination strategy and assessing the cost-effectiveness of different strategies. This, in turn, impacts commercial decisions on whether to invest in vaccine development. There is no single study that presents a global view of the incidence, morbidity and mortality caused by ***P. aeruginosa*** infection across all relevant clinical syndromes, including direct mortality (such as from hospital-acquired infections), and attributable mortality from colonisation in lung diseases. There is also no regional breakdown of the burden of ***P. aeruginosa***. It is particularly important to gain a clearer understanding of global disease burden for ***P. aeruginosa*** because it is a pathogen where current global estimates may be especially conservative. Further work on epidemiology may be aided by the creation of disease registries for cystic fibrosis, bronchiectasis, and other high-risk conditions since these are populations of interest for vaccination. Registries may also facilitate vaccine research by aiding participant recruitment.

Salmonella (non-typhoidal)

Executive summary

In high-income countries, non-typhoidal ***Salmonella*** (NTS) causes mostly gastrointestinal disease. However, invasive NTS (iNTS), which is endemic in Africa, also causes systemic infection with fever. NTS (including iNTS) is characterised by a very high incidence (~150M cases per year) and mortality (~120,000 per year). Whilst iNTS makes up only ~2% of all NTS cases, it accounts for ~50% of all NTS mortality. Due to this outsized impact, vaccine development and policy discussions have focused almost exclusively on iNTS.

The related pathogen ***Salmonella*** Typhi (*S.* Typhi) has received significantly more attention and resources than NTS and, as a result, multiple vaccines are on the market. Vaccine development for iNTS lags behind due to less scientific and commercial interest. Nevertheless, development of a protective vaccine should technically be feasible.

Uptake of an iNTS vaccine in low-income countries would be likely, as incidence and mortality are high, especially in endemic regions in Africa. However, a vaccine for iNTS would not have a significant market outside of endemic regions. In high-income countries (and potentially middle-income countries), a vaccine would only be used as travellers´ vaccine given the low disease burden caused by iNTS infection.

Recommendations:

Non-typhoidal ***Salmonella*** falls into a cluster of pathogens for which the priority is to bring a vaccine to market. The primary recommendation is to encourage and accelerate clinical development, as developing an efficacious vaccine seems technically feasible. The secondary recommendations are to better understand the epidemiology and burden of iNTS infection at a global and regional level and to incentivise multi-pathogen/ combination vaccines in the long term to expand coverage of iNTS to non-invasive enteric strains.

SCORECARD NON-TYPHOIDAL *SALMONELLA*

Health impact:

Direct health impact

1.0	0.0
Mortality	Morbidity

Impact on AMR reduction

1.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Children

Alternative interventions
None identified

Probability of R&D success:

0.5	1.5	1.5
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
None identified

Acceleration potential
Drive clinical development

Major barriers to development
Weak pipeline

Probability of uptake:

1.0	1.0	2.0	1.5
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Population in endemic areas / Routine vaccination where endemic (Africa); Travellers' vaccination in high-income countries

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

Salmonella are Gram-negative bacteria of the family ***Enterobacteriaceae*** but listed separately on the WHO priority pathogen list. There are more than 2,500 NTS serovars with ***Salmonella*** Typhimurium and ***Salmonella Enteritidis*** accounting for approximately 50% of all human isolates [331].

iNTS is a subset of NTS that causes more serious symptoms and 50% of all NTS mortality and is most common in Africa [332]. iNTS strains typically have a distinct genotype and invasive disease is associated with HIV, anemia, malnutrition and malaria [333]. Global awareness of the severity of iNTS is low, and one expert states "some people think iNTS is mild but in Africa it's a very different problem. There's a lack of awareness in the West, combined with a lack of advocacy in Africa" [28]. Experts also believe that until recently iNTS was under-recognised and mis-diagnosed as typhoid fever, as one explains "even clinicians in Africa would have assumed iNTS cases to be typhoid" [28].

iNTS is primarily spread by the faeco-oral route and can rarely be spread through direct person-to-person contact [334,335]. Symptoms of non-typhoidal salmonellosis include acute onset of fever, abdominal pain, diarrhoea, nausea and sometimes vomiting [336]. Symptoms of invasive non-typhoidal salmonellosis include fever, hepatosplenomegaly, and respiratory symptoms [337]. Groups at highest risk for iNTS infection include HIV-infected persons, malaria-infected persons, and malnourished children [337].

Potential health impact

Direct health impact

Robust global data on disease burden is not available. Neither the IHME nor WHO provides estimates and a review of the research literature identified few relevant studies. The available data suggests intermediate mortality (~120,000 deaths per year) and low morbidity (~150,000 years lived with disability per year) for NTS infection globally [18]. Mortality from iNTS accounts for nearly 50% of these deaths (~55,000 deaths per year) globally [18]. The data on morbidity and mortality was taken from an article published by Havelaar *et al.* in ***PLoS Medicine*** in 2015 and only includes infections in non-HIV infected individuals [18]. Whilst offering comprehensive and up-to-date epidemiological data on foodborne diseases, experts highlighted that there is some controversy around this data and IHME is currently working on publishing their view on iNTS burden. One expert expresses frustration with the current state of epidemiological data on iNTS infection, stating that "lack of data regarding the epidemiology of the disease is a big impediment" [28]. Another noted that "we currently only have very limited data on iNTS disease burden" [28].

Scoring: Based on the above analysis, mortality was categorised as medium (score of 1 out of 2) and morbidity was categorised as low (score of 0 out of 2).

Sub-population benefits

The populations likely to benefit from a vaccine for iNTS are infants and young children, particularly in endemic regions, and individuals infected with HIV or malaria.

Antibiotic use

Fluoroquinolones such as ciprofloxacin or levofloxacin are a typical choice for empiric antibiotic treatment, with trimethoprim-sulfamethoxazole, ampicillin or third generation cephalosporins, such as ceftriaxone or cefotaxime , being reasonable alternatives [338].

Scoring: Based on the above analysis, antibiotic use was categorised as medium (score of 1 out of 2). This estimate is based on an annual incidence of ~80 million cases treated with a three day course of antibiotics.

Urgency of AMR threat

The WHO lists ***Salmonella*** spp. as 'high' in its priority list of R&D for new antibiotics [6,339] but it does not appear on the CDC list of biggest threats from AMR [7]. Reduced susceptibility and resistance of NTS to fluoroquinolones and third generation cephalosporins (such as ceftriaxone) is increasing, with resistance frequently reported in Asia [338]. Ceftriaxone-resistant strains have recently doubled in the United States to approximately 5% [338].

Scoring: Based on the above analysis, the urgency of AMR threat was categorised as medium (score of 1 out of 2).

Probability of R&D success

Pipeline robustness

The pipeline for vaccines against iNTS comprises five candidates in pre-clinical development.

Although the pipeline is limited, experts are optimistic about the probability of R&D success, given the biological similarities among ***Salmonella*** strains and recent success in developing a conjugated vaccine against ***S.*** Typhi that has received prequalification from the WHO [147]. One expert summarises the future of vaccine development, saying "I am very confident that vaccine development will be possible given that we know immunogenic targets" [28].

CURRENT PIPELINE NON-TYPHOIDAL *SALMONELLA*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	02	-	-	-	-	02
Number of **commercial** vaccines	03	-	02	-	-	03
Total number of vaccines	05	-	-	-	-	05

Hence, the limited activity in the pipeline does not reflect the feasibility of developing an efficacious vaccine against iNTS, but rather highlights a clear lack of resources and interest to drive pre-clinical and clinical activities forward.

Scoring: Based on the above analysis, the pipeline was categorised as fairly low (score of 0.5 out of 2).

Pathogen biology

Both antibodies and complement can kill ***Salmonella in vitro***, suggesting that at least partial immunity to iNTS likely exists [331]. Patients previously infected with NTS develop serum antibodies that have ***in vitro*** bactericidal activity partly by mediating intracellular oxidation [331]. Epidemiological studies in sub-Saharan Africa have shown that antibodies against NTS correspond with a decrease in age-related incidence of iNTS disease [331].

Vi antigens have proven to be useful targets for developing a vaccine against the related pathogen, ***S.*** **Typhi**. However, iNTS does not express these antigens and a different vaccine development strategy is needed. Several promising targets and approaches are in pre-clinical development. It is unclear if immunity against these targets will be protective against gastroenteritis and invasive disease, but it is suggested that covering between five and six serovars could protect against the most relevant forms of gastroenteritis and invasive ***Salmonella*** worldwide [331].

Approaches in development include: Generalized Modules for Membrane Antigens (GMMA) (providing surface polysaccharides and outer membrane proteins in native conformation), glycoconjugation (linking LPS-derived O polysaccharide to carrier proteins) and protein vaccines (conserved recombinant or purified surface or outer membrane protein antigens (such as flagellin, porins OmpC, F, D)) [331].

Scoring: Based on the above analysis, pathogen biology was categorised as fairly high (score of 1.5 out of 2).

Pre-clinical and clinical R&D

Relatively robust pre-clinical models are available for iNTS. Mice are permissive to ***S.*** **Typhimurium** and ***S. Enteritidis*** systemic infection, both of which cause invasive disease without gastritis in mice [331]. To produce an NTS enterocolitis infection, mice are pre-treated with streptomycin or other antibiotics prior to bacterial challenge [331]. Although these models are more informative than other animal models for some related pathogens (such as ***S.*** **Typhi**/***S.*** **Paratyphi**), there are noteworthy differences between mouse and human NTS infections.

Correlates of protection have not yet been identified, but data from Malawi show that antibodies to ***S.*** **Typhimurium** (including the surface lipopolysaccharide) are associated with lower risk of NTS bacteraemia, particularly in the first few months of life when maternal antibodies are present [331]. The serum bactericidal activity of these

antibodies can be measured via an ***in vitro*** assay [331]. Whilst helpful for clinical trial design, this correlation is not yet adequately characterised to serve as a quasi-correlate of protection (similar to anti-Vi IgG for ***S.*** Typhi).

Clinical trials for iNTS are likely feasible, but not all of the necessary elements for clinical development are currently in place. Human challenge models have been considered but have not yet been established due to the early developmental stage of iNTS vaccine candidates [340]. According to experts, clinical trial infrastructure in endemic regions is in place and incidence is high, making efficacy trials feasible in Africa [28].

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as fairly high (score of 1.5 out of 2).

Probability of uptake

Expected policy stance

A vaccine against iNTS would be particularly beneficial to children in endemic areas. Therefore, routine vaccination of children in these regions is a likely strategy. A vaccine would also potentially be used as a travellers' vaccine.

There are reasonable arguments that would suggest policy support for an iNTS vaccine. NTS infection has a greater incidence than ***S.*** Typhi infection, and higher mortality than ***S.*** Paratyphi infection [31]. Experts also cite support from WHO as a reason to anticipate policy support for a vaccine targeting iNTS, with one expert stating that "WHO has a programme to support non-typhoidal vaccines for ***Salmonella*** infections" [28].

Scoring: Based on the above analysis, expected policy stance was categorised as medium (score of 1 out of 2).

Payer, government or Gavi support

Payers in high-income countries are unlikely to support vaccination against iNTS due to the low burden of disease in these regions. However, given the high incidence of iNTS in endemic regions, a travellers' vaccine might be endorsed. Support for an iNTS vaccine is also unlikely in non-endemic middle-income countries, although support for use as a travellers' vaccine could be possible.

In low-income countries, an iNTS vaccine would align with Gavi's aim to reduce mortality and invest in diseases where there is a disproportionate impact amongst vulnerable groups. The burden of iNTS is concentrated in African countries, a high proportion of which have Gavi support. A combination vaccine against enteric diseases could further attractiveness of an iNTS vaccine.

Scoring: Based on the above analysis, payer, government, or Gavi support was categorised as high (score of 2 out of 2).

Barriers to uptake

No new touchpoints or changes to existing clinical practices would be required for iNTS vaccination, as it would be included as part of childhood vaccination programmes or travellers' vaccination. However, because the burden is predominantly in Africa, the implementation of vaccination programmes may require additional infrastructure for storage and supply chain [28].

Scoring: Based on the above analysis, barriers to uptake was categorised as fairly low (score of 1.5 out of 2).

Commercial attractiveness

The commercial attractiveness of an iNTS vaccine is limited by the likelihood of restricted demand in high- and middle-income countries where it would be used only as a travel vaccine, coupled with uncertainty surrounding the likelihood of Gavi support in low-income countries.

Scoring: Based on the above analysis, commercial attractiveness was categorised as medium (score of 1 out of 2).

Recommendations

Non-typhoidal ***Salmonella*** falls into a cluster of pathogens for which the priority is to bring a vaccine to market.

Primary recommendation

The primary recommendation is to encourage and accelerate clinical development. Key funders of enteric disease research should be encouraged to support clinical trials for promising vaccine candidates. Although the pipeline appears weak, there are pre-clinical candidates in development that are not listed in official databases. Thus it is stronger than it appears. Additionally, iNTS is a relatively well characterised pathogen, sharing commonalties with ***S.*** **Typhi**, which has demonstrated proof of principle for vaccine development. With greater focus of resources and expertise, candidates could be accelerated through the value chain with relative speed. Opportunities for funders to strategically coordinate efforts facilitating the pooling of resources and funding of later stage trials for iNTS should also be encouraged. Funders should also support technical advancements that enable cheaper vaccine production to ensure uptake in low-income countries. These may include less expensive conjugation methods and GMMA.

Secondary recommendations

A secondary recommendation is to better understand the epidemiology and burden of iNTS. A better understanding of the global and regional burden of iNTS infection is needed to inform policy making and increase the likelihood of Gavi support. Rates of misdiagnosis are high for enteric disease, and treatment may be empiric, so it is important to conduct high-quality studies using laboratory-based diagnostic techniques to provide a more accurate picture of the disease burden [75,341]. According to experts, efforts at IHME are currently underway to establish a better fact base on disease burden of iNTS [28], an important step toward better understanding of the burden of disease.

An additional secondary recommendation is to incentivise the development of multi-pathogen or combination vaccines for enteric diseases that include iNTS, given the strong policy interest in enteric vaccine combinations.

Salmonella Paratyphi

Executive summary

Salmonella* Paratyphi** (S.* Paratyphi**) is an infection with relatively low incidence that causes paratyphoid fever. ***S.* Paratyphi** causes approximately 25,000 deaths and approximately 10,000 years lived with disability [31].

No vaccine against ***S.* Paratyphi** is currently available. Whilst there is a vaccine for ***S.* Typhi**, vaccine development for ***S.* Paratyphi** lags behind due to less scientific and commercial interest. Nevertheless, development of a protective vaccine should technically be feasible given the biological similarities between the pathogens as they are closely related as serovars of the same subspecies *Salmonella enterica* subspecies enterica. However, as most prevalent ***S.* Paratyphi** strains do not express the Vi capsular antigen (which is targeted by the recently licensed ***S.* Typhi** vaccine), potential ***S.* Paratyphi** vaccines have to include alternative antigens, such as the O-specific polysaccharide.

Because paratyphoid fever has low incidence and low associated mortality and morbidity, uptake of a standalone vaccine is unlikely. Therefore, the priority should be to explore combination vaccines with ***S.* Typhi**.

Recommendations:

***S.* Paratyphi** falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority. The primary recommendation is to support development of vaccines combining ***S.* Paratyphi** and ***S.* Typhi**. The secondary recommendation is accelerating clinical development.

Throughout this analysis, scoring is based on a standalone vaccine for ***S.* Paratyphi** to maintain a consistent approach to scoring for all pathogens.

SCORECARD *SALMONELLA* PARATYPHI

Health impact:

Direct health impact

0.0	0.0
Mortality	Morbidity

Impact on AMR reduction

0.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Children

Alternative interventions
None identified

Probability of R&D success:

0.5	1.5	1.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
Potential combination with *S.* Typhi vaccine

Acceleration potential
Potential combination with *S.* Typhi vaccine

Major barriers to development
Low incidence

Probability of uptake:

0.0	1.0	0.0	1.5
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Greatest need in low-income countries / Routine infant vaccination where endemic; Travellers' vaccination in high-income countries

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

Salmonella enterica serovar **Paratyphi** (***S.*** **Paratyphi**) is a Gram-negative bacterium of the family ***Enterobacteriaceae***. ***S.*** **Paratyphi** A and B cause enteric fever [342]. ***S.*** **Paratyphi** A is the most common serovar [342], and referred to throughout this chapter if not specified otherwise. Experts report limited ongoing research into other serovars, with one commenting "I am not aware of much work on ***S.*** **Paratyphi** B and C, but these serovars are not a big problem" [28].

S. **Paratyphi** is spread by the faeco-oral route and rarely through direct human contact [334,335]. Symptoms of infection with ***S.*** **Paratyphi** include high fever, headache, loss of appetite, vomiting, constipation or diarrhoea, and splenomegaly [343]. Groups at highest risk of infection are individuals with increased susceptibility associated with gastric achlorhydria [344] and those with immunosuppressive illnesses such as AIDS [345].

Over three million cases of ***S.*** **Paratyphi** infection are reported per year [31], predominately in Asia [32]. Unlike ***S.*** **Typhi** and invasive non-typhoidal ***Salmonella***, ***S.*** **Paratyphi** is not common in sub-Saharan Africa [28,342].

Potential health impact

Direct health impact

Data from the IHME 2016 estimates suggest low mortality (~25,000 deaths per year) and low morbidity (~10,000 years lived with disability per year) globally caused by ***S.*** **Paratyphi** infection [31]. This source uses a defined methodology and is used in the global health community. The data can therefore be viewed with a reasonable level of confidence.

Scoring: Based on the above analysis, mortality was categorised as low (score of 0 out of 2) and morbidity was categorised as low (score of 0 out of 2).

Sub-population benefits

A vaccine against ***S.*** **Paratyphi** would provide benefits to infants and young children – the population at greatest risk for infection – and to patients in areas with elevated risk because of poor sanitation.

Antibiotic use

S. **Paratyphi** infection is primarily treated with fluoroquinolones, third-generation cephalosporins, and azithromycin. Carbapenems are reserved for suspected infection with extensively drug-resistant strains [346]. Many experts consider fluoroquinolones to be the drug of choice for susceptible isolates and turn to azithromycin and cephalosporin when fluoroquinolones cannot be used.

Scoring: Based on the above analysis, antibiotic use was categorised as low (score of 0 out of 2). This estimate is based on an annual incidence of ~ four million paratyphoid cases treated with a two week course of antibiotics.

Urgency of AMR threat

Salmonella **spp.** (the genus to which ***S.*** **Paratyphi** belongs) are listed as 'high' in the WHO priority list of research and development for new antibiotics. Multi-drug resistant strains resistant to ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol are widespread, preventing these antibiotics from being used to treat ***S.*** **Paratyphi** infection [346]. The presence of multi-drug resistant strains varies widely, from 10-80% in regions around the world [346], and full resistance to fluoroquinolones has also been reported. Most strains remain susceptible to azithromycin and ceftriaxone but resistance and extended-spectrum beta-lactamase producers have been reported [346].

Scoring: Based on the above analysis, urgency of AMR threat was categorised as medium (score of 1 out of 2).

Probability of R&D success

Pipeline robustness

The pipeline for ***S.*** **Paratyphi** is not highly active: three vaccines against ***S.*** **Paratyphi** are currently in development. Two are in pre-clinical development, one is in Phase I. Another candidate from Lanzhou Institute of Biological Products is listed in Phase III in commercial databases; however, given the limited information that is publicly available, it is unclear whether this candidate has reached Phase III or is still in Phase II stage of clinical development.

Three out of the four vaccines captured by the analyses are bivalent vaccines comprising both a ***S.*** **Paratyphi** and a ***S.*** **Typhi** component to cover both typhoidal ***Salmonella*** strains[342], reflecting the likely low uptake of a standalone ***S.*** **Paratyphi** vaccine. Experts are confident about the probability of R&D success for these vaccines in view of the recent success in developing the conjugated ***S.*** **Typhi** vaccine, which targets a pathogen with significant biological similarities to ***S.*** **Paratyphi**.

The scant activity in the pipeline does not reflect the feasibility of developing an efficacious vaccine against ***S.*** **Paratyphi**, but rather shows that commercial and academic researchers prioritised developing an ***S.*** **Typhi** vaccine, given the higher disease burden caused by typhoid fever.

CURRENT PIPELINE *SALMONELLA* PARATYPHI

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	01	-	-	01[1]	-	02
Number of **commercial** vaccines	01	01	-	-	-	02
Total number of vaccines	02	01	-	01[1]	-	04

1) Candidate from Lanzhou Institute of Biological Products listed in Phase III in commercial databases; however, given the limited information that is publicly available, we are unclear whether this candidate has reached Phase III or is still in Phase II stage of clinical development.

Scoring: Based on the above analysis, pipeline robustness was categorised as fairly low (score of 0.5 out of 2).

Pathogen biology

Natural and cross-strain immunity to ***S.*** **Paratyphi** appear to be limited; previous infection confers only partial protection against reinfection or disease severity [342].

The recently developed vaccine for typhoid fever – closely related to ***S.*** **Paratyphi** infection – targets the Vi antigen. As **Paratyphi** A and B do not express these antigens [347], the vaccine against ***S.*** **Typhi** does not induce cross-protection against these ***S.*** **Paratyphi** strains. Hence, a vaccine targeting paratyphoid fever will need to include a different set of antigens. Suitable options are O (polysaccharide antigens) and H (flagellar antigens) that are expressed by ***S.*** **Paratyphi** strains. The vaccine candidates in development therefore mostly target the O-specific polysaccharide (e.g. O:2 for ***S.*** **Paratyphi** A) conjugated to various different protein carriers [342] that enhance immunogenicity and convert the T-cell independent immune responses to a T-cell dependent response characterised by affinity maturation, subclass switching and induction of memory [348]. Other examples for candidates in development are live attenuated pathogen [342] or vaccines based on Generalized Modules for Membrane Antigens (GMMA) [349].

Scoring: Based on the above analysis, pathogen biology was categorised as fairly high (score of 1.5 out of 2).

Pre-clinical and clinical R&D

Models in mice have been the most utilised pre-clinical models. However, as ***S.*** **Typhi** and ***S.*** **Paratyphi** A are human host restricted and normally asymptomatic in mice, a lethal infection has to be produced in mice by suspending the bacteria in hog gastric mucin and then injecting the suspension intraperitoneally [350]. This, however, does not accurately mirror the disease, which infects via the oral route and some researchers do not see existing models as clinically relevant [342]. Results from other models [350] and larger animal models, such as non-human primates, may provide a more complete assessment of vaccine candidates and should be prioritised for vaccine candidates already evaluated in small animal models.

Clinical research involves several key challenges. There is an experimental human challenge model with ***S.*** **Paratyphi** A now established [351]. However, correlates of protection have not been identified for ***S.*** **Paratyphi** A in humans. In vitro assays have quantified a positive correlation between serum antibody levels and ***in vitro*** bactericidal activity induced by either natural infection or immunisation, but this correlation is not yet adequately characterised to guide clinical trial design [342].

Experts also express concerns that although clinical trial infrastructure to run efficacy trials is in place in endemic regions, showing efficacy in field trials may be difficult and costly because of the low incidence of ***S.*** **Paratyphi** infection. This concern applies regardless of whether a

vaccine is developed as a combination vaccine with a *S.* Typhi component or comprises antigens from other enteric diseases [28]. The WHO published a guidance to develop a regulatory pathway for typhoid conjugate vaccines, but no such pathway has been developed for paratyphoid vaccines. The typhoid framework could serve as a surrogate until one is established [342]; the *S.* Typhi vaccine was licensed on the basis of a Phase II study in an endemic setting that only demonstrated immunogenicity and safety. Efficacy was subsequently demonstrated in human challenge studies [352] and effectiveness studies are underway. A similar pathway to regulatory approval is anticipated for *S.* Paratyphi.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as medium (score of 1 out of 2).

Probability of uptake

Expected policy stance

A vaccine for *S.* Paratyphi would be particularly helpful for children in the endemic setting. A protective vaccine could therefore be administered to all children in endemic regions; travellers to endemic regions would also likely receive the vaccine.

Because *S.* Paratyphi has low incidence and low mortality [31], policymakers are unlikely to support a standalone vaccine, but as mentioned would prefer a combination vaccine with *S.* Typhi [28]. Nevertheless, in a publication on paratyphoid fever vaccination recommendations prepared for the WHO Product Development for Vaccines Advisory Committee in 2014, vaccine development was thought to be a viable means for disease control as an adjunct to existing interventions [349].

Scoring: Based on the analysis described above, expected policy stance was characterised as medium (score of 1 out of 2).

Payer, government, or Gavi support

The low burden of disease in high and middle-income countries renders payer support unlikely. A combination vaccine is more likely to receive support as a travellers´vaccine.

Gavi has not taken any concrete steps towards designating a priority for vaccines against *S.* Paratyphi A. Gavi is unlikely to support a standalone vaccine but may support a combined enteric vaccine with *S.* Typhi [342].

Scoring: Based on the above analysis, payer, government, or Gavi support was categorised as low (score of 0 out of 2).

Barriers to uptake

Few cultural and logistical barriers would prevent uptake of a *S.* Paratyphi vaccine. No new touchpoints would be required because the vaccine would likely be delivered as part of childhood vaccination programmes or offered to travellers. However, distribution could require additional infrastructure for supply chain and storage because the burden is predominantly in low-income countries.

No new clinical practices would need to be established for a *S.* Paratyphi vaccine. Childhood vaccines and travellers' vaccines are routinely recommended by clinicians.

Scoring: Based on the above analysis, barriers to uptake was categorised as fairly low (score of 1.5 out of 2).

Commercial attractiveness

Commercial attractiveness of a standalone vaccine is low given the likely limited demand in high-income countries and middle-income countries, where the only market for a *S.* Paratyphi vaccine is for travellers. A combined *S.* Typhi/*S.* Paratyphi vaccine would be more commercially attractive than a standalone vaccine for *S.* Paratyphi; combinations with other enteric pathogens could also be attractive. As one expert states "It would be great to have a vaccine against 'enteric disease'" [28].

Scoring: Based on the above analysis, commercial attractiveness was categorised as low (score of 0 out of 2).

Recommendations

S. Paratyphi falls into a cluster of pathogens for which collecting data and exploring alternatives to vaccination are the priority.

Primary recommendation

The primary recommendation is to support research and development for a combination vaccine with *S.* Typhi. In the longer-term, it would be worthwhile to explore combination with other enteric vaccines given strong interest from policymakers in enteric vaccine combinations.

Secondary recommendation

The secondary recommendation is to accelerate clinical development. Key funders should be encouraged to support Phase III trials for promising combined *S.* Typhi/*S.* Paratyphi vaccine candidates. Gavi should be encouraged to provide an advanced market guarantee to pharmaceutical companies taking combined *S.* Typhi/ *S.* Paratyphi candidates to Phase III trials. Finally, support for technical advances such as less expensive conjugation methods that enable cheaper vaccine production could help ensure uptake in low- and middle-income countries.

Salmonella Typhi

Executive summary

Salmonella Typhi (***S.*** Typhi) causes typhoid fever, a systemic infectious disease characterised by symptoms of fever and abdominal pain. There are ~12 million cases and ~130,000 deaths annually.

Previously available vaccines (live attenuated Ty21a oral vaccines and Vi polysaccharide vaccines) had limitations in their capacity to induce long-lasting protective immunity in children. A new, conjugated ***S.*** **Typhi** vaccine has recently been pre-qualified by the WHO and is supported by Gavi for introduction in 2019, following effectiveness trials. Upon completion of effectiveness trials, efforts should focus on rapidly introducing the vaccine.

Recommendations:

S. **Typhi** falls into a cluster of pathogens for which the priority is to increase vaccine uptake. The primary recommendation is to drive coverage and equity of the recently developed conjugated typhoid vaccine, provided results of effectiveness studies are as positive as expected. This vaccine is likely to improve upon the durability and immunogenicity of earlier-generation ***S.*** **Typhi** vaccines. The secondary recommendation is to incentivise development of multi-pathogen vaccines, such as vaccines that also target ***S.*** **Paratyphi** in combination with other enteric diseases.

SCORECARD *SALMONELLA* TYPHI

Health impact:

Direct health impact

1.0	0.0
Mortality	Morbidity

Impact on AMR reduction

1.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Children

Alternative interventions
None identified

Probability of R&D success:

2.0	2.0	2.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
Potential combination with *S.* Paratyphi; other enteric diseases

Acceleration potential
Not applicable; vaccines on market

Major barriers to development
Not applicable; vaccines on market

Probability of uptake:

2.0	2.0	2.0	2.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Greatest need in low-income countries / Routine infant vaccination where endemic; Travellers' vaccination in high-income countries

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

Salmonella are Gram-negative bacteria of the family ***Enterobacteriaceae*** but listed separately on the WHO priority pathogen list. Typhoid fever is an enteric fever caused by ***Salmonella enterica*** serovar **Typhi** (***S.*** **Typhi**). Typhoid fever is a systemic febrile infection that occurs only in humans [352] and is different from the more common self-limited acute gastroenteritis caused by other ***Salmonella*** serotypes [342]. Typhoid fever is characterised by high fever, lassitude, abdominal pain, headache, loss of appetite and nausea, dry cough, and occasionally a rash of flat, rose-coloured spots at peak of fever after 7-10 days [353].

Geographically, ***S.*** **Typhi** infection is concentrated in South and South East Asia, and sub-Saharan Africa with many island nations of Oceania also experiencing high incidences and large outbreaks [352]. It is less common in industrialised regions such as the United States, Canada, western Europe, Australia, and Japan [354]. Transmission is primarily by the faeco-oral route but in rare cases can be transmitted directly from person to person through food handling [334,335]. Groups at highest risk for ***S.*** **Typhi** include individuals with immunosuppressive illnesses such as AIDS [345] and those with gastric achlorhydria, which increases susceptibility to ***S.*** **Typhi** infection [344]. According to the IHME, there are an estimated 12 million cases of typhoid fever per year globally [31].

Potential health impact

Direct health impact

The IHME gathers data on the burden of ***S.*** **Typhi** infection. This data source has a defined methodology and is used and accepted in the global health community. The IHME estimates that ***S.*** **Typhi** causes 130,000 deaths per year and 113,000 years lived with disability per year [31].

Scoring: Based on the above analysis, mortality was characterised as medium (score of 1 out of 2) and morbidity was characterised as low (score of 0 out of 2).

Sub-population benefits

Infants and young children, and patients with conditions that predispose them to infection (such as immunosuppressive illnesses including AIDS [345] and gastric achlorhydria, which increases susceptibility to ***S.*** **Typhi** infection [344]) are most likely to benefit from vaccination.

Antibiotic use

S. **Typhi** infections are primarily treated with fluoroquinolones, third-generation cephalosporins, and azithromycin. Carbapenems are reserved for suspected infection with extensively drug-resistant strains [346]. Many experts consider fluoroquinolones such as ciprofloxacin or ofloxacin to be the drug of choice for susceptible isolates [28]. When fluoroquinolones cannot be used, azithromycin or cephalosporins are alternatives.

Scoring: Based on the above analysis, antibiotic use was categorised as medium (score of 1 out of 2). This estimate is based on an annual incidence of ~12 million typhoid cases and treated with a two week course of antibiotics.

Urgency of AMR threat

WHO has listed ***Salmonella*** **spp.** as 'high' in its priority list of R&D for new antibiotics and the CDC lists it as a 'serious' threat in its list of biggest threats from AMR [7].

Multi-drug resistant strains to ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol are widespread globally preventing these agents being used to treat ***S.*** **Typhi** [346]. The presence of multi-drug resistant strains varies widely from 10-80% globally [346].. Most strains remain susceptible to azithromycin and ceftriaxone but an outbreak of extensively drug-resistant typhoid with resistance to ampicillin, trimethoprim-sufamethoxazole, chloramphenicol, fluoroquinolones, and ceftriazone was recently reported[355].

Scoring: Based on the above analysis, the urgency of AMR threat was characterised as medium (score of 1 out of 2).

Probability of R&D success

Pipeline robustness

The pipeline for development of vaccines against ***S.*** **Typhi** comprises a total of 20 marketed vaccines and 12 vaccines currently in development. Six vaccines are in pre-clinical development, two are in Phase I, two are in Phase II, and two are in Phase III.

Marketed vaccines fall into two groups: live attenuated Ty21a oral vaccines and Vi polysaccharide vaccines. The live attenuated Ty21a oral vaccine was developed in the early 1970s by chemical-induced mutagenesis of a pathogenic ***S.*** **Typhi** strain that no longer expressed the Vi polysaccharide [352]. The limitation of this vaccine is that the level of protective immunity varies widely depending on

the vaccine formulation, number of doses administered, and interval between doses. The Vi polysaccharide vaccine comprises a highly purified Vi polysaccharide. However, unconjugated polysaccharide vaccines – including this vaccine – are limited by poor immunogenicity in infants and young children and by short-lived duration of protection [352].

To overcome these limitations novel strategies have been pursued. Recently two newer generation Typhoid conjugate vaccines (TCV) were licensed. Typbar-TCV®, and PedaTyph™ [352]. Both TCV consist of the Vi polysaccharide conjugated to a protein carrier [352] that enhances immunogenicity and converts the short-lasting T-cell independent Vi-specific immune response to a T-cell dependent response which is preferred given the induction of antibodies with higher affinity and also of long-lasting memory [348]. Experts explain that this modification is critical to improving on previous vaccines, with one expert explaining "conjugation is very important because that is what drives immunity in children" [28]. This approach has shown safety and efficacy in field trials, as well as efficacy in controlled human infection studies [356] and one expert anticipates "I expect effectiveness in the field to be even higher" [28].

Typbar TCV® is currently in effectiveness trial studies in several countries [357] as experts note they are "looking for effectiveness in Bangladesh, Nepal, India, Malawi and outbreak response in Pakistan" [28]. Other TCV candidates are in clinical development or already undergoing licensure review [352].

Scoring: Based on the above analysis, pipeline robustness was categorised as high (score of 2 out of 2).

Pathogen biology

Although repeat clinical episodes of ***S.* Typhi** infection have been described, they are uncommon, suggesting that immune responses are mostly protective following initial episodes of infection [352].

Immunological protection against typhoid fever is believed to involve both cell-mediated and humoral responses given the fact that ***Salmonellae*** are facultative intracellular pathogens and exist both extracellularly and within intracellular niches (specifically monocytes and macrophages). Following natural infection, specific antibodies are detected in both serum and in the intestines.

Scoring: Based on the above analysis, pathogen biology was categorised as high (score of 2 out of 2).

Pre-clinical and clinical R&D

Many, varied animal models are in use for pre-clinical research on ***S.* Typhi** vaccine candidates [350].

Mouse models have been the most utilised. However, as ***S.* Typhi** is human host restricted and normally asymptomatic in mice, a lethal infection has to be produced in mice by suspending the bacteria in hog gastric mucin and then injecting the suspension intraperitoneally. Results from other models including larger animal models, such

CURRENT PIPELINE *SALMONELLA* TYPHI

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	02	-	01	01	-	04
Number of **commercial** vaccines	04	02	01	01	20	28
Total number of vaccines	06	02	02	02	20	32

as non-human primates, may provide a more complete assessment of vaccine candidates and should be prioritised for vaccine candidates already evaluated in small animal models [350].

WHO deems estimation of total anti-Vi IgG to be an appropriate measure of vaccine immunogenicity for *S.* Typhi, and suggests evaluation of new conjugate vaccines against Vi polysaccharide in immunogenicity trials [358], providing a quasi-correlate of protection that facilitates both pre-clinical and clinical research.

Controlled human infection models exist and have been part of established pathways to licensure [14,17] and sufficient clinical trial infrastructure exists in endemic regions [359]. Finally, there is an established route to approval for *S.* Typhi vaccines.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as high (score of 2 out of 2).

Probability of uptake

Expected policy stance

The typhoid conjugate vaccine is particularly helpful for children in endemic settings. A protective vaccine would therefore likely be administered to all children in endemic regions. Furthermore, a potential vaccine would be useful for travellers.

Policy support for *S.* Typhi vaccination is strong as *S.* Typhi has a high incidence of ~12 million cases per year, with high mortality [31]. Even before the approval of TCV, the need for improved vaccines was recognised by both experts and policy makers, with one expert noting "[*S.* Typhi was] a prime candidate for WHO support. We have vaccines against typhoid, but with short duration of protection" [28]. WHO recommends a single dose of TCV at six-nine months of age in endemic settings, and studies are examining co-administration possibilities at nine months [28].

Scoring: Based on the above analysis, expected policy stance was categorised as high (score of 2 out of 2).

Payer, government or Gavi support

A Typhoid vaccine is already recommended for travellers by UK and American agencies [360,361], and improved vaccines are likely to continue to receive support for travellers in high-income countries.

In middle-income countries, the high disease burden makes support likely in areas where *S.* Typhi infection is endemic. Support is also likely in low-income countries as in May 2018 Gavi earmarked $85 million for a prequalified TCV [362].

Scoring: Based on the above analysis, payer, government, or Gavi support was categorised as high (score of 2 out of 2).

Barriers to uptake

Few barriers exist for a *S.* Typhi vaccination programme. Vaccination against *S.* Typhi is already part of childhood vaccination programmes and offered to travellers, so no new touchpoints or changes to existing clinical practices would be required.

Scoring: Based on the above analysis, barriers to uptake were categorised as low (score of 2 out of 2).

Commercial attractiveness

Commercial attractiveness is high in view of the existence of recently licenced commercial vaccines, Gavi's stated interest in and support for vaccination against *S.* Typhi in low-income countries, likely uptake in middle-income countries where infection is endemic, and the travellers´ vaccine market in high-income countries.

Scoring: Based on the above analysis, commercial attractiveness was categorised as high (score of 2 out of 2).

Recommendations

S. Typhi falls into a cluster of pathogens for which the priority is to increase vaccine uptake.

Primary recommendation

The primary recommendation is to drive coverage and equity. Current coverage with TCV is low given its recent licensure and ongoing effectiveness trials. Other vaccine candidates in development by alternative producers should also be supported to ensure healthy competition and production capacity in the market.

Secondary recommendation

The secondary recommendation is to incentivise multi-pathogen/combination vaccines, including combination vaccines with *S.* Paratyphi and with non-invasive enteric strains given the strong policy interest in enteric vaccine combinations.

Shigella

Executive summary

Shigella is one of the most common bacterial causes of diarrhoeal illnesses – responsible for approximately 200,000 deaths per year primarily in low- and middle-income countries. According to the GEMS study, in sub-Saharan Africa and South Asia, ***Shigella*** was among the top four causes of potentially life-threatening diarrheal illness among children less than five years old brought to a center for treatment of diarrhea [363,364].

Experts acknowledge that enteric diseases have a massive impact on the development of anti-microbial resistance (AMR) due to the high quantities of antimicrobials used to treat these infections. Therefore, even a "partially efficacious vaccine that reduces the severity of the disease rather than preventing the disease could have a huge impact as patients would seek antimicrobial treatment less often" [28].

No vaccine is currently available, but experts believe a ***Shigella*** vaccine is feasible due to defined and promising target antigens and feasible technical R&D. A ***Shigella*** vaccine would have high probability of uptake across low and middle-income countries, primarily due to likelihood of Gavi support, where incidence is highest.

Recommendations

Shigella falls into a cluster of pathogens for which bringing a vaccine to market is the priority. A ***Shigella*** vaccine would potentially have a high impact due to high incidence and significant associated morbidity and mortality, particularly in low- and middle-income countries.

The primary recommendation is to accelerate clinical development of the most advanced vaccine candidates and the secondary recommendation is to incentivise combination vaccines with other enteric diseases such as *E. coli*.

SCORECARD *SHIGELLA* SPP.

Health impact:

Direct health impact

1.0	2.0
Mortality	Morbidity

Impact on AMR reduction

1.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
None identified

Sub-population benefits
Immunocompromised individuals
Children
Men who have sex with men

Alternative interventions
None identified

Probability of R&D success:

1.5	1.5	1.5
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
Potential combination with other enteric vaccines

Acceleration potential
Drive clinical development

Major barriers to development
None identified

Probability of uptake:

1.0	2.0	2.0	1.5
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Greatest need in low-income countries / Routine infant vaccination where endemic; Travellers' vaccination in high-income countries

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

Shigella are Gram-negative, non-motile bacteria closely related to ***Escherichia coli*** (***E. coli***). There are four different species of ***Shigella*** (***S. sonnei, S. flexneri, S. boydii***, and ***S. dysenteriae*** [365]) that can cause diarrhoeal disease. ***Shigella*** is transmitted via the faeco-oral route, through direct person-to-person or sexual contact, or indirectly through contaminated food, water, or fomites [366].

Typical symptoms of ***Shigella*** infection include diarrhoeal disease (frequent, loose stools with blood and mucus), fever, and abdominal cramps, and pain [366]. Groups at highest risk for ***Shigella*** include young children, travellers, men who have sex with men, and people whose immune systems are weakened due to illness or medical treatment [367].

Shigella is more common in low-income countries than in middle- or high-income countries. Mortality from ***Shigella*** is highest in the WHO African region (10 per 100,000) and South East Asia (4 per 100,000) [31]. Over 190 million cases of ***Shigella*** occur globally per year [368].

Potential health impact

Direct health impact

Data on mortality and morbidity were taken from the IHME 2016 estimates. ***Shigella*** infection is associated with an estimated 212,000 deaths and 450,000 years lived with disability annually [31]. This source uses a defined methodology and is used in the global health community. The data can therefore be viewed with a reasonable level of confidence. Additional support comes from the GEMS study that found in sub-Saharan Africa and South Asia, ***Shigella*** infection was among the top four causes of potentially life-threatening diarrheal illness among children less than five years old brought to a center for treatment of diarrhea [363,369].

Scoring: Based on the above analysis, mortality was categorised as medium (score of 1 out of 2). Morbidity was categorised as high (score of 2 out of 2).

Secondary health impact

The secondary health impact of a ***Shigella*** vaccine is unclear; there is some debate regarding impact of diarrhoeal disease on growth trajectories for children, especially those with multiple diarrhoeal episodes [67,68]. However, it is possible that these children experience catch-up growth and return to normal growth trajectories [69].

Sub-population benefits

The groups who will benefit the most from a ***Shigella*** vaccine are those at greatest risk of infection: immunocompromised patients, including those with HIV and cancer patients; men who have sex with men; and young children.

Antibiotic use

First line treatment varies depending on regional resistance patterns but is typically a course of treatment with fluoroquinolone. Although treatment duration varies; a three-day course is typical [370].

Scoring: Based on the above analysis, antibiotic use was categorised as medium (score 1 out of 2). This estimate is based on an annual incidence of ~50 million Shigellosis cases treated with a three day course of antibiotics.

Urgency of AMR threat

Shigella is listed as 'medium' in the WHO priority list of R&D for new antibiotics and as a 'serious' threat in the CDC's list of biggest threats from AMR. In Asia and Africa, 65-85% of ***Shigella*** infections are resistant to nalidixic acid and trimethoprim-sulfamethoxazole, and 20-30% are resistant to fluoroquinolones [370]. A strain in Vietnam has displayed resistance to third generation cephalosporins and fluoroquinolones [370], and strains in Bangladesh requiring treatment with the last-line antibiotic meropenem have been reported [371].

Scoring: Based on the above analysis, AMR threat was categorised as medium (score of 1 out of 2),

Probability of R&D success

Pipeliness robustness

The pipeline for a ***Shigella*** vaccine includes a moderate number of candidates. A total of 19 vaccines are in development; 15 are in pre-clinical development, two are in Phase I, and two are in Phase II.

Experts strongly believe that a vaccine for ***Shigella*** will be successfully developed and marketed; however, given the length of time that development takes, it will likely be five to ten years before a vaccine is licensed. One expert notes "GSK has two different candidates in Phase II; however, a marketed vaccine is not expected earlier than in seven to 10 years, given that these vaccines candidates are still monovalent and will likely be optimised before progressing to late stage clinical trials" [28].

Scoring: Based on the above analysis, pipeline robustness was categorised as fairly high (score of 1.5 out of 2).

CURRENT PIPELINE *SHIGELLA* SPP.

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	08	02	-	-	-	10
Number of **commercial** vaccines	07	-	02	-	-	09
Total number of vaccines	15	02	02	-	-	19

Pathogen biology

Serotype-specific natural immunity is induced by infection. However, the large variety of ***Shigella*** species and serotypes (four major species and 50 different serotypes) make reinfections possible. Serum and mucosal antibody responses to ***Shigella*** are predominantly homologous responses directed against a serotype-specific ***Shigella*** LPS-associated O antigen [371]. Immune responses to ***Shigella*** are robust and lead to the induction of memory-B cell responses. However, evidence of their ability to cross-protect against diverse serotypes is inconclusive [371]. Furthermore, systemic and mucosal responses against conserved invasion plasmid antigens (Ipa B, Ipa D) do not seem to be very immunogenic in the natural setting [371]. It is therefore likely that multivalent vaccines will be needed to prevent shigellosis.

Because natural ***Shigella*** immunity is serotype-specific, LPS-associated O-specific polysaccharide (O-SP) antigens are logical possible vaccine targets. Targeting the O-SP antigens of ***S. flexneri*** 2a, 3a, and 6 as well as ***S. sonnei*** should cover the majority of all ***Shigella*** illnesses and protect against 64% of ***Shigella*** strains directly and 88% of all strains when considering cross-protection. One expert confirmed the value of this approach by explaining "The perfect strain selection depends a bit on your geographic location, but by covering four serotypes you could cover 75% of the cases" [28].

Scoring: Based on the above analysis, pathogen biology was categorised as fairly high (score of 1.5 out of 2).

Pre-clinical and clinical R&D

As humans are the only natural host for ***Shigella***, it has been difficult to establish predictive animal models. Several animal challenge models currently exist, but "none mirrors human infections well" [28] according to experts. Current models include a guinea pig keratoconjunctivitis model, a murine pulmonary model, a cynomolgus monkey ***S. dysenteriae*** 1 model, and a guinea pig and piglet oral and intrarectal challenge model. Immunoassays that can correlate clinical severity with immunological status also exist. Two types of assays are in development, one is an opsonophagocytic assay and the other is a serum bactericidal assay. Initial data from these models show feasibility for ***Shigella*** vaccine development.

Human controlled infection models have been established using either the ***S. sonnei*** strain 53G or the ***S. flexneri*** 2a strain 2457T. Given the lack of appropriate animal models, these have proven to be very useful for early assessment of vaccine efficacy [372–375]. However, experts caution that "the flipside is that challenge models slow vaccine development because people want to [use challenge models to] test in North American adults and not in kids who are affected" [28].

Field efficacy trials should be possible as incidence of ***Shigella*** infection is high in endemic regions, allowing for adequate trial enrollment. Also, a new quantitative PCR assay is available that is more sensitive than traditional culture methods. This will provide critical support for R&D efforts as traditional culture methods may have seriously underestimated the burden of ***Shigella***-associated illness [363].

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as high (score of 2 out of 2).

Probability of uptake

Expected policy stance

A ***Shigella*** vaccine would likely be offered as a routine childhood vaccination in endemic regions, predominately in low- and middle-income countries, and as an elective travellers' vaccine. Policymakers are likely to support a ***Shigella*** vaccine, primarily to reduce the high mortality burden, and WHO is currently preparing a ***Shigella*** vaccine pathways document [376]. An expert characterises the choice to support a ***Shigella*** vaccine as "straightforward because this is a high burden of disease that affects children" [28]. Experts acknowledge that enteric diseases have a massive impact on the development of AMR due to the high quantities of antimicrobials used in their treatment. Therefore, even a "partially efficacious vaccine that reduces the severity of the disease rather than preventing the disease could have a huge impact as patients would seek antimicrobial treatment less often".

Scoring: Based on the above analysis, the expected policy stance was categorised as high (score of 2 out of 2).

Likelihood of payer, government, or Gavi support

High-income countries would likely treat a ***Shigella*** vaccine similarly to the typhoid fever vaccine, which is recommended as a travellers' vaccine [360,377]. In middle-income countries the incidence and mortality of ***Shigella*** infection are high and governments and payers are likely to endorse a vaccine against ***Shigella***. The probability of investment by Gavi is high because of the high mortality of ***Shigella*** in low-income countries.

Scoring: Based on the above analysis, likelihood of payer, government, or Gavi support was categorised as high (score of 2 out of 2).

Barriers to uptake

Relatively few barriers will limit uptake of a ***Shigella*** vaccine. A vaccine would not require a new vaccination touchpoint, as it would likely be delivered as part of childhood vaccination programmes or travellers' vaccine appointment schedules. However, since the greatest burden of disease is in low-income countries, additional costs may be incurred for development of supply chain and storage. New clinical practices would not be required as childhood vaccines and travellers' vaccines are routinely recommended by clinicians.

Scoring: Based on the above analysis, barriers to uptake were categorised as fairly low (score of 1.5 out of 2).

Commercial attractiveness

Although this is not an inherently attractive commercial market, there is robust global health interest in a ***Shigella*** vaccine. Therefore, R&D is being subsidised by funders like the Gates Foundation and procurement will likely be supported by Gavi.

Scoring: Based on the above analysis, commercial attractiveness was categorised as medium (score of 1 out of 2).

Recommendations

Shigella falls into a cluster of pathogens for which bringing a vaccine to market is the priority.

Primary recommendation

The primary recommendation for ***Shigella*** is to accelerate clinical development. An expert states, "we should get the vaccine into kids [the target population] as quickly as possible, as only this data can really support a go or no-go decision" [28]. Key funders of enteric disease research should be encouraged to support large Phase III trials for promising clinical vaccine candidates. Given the lack of a strong commercial market, additional support via market shaping mechanisms should be considered to accelerate clinical development and help bring vaccines to market. Opportunities for funders to strategically coordinate efforts would allow them to pool resources and fund later-stage trials for ***Shigella***.

Secondary recommendations

Development of combination vaccines should be incentivised. ETEC vaccines were mentioned by experts as possible combination candidates, and in the longer term a combination vaccine could include other enteric diseases [28]. Funders should support R&D to explore combination potential given the strong policy interest in enteric vaccine combinations.

Staphylococcus aureus

Executive summary

Staphylococcus aureus (***S. aureus***) is a major cause of skin infections and, when invasive, can also cause more serious conditions, including endocarditis and pneumonia. ***S. aureus*** is associated with a significant disease burden, accounting for approximately 10% of pneumonia cases [33] and 30% of cellulitis cases [378]. Anti-microbial resistance (AMR) is a serious concern; methicillin-resistant ***Staphylococcus aureus*** (MRSA) is widespread and approximately 50% of all staphylococcus infections are now methicillin resistant [379,380] and the risk of horizontal gene transfer from other resistant pathogens is a serious concern.

No vaccine targeting ***S. aureus*** is currently available. Whilst development remains challenging with several recent failures, there is strong interest from industry in bringing a vaccine to market. The ***S. aureus*** vaccine pipeline comprises 27 candidates, with four in clinical development. However, specific challenges to development of a ***S. aureus*** vaccine have been identified, including a lack of natural immunity to ***S. aureus***, poor characterisation of vaccine targets and the lack of a reliable animal model. The need to target a variety of populations with a ***S. aureus*** vaccine also presents challenges to research and development.

The initial target population is likely to be elective surgery patients; however, beyond this initial group, the target population will include immunocompromised patients who are less likely to mount an effective immune response. A vaccine would likely see reasonable uptake in high- and middle-income countries because the high economic burden would drive a favourable cost-effectiveness assessment. However, uptake in low-income countries would likely require novel financing mechanisms as Gavi support is unlikely.

Recommendations

S. aureus falls into a cluster of pathogens for which advancing early R&D is the priority. The morbidity and mortality associated with ***S. aureus*** infection in high-income countries suggest there is an attractive market for a vaccine targeting high-risk groups, with significant commercially-driven activity. The primary recommendation

SCORECARD *STAPHYLOCOCCUS AUREUS*

Health impact:

Direct health impact

1.0	0.0
Mortality	Morbidity

Impact on AMR reduction

1.0	2.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
May allow more high-risk surgical procedures to be conducted

Sub-population benefits
Immunocompromised individuals
Individuals with chronic conditions
Surgical patients

Alternative interventions
Passive immunisation

Probability of R&D success:

0.5	1.0	1.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
None identified

Acceleration potential
Improve understanding of pathogen biology

Major barriers to development
Lack of good vaccine antigens

Probability of uptake:

2.0	1.0	2.0	1.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Those at high-risk of hospitalisation / High-risk groups such as pre-surgical patients, Uncertain potential for inclusion in routine vaccination schedules

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

is to pursue additional pre-clinical research in order to establish the feasibility of bringing an effective vaccine to market. Secondary recommendations comprise exploring alternative treatments or prevention strategies, such as monoclonal antibodies that induce passive immunity (although these face many of the same R&D development challenges as vaccines), developing a better understanding of the disease burden and epidemiology of ***S. aureus*** infection, especially in low- and middle-income countries, and improving the translatability of clinical ***S. aureus*** vaccine studies.

Pathogen overview

S. aureus is a Gram-positive commensal bacterium that is associated with both community- and hospital-acquired infections. ***S. aureus*** is commonly found on the skin or in the nasopharynx and can be transmitted through skin-to-skin contact [381]. The most common manifestations of ***S. aureus*** infection are cellulitis and lower respiratory tract infection, but it can affect a variety of organs and tissues, causing endocarditis, osteomyelitis, and septic arthritis [381,382].

Symptoms vary depending on the site of infection. Cellulitis typically manifests as local warmth, erythema, pain, and fever, while lower respiratory tract infection is associated with productive cough, shortness of breath, fever, tachypnoea, and reduced oxygen saturation.

Groups at high risk for ***S. aureus*** infection include populations with weakened immune systems, people with chronic conditions (including diabetes, cancer, HIV, vascular disease, eczema and lung disease), surgical patients, and both very young and elderly populations.

S. aureus infection has a global distribution, but there are some gaps in understanding of the specific disease epidemiology in low- and middle-income countries [383].

Potential health impact

Direct health impact

Global data on disease burden is not available from the IHME, WHO or in the research literature, but data suggests that ***S. aureus*** causes significant disease burden. Globally, ***S. aureus*** is responsible for approximately 30% of cases of cellulitis [384], 30% of cases of endocarditis [385], 10% of cases of pneumonia [33], and 3% of cases of meningitis [381]. Given the lack of direct data on the burden of ***S. aureus***, it is challenging to precisely assess the global burden with confidence. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was categorised as medium (score of 1 out of 2) and morbidity was categorised as low (score of 0 out of 2).

Secondary health impact

The secondary health impact of a ***S. aureus*** vaccine would likely be greatest for patients undergoing surgery. An effective vaccine may decrease the risk of post-operative infections, giving physicians greater confidence in recommending surgery where patients are likely to derive benefit. As one expert explains, "it is important to have vaccines for pathogens that are problematic in the hospital like Staph aureus" [28].

Sub-population benefits

The sub-populations most likely to benefit from a vaccine against ***S. aureus*** are immunocompromised individuals and those with chronic health conditions, amongst whom the infection is most severe [386]. Young children and the elderly may also benefit. Finally, because a significant portion of surgical site infections are caused by ***S. aureus*** [2] – resulting in prolonged hospital stays and increased morbidity and mortality – surgical patients would also benefit from a vaccine.

Antibiotic use

First-line antibiotic treatment for ***S. aureus*** infection includes penicillins and cephalosporins. The treatment course is typically seven days but varies depending on the specific condition. Treatment of endocarditis, for example, can require a one-month course of antibiotic treatment.

Scoring: Based on the above analysis, antibiotic use was categorised as medium (score 1 out of 2). This estimate is based on an annual incidence of ~35 million LRTIs treated with a seven day course of antibiotics, ~18 million cellulitis cases treated with a five day course of antibiotics and ~400,000 endocarditis cases treated with a one month course of antibiotics.

Urgency of AMR threat

The WHO and the CDC have both expressed concern about the future of ***S. aureus*** treatment. Both have placed methicillin-resistant ***S. aureus*** (MRSA) on their AMR watch lists, and the WHO has listed ***S. aureus*** as a 'high' priority for development of new antibiotics [6]. The CDC has also listed vancomycin resistant ***S. aureus*** (VRSA) as a 'concerning' threat [7].

MRSA was first reported shortly after the introduction of methicillin in 1961, but it was uncommon outside of a healthcare environment until the 1990s [387]. Methicillin resistance is now found in approximately 50% of all

staphylococcus infections [380]. Vancomycin is currently the main recourse for combating MRSA, but strains of ***S. aureus*** with reduced susceptibility to vancomycin have also developed. Vancomycin intermediate ***S. aureus*** (VISA) was first described in 1996 [388] and has now been documented across most of the globe [388–390]. Acquired vancomycin resistance is currently rare, but at least 14 cases of VRSA have been reported in the United States [391]. Furthermore, colonisation with MRSA and VRE is very common, and the potential for horizontal transfer of the ***vanA*** gene raises the risk of more extensive VRSA development [391]. Finally, resistance to daptomycin – a last line treatment for ***S. aureus*** – has been reported [392,393].

Scoring: Based on the above analysis, the urgency of AMR threat was categorised as high (score of 2 out of 2).

Probability of R&D success

Pipeline robustness

The ***S. aureus*** vaccine pipeline was categorised as weak. Although the ***S. aureus*** vaccine pipeline is relatively active – with one expert stating that "the Staph market is busy with several companies developing vaccines" – experts are predominately not optimistic about the probability of success for vaccines in the current pipeline. The pipeline comprises a total of 27 vaccine candidates: 23 in pre-clinical development, two in Phase I trials, and two in Phase II trials. However, despite strong commitment from industry, there are no marketed vaccines and experts agree that development will be difficult. The most advanced vaccines currently in development are Pfizer's four-antigen vaccine (SA4Ag), which is in a Phase II adaptive trial and has been granted FDA Fast Track designation, and NovaDigm's NDV-3, which is also in Phase II trials. The probability of success for these vaccines is unclear; notably, a Phase III trial of the Merck 710 vaccine was recently halted because of safety concerns (discussed in more detail in a subsequent section) [394]. One expert explains that whilst there is "at least 50/50 chance to get a vaccine to market, we've seen vaccines failing in late clinical trials and we don't know the reason why" [28].

Other experts believe that the number of vaccines in the ***S. aureus*** pipeline might not accurately reflect the state of knowledge about this pathogen. Having experienced expensive failures of promising vaccines, it is possible that the development of successful candidates now depends on better understanding of the pathogen and its interaction with hosts [395].

Scoring: Based on the above analysis, pipeline robustness was categorised as fairly low (score of 0.5 out of 2).

CURRENT PIPELINE *STAPHYLOCOCCUS AUREUS*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	08	-	-	-	-	08
Number of **commercial** vaccines	15	03	02	-	-	19
Total number of vaccines	23	03	02	-	-	28

Pathogen biology

S. aureus can exist within the normal human flora and has evolved a number of strategies to colonise and evade host immunity as a result [396]. Notably, prior ***S. aureus*** infection does not provide protection against re-infection [397], but infections among carriers may be less severe, indicating that prolonged colonisation leads to a limited form of immunity [398]. Adults typically have pre-existing ***S. aureus***-specific antibodies, including antibodies against capsule and clumping factor A, but these typically do not have opsonophagocytic or neutralising properties and do not provide protection against infection [386].

To date, candidates that have seemed promising in animal models have not yet demonstrated efficacy in human trials [386]. However, several vaccine targets have been identified. Vaccine candidates have targeted individual cell surface components, such as the ***S. aureus*** capsule and extracellular polysaccharides, and cell wall associated proteins including attachment proteins, invasion proteins, and receptors. Given the failure of single antigen approaches, vaccine development currently focuses on multi-antigen approaches. For example, Pfizer's SA4Ag candidate includes clumping factor A (ClfA), the manganese transport component (MntC), and capsular polysaccharides 5 and 8 conjugated to CRM_{197} [386].

Even with vaccine candidates identified, critical gaps in the understanding of pathogen biology persist. Mechanisms for phagocyte-mediated killing of ***S. aureus*** remain to be established and are likely essential for the development of a successful vaccine, as polysaccharides do not seem to be essential for colonisation or invasive disease. One expert emphasises that a clearer understanding of pathogen biology is needed to facilitate vaccine development, stating, "[the] biology of Staph aureus is incompletely understood […] in some areas you get more virulence […] and we don't understand why" [28].

Scoring: Based on the above analysis, pathogen biology was categorised as medium (score of 1 out of 2).

Pre-clinical and clinical R&D

Animal models exist for ***S. aureus*** infection and have provided some useful insights but also have important limitations. Whilst mouse models have proven extremely useful in determining the role of many virulence factors and identifying host pathways that contribute to infection, they do not appear to predict the success of vaccines in humans [387]. One reason for this could be that ***S. aureus*** produces a number of virulence factors that have high species specificity toward the human molecular counterpart they target [399]. The next generation of animal models may be more successful; humanised mice have been developed that have increased susceptibility to ***S. aureus***. However, even with improved animal models, some aspects of pathogen-host interactions require further investigation; notably, protective immunity against ***S. aureus*** is not completely understood [387].

Clinical development programmes for ***S. aureus*** will involve some key challenges. The initial target population for vaccination is patients presenting for elective surgeries. However, targeting only pre-surgical patients may not reduce infection rates as much as expected. These patients may have already been exposed to antibiotics, as well as chlorohexidine/murpirocin (fusidic acid) treatment in an attempt to reduce the risk of infection. Reducing this risk further may be difficult. Experts ask: "are we trying to reduce the irreducible?" [28]. Other high-risk groups comprise patients at high risk of infection, including immunocompromised patients and those with chronic conditions. Less healthy populations might have difficulties mounting an effective immune response after vaccination, and it is not clear that the findings from immunocompromised patients can be generalised to other high-risk groups. Experts explain, "with frail patients […] we may need something that is more potent than with other pathogens at the community level" [28].

The lack of established correlates of protection also poses some challenges to trial design; understanding what immune responses predict protection would help simplify outcome measures included in clinical trials.

In summary, additional investigations are needed to help guide clinical trial design. Prospective studies are needed across a number of different surgery procedures and comorbidities to refine a target population for clinical development of a ***S. aureus*** vaccine, and further studies of infection rates are needed to understand optimal trial design and identify the numbers needed to adequately power a trial to detect an effect [58].

Trials conducted in humans to date have yielded mixed results and provide reasons for both caution and optimism regarding the probability of developing an effective ***S. aureus*** vaccine. However, whilst experts express concerns including "I am very worried about the ***S. aureus*** vaccine," [28], both recent and planned future trials provide grounds for optimism, as one expert emphasises "I wouldn't give up [on a ***S. aureus*** vaccine]".

The recent failure of Merck's Phase III trial of its V710 vaccine highlights the difficulties in developing vaccines for ***S. aureus***. This trial was a double-blind, randomised, placebo-controlled trial among 8031 surgical patients aged 18 years or older who were scheduled for surgery involving full median sternotomy at 165 sites in 26 countries. The trial objective was to determine whether V710, administered

14-60 days prior to surgery, reduced postoperative ***S. aureus*** infection. The trial was halted after the second interim analysis because mortality rates in patients with staphylococcal infections were significantly higher in the intervention arm, though the difference in overall mortality between the trial arms was not statistically significant [394]. A subsequent analysis of the study results identified three coincident factors that predisposed patients to mortality: low pre-vaccination IL-2 levels, receipt of the V710 vaccine, and infection with ***S. aureus*** [400]. The identification of host factors that may adversely affect the safety of an ***S. aureus*** vaccine has contributed to experts' concerns that development of a safe and effective vaccine could prove challenging.

Subsequent trials of other vaccine candidates have provided reasons for optimism despite the need to discontinue the trial of V710. The four-antigen ***S. aureus*** candidate SA4Ag was examined in a Phase II trial initiated in 2015. This was a double-blind, placebo-controlled randomised trial to evaluate safety, dosing, and immunogenicity of the SA4Ag vaccine. The trial enrolled 454 healthy adults aged 18-85 years scheduled to undergo elective open spinal fusion surgery. Single dose vaccination safely induced an immune response that was durable through a 12-month follow-up period [401].

NovaDigm also has a candidate vaccine in clinical trials; the company announced its Phase IIa trial of NDV-3 in April 2018. This is a double-blind, placebo-controlled, randomised trial to evaluate safety, immunogenicity, and efficacy of NDV-3 in reducing nasal and oral acquisition of ***S. aureus***. NovaDigm plans to recruit approximately 400 United States Army Infantry trainees at Fort Benning, Georgia [402] with follow-up to occur throughout the 14-week training cycle to assess ***S. aureus*** colonisation status.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as medium (score of 1 out of 2).

Probability of uptake

Expected policy stance

The probable initial target population for an ***S. aureus*** vaccine will comprise those presenting for elective surgeries, with eventual expansion to other high-risk groups and routine vaccination in the elderly. Other high-risk groups comprise immune-compromised patients, individuals with chronic conditions, patients undergoing non-elective surgeries, and the very young. However, some experts suggest that a routine vaccination strategy "is more suitable [than a targeted approach]" [6]. Indeed, one expert notes that "the consequences of these intensive surgical procedures and the burden globally is so high that one, in the longer run, could accept universal immunisation" [28].

The WHO and CDC concur that the spread antimicrobial resistant strains of ***S. aureus*** is concerning. In 2016, the World Economic Forum published an article on vaccines for ***S. aureus***, highlighting acceptance that vaccination may contribute to containing the spread of the pathogen [28,403]. In general, experts suggest that there is a likelihood of policy support; with one stating that "the WHO would have to support a vaccine because their member states will have ***Staphylococcus aureus*** problems" [6]. However, following the meeting of the WHO's Product Development for Vaccines Advisory committee (PDVAC) meeting in 2017, no specific advocacy for the development of a ***S. aureus*** vaccine has arisen. Further, some experts suggest that barriers to identifying patients who may present for surgeries in a timely manner present a problem that would need to be overcome in order to garner support. One expert explains "the issue is, how do you vaccinate before people enter into the high-risk population?" [6].

Scoring: Based on the above analysis, the expected policy stance was characterised as medium (score of 1 out of 2).

Likelihood of payer, government, or Gavi support

Payers in high-income countries are likely to be willing to pay for a vaccine targeting ***S. aureus*** because of the costs associated with hospital-acquired ***S. aureus*** infections. Extensive media devoted to the pathogen and the high economic burden it presents may also drive a favourable cost-effectiveness assessment. Regulators also appear supportive and have agreed to adaptive trials to accelerate development in elective surgery patients [6]. However, regulatory barriers may exist regarding the burden of evidence needed to add new populations eligible for the vaccine, particularly if those populations are immunocompromised. Similarly, media attention and the likelihood of a favourable cost-effectiveness assessment suggest there may be support for vaccination against ***S. aureus*** in middle-income countries.

Support for a vaccine targeting ***S. aureus*** is unlikely in low-income countries. The evidence of disease burden in Gavi-eligible countries is likely insufficient for Gavi to make a positive investment decision. Therefore, Gavi support is unlikely, and novel financing mechanisms would be required.

Scoring: Based on the above analysis, likelihood of payer, government, or Gavi support was characterised as high (score of 2 out of 2).

Barriers to uptake

Some logistical factors will present some challenges to implementation of a vaccination programme. The initial target population – surgical patients – is in touch with healthcare services, and this is likely to drive adoption. However, a vaccination touchpoint would still need to be incorporated into the existing bundle of pre-surgical preparations, including the assessment of fitness for surgery. A new programme would need to be built for every high-risk population identified, as additional populations may have less contact with healthcare services or require a different type of touchpoint.

Scoring: Based on the above analysis, barriers to uptake were characterised as medium (score 1 out of 2).

Commercial attractiveness

Development of an ***S. aureus*** vaccine may be an attractive commercial opportunity given the burden of disease in high-income countries and increasing concerns about AMR. These factors provide what one expert described as "enormous motivation from pharma to reduce post-surgical severe Staph disease"[28].

Scoring: Based on the above analysis, commercial attractiveness was characterised as high (score 2 out of 2).

Recommendations

S. aureus falls into a cluster of pathogens for which advancing early R&D is the priority.

Primary recommendation

Investment in pre-clinical research will be critical for development of a vaccine against ***S. aureus***. Specific areas that warrant investigation are the identification of conserved non-capsular antigens that could be part of a multivalent vaccine, and the development of novel technologies such as mucosal adjuvants that are likely to facilitate vaccine development. Given the commensal nature of the pathogen, pre-clinical research should also seek to better understand the potential effect of vaccines on nasal flora.

Secondary recommendations

Alternative treatments for ***S. aureus*** infection merit exploration. In particular, the induction of passive immunity using monoclonal antibodies or other approaches may help to overcome the challenges involved in developing vaccines for hospital-acquired infections. These include the immunocompromised nature of many hospital patients, and the resultant reduced probability of mounting an effective immune response to a vaccine. Further, as many hospital admissions are unplanned, and vaccines require significant lead times to allow for the development of immunity, passive immunity may be preferred. However, development of monoclonal antibodies is costly and many of the development challenges are the same as for vaccines, including cost and the need to identify appropriate antigens.

A clearer understanding of the epidemiology and disease burden at a global and regional level with a specific focus on the burden of ***S. aureus*** infection in low-income countries and middle-income countries would help inform policy-making. Currently, no WHO or IHME estimates exist for ***S. aureus*** and little is known about the incidence and burden of ***S. aureus*** in low-income countries and newly industrialised regions. Experts believe that in these regions ***S. aureus*** has a similar impact to that seen in high-income countries [28], but existing studies in these regions yield diverse estimates that are likely to be confounded by incomplete case ascertainment. Greater clarity is therefore needed to characterise the potential cost-effectiveness of an ***S. aureus*** vaccine.

Given that current animal models do not appear to predict the success of vaccines in humans, it is also recommend that development of next-generation humanised animal models that promise to better mirror human disease and improve candidate translatability in early clinical trials is prioritised.

Streptococcus pneumoniae

Executive summary

The IHME estimates that ***Streptococcus pneumoniae*** (***S. pneumoniae***) is responsible for 1.2 million deaths and approximately 900,000 years lived with disability annually from pneumonia and meningitis. In addition, ***S. pneumoniae*** is responsible for an estimated 36% of the global burden of pneumonia and 27% of the global burden of otitis media. In aggregate, ***S. pneumoniae*** infection is associated with high mortality and morbidity.

Effective vaccines are available but global coverage remains low at ~40% [404], primarily due to high cost per dose. Polysaccharide conjugate vaccines (PCVs), such as PCV13 (Prevnar), are part of routine infant vaccination schedules in many high and middle-income countries and have excellent efficacy. However, high cost limits their use globally [405–407]. Coverage is particularly low in India and China [408,409]. By the end of 2016, Gavi had approved support for PCV introduction in 59 countries and plans to extend support, aided by an advance market commitment [410].

Current R&D aims to develop lower cost platforms and manufacturing, as well as to increase serotype coverage. The Serum Institute of India is developing a cheaper PCV vaccine which would potentially lower cost barriers and improve coverage [411].

Recommendations

S. pneumoniae falls into a cluster of pathogens for which the priority is to increase vaccine uptake. The greatest opportunity for tackling ***S. pneumoniae*** infection lies in increasing uptake. Therefore, the primary recommendation is to drive increases in equitable coverage with the existing vaccines. The secondary recommendation is to invest in pre-clinical research to help reduce costs and increase serotype coverage.

SCORECARD *STREPTOCOCCUS PNEUMONIAE*

Health impact:

Direct health impact

2.0	2.0
Mortality	Morbidity

Impact on AMR reduction

2.0	1.0
Antibiotic use	Urgency of AMR threat

Secondary health impact
Evidence of herd protection since introduction of routine PCV vaccination programmes

Sub-population benefits
Immunocompromised individuals
Pregnant women
Children

Alternative interventions
None identified

Probability of R&D success:

2.0	2.0	2.0
Pipeline robustness	Pathogen biology	Pre-clinical and clinical R&D

Combination potential
None identified

Acceleration potential
Not applicable; vaccines on market

Major barriers to development
Not applicable; vaccines on market

Probability of uptake:

2.0	2.0	2.0	1.0
Commercial attractiveness	Expected policy stance	Payer, government or Gavi support	Barriers to uptake

Who needs the vaccine / Potential vaccination strategy
Global population / Routine vaccination in first year of life

Note: The pathogens were scored on a scale of 0 to 2 on key indicators of health impact, probability of R&D success and probability of uptake. Scores of 0 represent the lowest possible score (e.g. low health impact, probability of R&D success or probability of uptake), whilst scores of 2 represent the highest possible score (e.g. high health impact, probability of R&D success or probability of uptake). Sections of the scorecard that did not receive a numerical score were assessed qualitatively.

Pathogen overview

S. pneumoniae is a Gram-positive bacterium often found as a commensal in the upper respiratory tract. Globally, most children will acquire ***S. pneumoniae*** in their nasopharynx in early life [412–416]. ***S. pneumoniae*** is transmitted through contact with respiratory droplets from patients or carriers. The most common manifestations are pneumonia and otitis media, but ***S. pneumoniae*** infection can also result in meningitis and sinusitis. Symptoms of pneumonia caused by ***S. pneumoniae*** include fever, chest pain, cough, rusty sputum, dyspnoea, tachypnoea/tachycardia, and hypoxia; otitis media caused by S. pneumonia manifests as ear pain, hearing difficulties, swollen ear drum, and fever.

Groups at risk of S. pneumonia infection include children under 5 years, particularly those under two years, and adults over 65 years. ***S. pneumoniae*** has a global distribution; however, in 2015 half of global pneumococcal deaths occurred in only four countries in Africa and Asia (India, Nigeria, the Democratic Republic of the Congo, and Pakistan) [417].

Potential health impact

Direct health impact

Robust global data on disease burden related to all ***S. pneumoniae***-associated infections is not available. IHME estimates for mortality and morbidity from pneumococcal meningitis and pneumococcal pneumonia are available for 2016. In 2016, pneumococcal meningitis was estimated to be responsible for 23,000 deaths and 600,000 years lived with disability and pneumococcal pneumonia was estimated to be responsible for 300,000 deaths and 1.2 million years lived with disability [31]. No robust global data is available for otitis media but a review of the literature suggests that ***S. pneumoniae*** is responsible for 27% of acute otitis media globally [418]. Taken together, this evidence suggests that ***S. pneumoniae*** infection causes significant health impact.

As mentioned, no publications report total mortality and morbidity for this pathogen, but ***S. pneumoniae*** mortality and morbidity from meningitis and pneumonia are reported by the IHME. This data source has an accepted methodology and is used in the global health community. In this assessment, IHME morbidity estimates were combined with estimates for the percentage of otitis media caused by ***S. pneumoniae*** infection taken from the literature. This estimate may be less precise than the IHME estimate. A full methodology for this assessment can be found in the appendix.

Scoring: Based on the above analysis, mortality was categorised as high (score of 2 out of 2) and morbidity was categorised as high (score of 2 out of 2).

Secondary health impact

There is significant evidence of herd protection for ***S. pneumoniae***. Vulnerable populations, including the elderly, benefit from the vaccination of infants, who are the primary reservoir of ***S. pneumoniae*** [419].

Sub-population benefits

Vaccines against ***S. pneumoniae*** particularly benefit children, pregnant women, and immunocompromised populations, including those with HIV.

Antibiotic use

Typical first-line antibiotic treatment includes beta-lactams and cephalosporins [420]. The treatment course varies depending on the specific condition; a typical course of antibiotics is seven days, but treatment for meningitis is usually longer. Antibiotic use is driven by acute otitis media and lower respiratory tract infection as these are the most common ***S. pneumoniae*** infections. The widespread use of antibiotics to treat these infections makes ***S. pneumoniae*** an attractive target for broader vaccine coverage, as one expert notes "the vaccine that would have the highest impact on antibiotic use would be ***S. pneumoniae***"[28].

Scoring: Based on the above analysis, antibiotic use was categorised as high (score of 2 out of 2). This estimate is based on an annual incidence of ~120 million LRTIs treated with a one week course of antibiotics, ~0.5 million meningitis cases treated with a two-week course of antibiotics and ~ 120 million acute otitis media cases treated with a one week course of antibiotics.

Urgency of AMR threat

The WHO and CDC have both expressed concern about the future of ***S. pneumoniae*** treatment. ***S. pneumoniae*** is listed as "medium" in the WHO priority list of R&D for new antibiotics and listed as a "serious" threat in the CDC list of biggest threats from AMR. Resistance to first-line penicillin varies by region from approximately 2% in the United States to up to 70% in Vietnam [421,422]. In 30% of severe cases, ***S. pneumoniae*** is fully resistant to one or more clinically relevant antibiotics [7].

Scoring: Based on the above analysis, the urgency of AMR threat was categorised as medium (score 1 out of 2)

Probability of R&D success

Pipeline robustness

The pipeline for development of vaccines against ***S. pneumoniae*** is robust, comprising a total of 56 vaccines, including seven marketed vaccines. Those still in development include 31 vaccines in pre-clinical studies, seven in Phase I, eight in Phase II, and three in Phase III.

Scoring: Based on the above analysis, pipeline robustness was categorised as high (score of 2 out of 2).

Profile and impact of current vaccines

The marketed vaccine PCV13 (Prevnar) provides a precedent for ***S. pneumoniae*** vaccine development. The overall vaccine efficacy of ≥1 dose of the 13 valent pneumococcal conjugate vaccine (PCV13) for preventing invasive pneumococcal disease due to vaccine serotypes is ~76% [423]. Overall vaccine efficacy is estimated to be 90% when ≥2 doses are given before 12 months of age, two doses are given on or after 12 months of age, or one dose is given on or after 24 months of age [423].

Whilst PCV13 is highly effective, in areas where the vaccine is widely used non-vaccine serotypes of ***S. pneumoniae*** increase in prevalence to fill the ecological niche that has been vacated by vaccine serotypes [424]. Experts acknowledge this, stating "we are seeing some serotype shifting in response to Prevnar and the challenge is to continue to expand coverage against additional serotypes" [28]. However, as noted by another expert, "[the] more virulent strains are the ones we try to include in our vaccine," [28]. Thus, the strains that increase in prevalence in response to vaccination may be less virulent.

Pathogen biology

Partial strain-specific natural immunity to ***S. pneumoniae*** is known to be possible [425–427]. However, the immune response to ***S. pneumoniae*** infection is still not entirely understood. It appears to be complex and multi-layered, and defence mechanisms include both cellular and secreted components of the immune system [425–427].

Vaccine targets for ***S. pneumoniae*** are well-characterised. Polysaccharides are established targets with a decades-long history of effective use in ***S. pneumoniae*** vaccines [428]. Conjugated vaccines (polysaccharides covalently bound to diphtheria toxoid) induce a more robust and long-lasting immune response [429]. Existing vaccines target a range of specific ***S. pneumoniae*** serotypes. However, a conserved antigen-based vaccine capable of inducing cross-strain immunity would address serotype shifts but has not yet been developed [428,430].

Scoring: Based on the above analysis, pathogen biology was categorised as high (score of 2 out of 2).

CURRENT PIPELINE *STREPTOCOCCUS PNEUMONIAE*

	Research / Pre-clinical	Phase I	Phase II	Phase III	Marketed	Total
Number of **academic** vaccines	07	01	-	-	-	08
Number of **commercial** vaccines	24	06	08	03	07	48
Total number of vaccines	31	07	08	03	07	56

Pre-clinical and clinical R&D

Animal models currently in use for pre-clinical ***S. pneumoniae*** research are well-established and have solid predictive capacity for clinical programmes. Characteristics of pneumococcal pneumonia, sepsis, and meningitis have successfully been reproduced in mice, rats, and rabbits [431]. Models for otitis media are also available and include the chinchilla [432], gerbil [433], and rat [434]. All of these models continue to be helpful tools in elucidating aspects of disease pathogenesis, characterising innate and adaptive immune responses to ***S. pneumoniae***, and testing the efficacy of antibiotics and other therapies, as well as potential vaccine candidates. Pre-clinical research is also facilitated by the identification of correlates of protection for ***S. pneumoniae*** [435].

Clinical research and development benefits substantially from prior vaccine development for ***S. pneumoniae***. Intranasal challenge studies are possible for ***S. pneumoniae*** [436], and trial infrastructure is in place. Efficacy trials for vaccines have been conducted previously, as have effectiveness studies [417]. However, some limitations do exist; whilst correlates of protection have been identified, serotype-specific correlates of protection vary widely [437]. Also, the relationship between IgG concentration after priming and long-term protection needs to be better understood [438]. Finally, diagnostics for surveillance still rely heavily on insensitive culture techniques, and new methods such as PCR and proteomics are needed.

Scoring: Based on the above analysis, pre-clinical and clinical R&D was categorised as high (score of 2 out of 2).

Probability of uptake

Expected policy stance

The target population for vaccination is infants and the vaccination is included in the routine vaccination schedule. The WHO recommends three primary doses, or two primary doses and a booster. The WHO recommends the inclusion of PCV as a priority in childhood immunisation programmes worldwide, particularly in countries with high mortality in children under 5 (>50/1000 live births) [439].

Scoring: Based on the above analysis, expected policy stance was categorised as high (score of 2 out of 2).

Payer, government, or Gavi support

Conjugated PCV vaccines are included in routine vaccination schedules in high- and middle-income countries and in some low-income countries. More than 50 Gavi countries have introduced PCV vaccines into their routine programmes [440]. In 2007 Gavi announced a pilot Advance Market Commitment (AMC) for funding these vaccines. The AMC was officially launched in 2009 and has helped result in coverage for Gavi countries being similar to the global average [404,440,441]. However, there is a lack of support in some middle-income countries, particularly in India and China. Both countries have PCV vaccination rates below 10% [408,409]. In China, PCV has not been integrated into the Chinese Expanded Program on Immunization, so individuals have to pay for pneumococcal vaccination themselves [442]. In India, local manufacturing at scale is likely to emerge. The Serum Institute of India is developing a 10-valent vaccine [411]. In both countries, in-country development of production capabilities for PCVs is ongoing, which will likely provide vaccines at a lower price point.

Scoring: Based on the analysis described above, payer, government, or Gavi support was categorised as high (score of 2 out of 2).

Barriers to uptake

The high price point of marketed ***S. pneumoniae*** vaccines has been a key challenge to expanding vaccination coverage. Current coverage is estimated at ~40% worldwide [404]. This is heavily driven by the high cost of the vaccine, which affects low-income countries and those "graduating" from Gavi support. According to one expert "lower cost multivalent vaccines could make a huge difference in uptake" [28]. For example, the PCV13 vaccine is produced using an established method, production costs are comparatively high and globally produced quantities are still low. There is a trend toward more cost-efficient production and the Serum Institute of India is collaborating with PATH to develop an affordable 10-valent PCV, focusing on the serotypes prevalent in 70% of the affected population (Asia, Africa, LAC, India) [411].

S. pneumoniae vaccination uses established vaccination touchpoints [1]. However, some logistical challenges to implementing a vaccination programme for ***S. pneumoniae*** exist. In addition to the cost of the vaccine, lack of evidence regarding the country-specific burden of ***S. pneumoniae*** infection and lack of local expertise in economic evaluation contribute to low current coverage rates. Child outmigration, travel distance to healthcare centres, low maternal education and low socio-economic status are also associated with reduced uptake [443]. Also, many countries do not have effective catch-up campaigns in place [407].

Scoring: Based on the above analysis, barriers to uptake was characterised as medium (score of 1 out of 2).

Commercial attractiveness

In this assessment, commercial attractiveness has been categorised as high, reflecting the commercial success of ***S. pneumoniae*** vaccines. Overall, the global pneumococcal vaccine market size was estimated to be $7 billion in 2017 [444].

Scoring: Based on the above analysis, commercial attractiveness was characterised as high (score of 2 out of 2).

Recommendations

S. pneumoniae falls into a cluster of pathogens for which the priority is to increase vaccine uptake.

Primary recommendation

The primary recommendation is to drive equity and coverage for ***S. pneumoniae*** vaccination. Current coverage in India and China is particularly low. In India, efforts should be made to accelerate local production and to invest in infrastructure for delivery. Ensuring better delivery is likely to increase coverage, as 62% of children aged 12-23 months received all basic vaccinations in 2015-2016 – a substantially higher proportion than those currently vaccinated against ***S. pneumoniae***. In China, local production should be developed, and the inclusion of vaccination against ***S. pneumoniae*** in the Expanded Program on Immunisation schedule should be explored. This would allow in-country manufacturers to plan vaccine production on a more secure demand level.

Secondary recommendation

The secondary recommendation is to invest in pre-clinical research. Whilst marketed vaccines exist, pre-clinical research could improve on existing vaccines and facilitate the development of vaccines that are cheaper to produce. Additional pre-clinical research could also address serotype shifts resulting from vaccine pressure by facilitating development of a conserved antigen-based vaccine that can induce cross-strain immunity; such a vaccine has not been developed to date. Pre-clinical research should also continue to support serotype expansion and serotype replacement, given the variation in serotype distribution across geographies. Finally, serotype-specific correlates of protection vary widely, and the relationship between IgG concentration after priming and long-term protection needs to be better understood.

Bibliography and Acknowledgements

Bibliography

1. O'Neill, J. Tackling drug-resistant infections globally: final report and recommendations. *Rev. Antimicrob. Resist.* (2016). doi:10.1016/j.jpha.2015.11.005

2. Jansen, K. U., Knirsch, C. & Anderson, A. S. The role of vaccines in preventing bacterial antimicrobial resistance. *Nat. Med.* **24,** 10–19 (2018).

3. Laxminarayan, R. *et al.* Access to effective antimicrobials: a worldwide challenge. *Lancet* **387,** 168–175 (2016).

4. Thompson, A. *et al.* Safety of 13-valent pneumococcal conjugate vaccine in infants and children: Meta-analysis of 13 clinical trials in 9 countries. *Vaccine* (2013). doi:10.1016/j.vaccine.2013.08.025

5. Davis, M. M. *et al.* Failure-to-success ratios, transition probabilities and phase lengths for prophylactic vaccines versus other pharmaceuticals in the development pipeline. *Vaccine* **29,** 9414–9416 (2011).

6. World Health Organisation. *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics*. (2017).

7. US Department of Health and Human Services. Centres for Disease Control and Prevention. *Antibiotic resistance threats in the United States*. (2013).

8. Rappuoli, R., Bloom, D. E. & Black, S. Deploy vaccines to fight superbugs. *Nature* **552,** 165–167 (2017).

9. FDA. *Guidance for Industry #213. http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM299624.pdf* (2013).

10. Wanted: a reward for antibiotic development. *Nat. Biotechnol.* **36,** 555–555 (2018).

11. CDC - Centers for Disease Control and. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. *MMWR. Morb. Mortal. Wkly. Rep.* (2005). doi:mm5436a1 [pii]

12. Kingwell, K. Vaccines take a shot at antimicrobial resistance. *Nat. Rev. Drug Discov.* **17,** 229 (2018).

13. Kennedy, D. A. & Read, A. F. Why does drug resistance readily evolve but vaccine resistance does not? *Proc. R. Soc. B Biol. Sci.* (2017). doi:10.1098/rspb.2016.2562

14. Avorn, J. The $2.6 Billion Pill — Methodologic and Policy Considerations. *N. Engl. J. Med.* **372,** 1877–1879 (2015).

15. Plotkin, S., Robinson, J. M., Cunningham, G., Iqbal, R. & Larsen, S. *The complexity and cost of vaccine manufacturing – An overview*. *Vaccine* **35,** 4064–4071 (2017).

16. Kotloff, K. L. *et al.* Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): A prospective, case-control study. *Lancet* (2013). doi:10.1016/S0140-6736(13)60844-2

17. Miller, M. *et al.* The MAL-ED study: A multinational and multidisciplinary approach to understand the relationship between enteric pathogens, malnutrition, gut physiology, physical growth, cognitive development, and immune responses in infants and children up to 2 years of . *Clin. Infect. Dis.* (2014). doi:10.1093/cid/ciu653

18. Havelaar, A. H. *et al.* World Health Organization Global Estimates and Regional Comparisons of the Burden of Foodborne Disease in 2010. *PLOS Med.* **12,** e1001923 (2015).

19. Hay, S. I. *et al.* Measuring and mapping the global burden of antimicrobial resistance. *BMC Med.* **16,** 78 (2018).

20. Lipsitch, M. & Siber, G. R. How can vaccines contribute to solving the antimicrobial resistance problem? *MBio* **7,** (2016).

21. Sherman, R. E. *et al.* Real-World Evidence — What Is It and What Can It Tell Us? *N. Engl. J. Med.* **375,** 2293–2297 (2016).

22. Bruxvoort, K., Sy, L. S., Luo, Y. & Tseng, H. F. Real-World Evidence for Regulatory Decisions: Concomitant Administration of Zoster Vaccine Live and Pneumococcal Polysaccharide Vaccine. *Am. J. Epidemiol.* (2018). doi:10.1093/aje/kwy076

23. Adegoke, A. A., Mvuyo, T. & Okoh, A. I. Ubiquitous Acinetobacter species as beneficial commensals but gradually being emboldened with antibiotic resistance genes. *J. Basic Microbiol.* **52,** 620–7 (2012).

24. Acinetobacter infection: Epidemiology, microbiology, pathogenesis, clinical features, and diagnosis - UpToDate. Available at: https://www.uptodate.com/contents/acinetobacter-infection-epidemiology-microbiology-pathogenesis-clinical-features-and-diagnosis. (Accessed: 30th July 2018)

25. Clinical presentation and diagnostic evaluation of ventilator-associated pneumonia - UpToDate. Available at: https://www.uptodate.com/contents/clinical-presentation-and-diagnostic-evaluation-of-ventilator-associated-pneumonia. (Accessed: 31st July 2018)

26. Acute complicated urinary tract infection (including pyelonephritis) in adults - UpToDate. Available at: https://www.uptodate.com/contents/acute-complicated-urinary-tract-infection-including-pyelonephritis-in-adults. (Accessed: 30th July 2018)

27. Yakupogullari, Y. *et al.* Is airborne transmission of Acinetobacter baumannii possible: A prospective molecular epidemiologic study in a tertiary care hospital. *Am. J. Infect. Control* **44,** 1595–1599 (2016).

28. Expert interview.

29. Peleg, A. Y., Seifert, H. & Paterson, D. L. Acinetobacter baumannii: emergence of a successful pathogen. *Clin. Microbiol. Rev.* **21,** 538–82 (2008).

30. Serota, D. P., Sexton, M. E., Kraft, C. S. & Palacio, F. Severe Community-Acquired Pneumonia due to Acinetobacter baumannii in North America: Case Report and Review of the Literature. *Open forum Infect. Dis.* **5,** ofy044 (2018).

31. IHME data.

32. WHO.

33. Gadsby, N. J. *et al.* Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia. *Clin. Infect. Dis.* **62,** 817–823 (2016).

34. Simonsen, K. A., Anderson-Berry, A. L., Delair, S. F. & Davies, H. D. Early-Onset Neonatal Sepsis. *Clin. Microbiol. Rev.* **27,** 21–47 (2014).

35. Tsai, W.-C. *et al.* Clinical characteristics, pathogens implicated and therapeutic outcomes of mixed infection in adult bacterial meningitis. *Kaohsiung J. Med. Sci.* **28,** 531–537 (2012).

36. Custovic, A. *et al.* Epidemiological Monitoring of Nosocomial Infections Caused by Acinetobacter Baumannii. *Med. Arch.* **68,** 402 (2014).

37. Marais, E., de Jong, G., Ferraz, V., Maloba, B. & Dusé, A. G. Interhospital transfer of pan-resistant Acinetobacter strains in Johannesburg, South Africa. *Am. J. Infect. Control* **32,** 278–281 (2004).

38. Saleem, A. F., Ahmed, I., Mir, F., Ali, S. R. & Zaidi, A. K. Pan-resistant Acinetobacter infection in neonates in Karachi, Pakistan. *J. Infect. Dev. Ctries.* **4,** 30–7 (2009).

39. Oikonomou, O. *et al.* Rapid dissemination of colistin and carbapenem resistant Acinetobacter baumannii in Central Greece: mechanisms of resistance, molecular identification and epidemiological data. *BMC Infect. Dis.* **15,** 559 (2015).

40. Evaluate Pharma.

41. PharmaProjects.

42. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/. (Accessed: 24th July 2018)

43. Qiu, H. *et al.* Host resistance to intranasal Acinetobacter baumannii reinfection in mice. *Pathog. Dis.* **74,** ftw048 (2016).

44. Ahmad, T. A., Tawfik, D. M., Sheweita, S. A., Haroun, M. & El-sayed, L. H. Trials in Vaccinology Development of immunization trials against Acinetobacter baumannii. *Trials Vaccinol.* **5,** 53–60 (2016).

45. Chiang, M. *et al.* Identification of novel vaccine candidates against Acinetobacter baumannii using reverse vaccinology. *Hum. Vaccin. Immunother.* **5515,** (2015).

46. Harris, G., KuoLee, R., Xu, H. H. & Chen, W. Mouse Models of Acinetobacter baumanniiInfection. *Curr. Protoc. Microbiol.* **46,** 6G.3.1-6G.3.23 (2017).

47. Demirjian, A. & Levy, O. Safety and efficacy of neonatal vaccination. *Eur. J. Immunol.* **39,** 36–46 (2009).

48. Morris, M. C. & Surendran, N. Neonatal Vaccination: Challenges and Intervention Strategies. *Neonatology* **109,** 161–9 (2016).

49. Warfel, J. M., Papin, J. F., Wolf, R. F., Zimmerman, L. I. & Merkel, T. J. Maternal and neonatal vaccination protects newborn baboons from pertussis infection. *J. Infect. Dis.* **210,** 604–10 (2014).

50. Ginsburg, A. S., Meulen, A. S.-T. & Klugman, K. P. Prevention of neonatal pneumonia and sepsis via maternal immunisation. *Lancet. Glob. Heal.* **2,** e679-80 (2014).

51. Can I have vaccinations when I'm pregnant? - NHS. UK. Available at: https://www.nhs.uk/conditions/pregnancy-and-baby/vaccinations-pregnant/. (Accessed: 6th August 2018)

52. Perez, F. & Bonomo, R. A. Vaccines for Acinetobacter baumannii: thinking "out of the box" *Vaccine* **32,** 2537–9 (2014).

53. Nielsen, T. B. *et al.* Monoclonal Antibody Protects Against Acinetobacter baumannii Infection by Enhancing Bacterial Clearance and Evading Sepsis. *J. Infect. Dis.* **216,** 489–501 (2017).

54. LaVergne, S. *et al.* Phage Therapy for a Multidrug-Resistant Acinetobacter baumannii Craniectomy Site Infection. *Open Forum Infect. Dis.* **5,** (2018).

55. Reindel, R. & Fiore, C. R. Phage Therapy: Considerations and Challenges for Development. *Clin. Infect. Dis.* **64,** 1589–1590 (2017).

56. Enne, V. I., Personne, Y., Grgic, L., Gant, V. & Zumla, A. Aetiology of hospital-acquired pneumonia and trends in antimicrobial resistance. *Curr. Opin. Pulm. Med.* **20,** 252–8 (2014).

57. Helal, S., El Anany, M., Ghaith, D. & Rabeea, S. The Role of MDR-Acinetobacter baumannii in Orthopedic Surgical Site Infections. *Surg. Infect. (Larchmt).* **16,** 518–22 (2015).

58. Aiken, A. M. *et al.* Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. *Lancet* **378,** 2021–2027 (2011).

59. Clinical manifestations, diagnosis, and treatment of Campylobacter infection - UpToDate. Available at: https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-treatment-of-campylobacter-infection. (Accessed: 2nd August 2018)

60. Clinical manifestations, diagnosis, and treatment of Campylobacter infection - UpToDate.

61. The Bill and Melinda Gates Foundation. Campylobacter spp. Transmission Dynamics in Low- and Middle-Income Countries. (2018). Available at: https://gcgh.grandchallenges.org/challenge/campylobacter-spp-transmission-dynamics-low-and-middle-income-countries. (Accessed: 6th August 2018)

62. Kaakoush, N. O., Castaño-Rodríguez, N., Mitchell, H. M. & Man, S. M. Global Epidemiology of Campylobacter Infection. *Clin. Microbiol. Rev.* **28,** 687–720 (2015).

63. Manfredi, R., Calza, L. & Chiodo, F. Enteric and disseminated campylobacter species infection during HIV disease: a persisting but significantly modified association in the HAART era. *Am. J. Gastroenterol.* **97,** 510–511 (2002).

64. IHME.

65. Lecuit, M. *et al.* Immunoproliferative small intestinal disease associated with Campylobacter jejuni. *N. Engl. J. Med.* **350,** 239–48 (2004).

66. Baginsky, L. A. *et al.* Campylobacter jejuni Infection in Intestinal Lymphoma: A Strong Association with Immunoproliferative Small Intestinal Disease. *Blood* **104,** (2004).

67. Guerrant, R. L., DeBoer, M. D., Moore, S. R., Scharf, R. J. & Lima, A. A. M. The impoverished gut--a triple burden of diarrhoea, stunting and chronic disease. *Nat. Rev. Gastroenterol. Hepatol.* **10,** 220–9 (2013).

68. MAL-ED. Relationship between growth and illness, enteropathogens and dietary intakes in the first 2 years of life: findings from the MAL-ED birth cohort study. *BMJ Glob. Heal.* **2,** e000370 (2017).

69. Richard, S. A. *et al.* Catch-up growth occurs after diarrhea in early childhood. *J. Nutr.* **144,** 965–71 (2014).

70. Kaakoush, N. O., Castaño-Rodríguez, N., Mitchell, H. M. & Man, S. M. Global Epidemiology of Campylobacter Infection. *Clin. Microbiol. Rev.* **28,** 687–720 (2015).

71. Riddle, M. S. & Guerry, P. Status of vaccine research and development for Campylobacter jejuni. *Vaccine* **34,** 2903–2906 (2016).

72. Bolick, D. T. *et al.* The Critical Role of Zinc in a New Murine Model of Enterotoxigenic E. coli (ETEC) Diarrhea. *Infect. Immun.* **86,** e00183-18 (2018).

73. WHO. The global view of campylobacteriosis Report of an expert consultation. (2014).

74. Kirk, M. D. *et al.* World Health Organization Estimates of the Global and Regional Disease Burden of 22 Foodborne Bacterial, Protozoal, and Viral Diseases, 2010: A Data Synthesis. *PLOS Med.* **12,** e1001921 (2015).

75. Gordon, M. A. Invasive nontyphoidal Salmonella disease: epidemiology, pathogenesis and diagnosis. *Curr. Opin. Infect. Dis.* **24,** 484–9 (2011).

76. Facciolà, A. *et al.* Campylobacter: from microbiology to prevention. *J. Prev. Med. Hyg.* **58,** E79–E92 (2017).

77. Kobierecka, P. A. *et al.* Chicken Anti-Campylobacter Vaccine - Comparison of Various Carriers and Routes of Immunization. *Front. Microbiol.* **7,** 740 (2016).

78. Gregorio, G. V, Gonzales, M. L. M., Dans, L. F. & Martinez, E. G. Polymer-based oral rehydration solution for treating acute watery diarrhoea. *Cochrane Database Syst. Rev.* **12,** CD006519 (2016).

79. Lazzerini, M. & Wanzira, H. Oral zinc for treating diarrhoea in children. *Cochrane Database Syst. Rev.* **12,** CD005436 (2016).

80. Bolick, D. T. *et al.* The Critical Role of Zinc in a New Murine Model of Enterotoxigenic E. coli (ETEC) Diarrhea. *Infect. Immun.* **86,** e00183-18 (2018).

81. Giallourou, N. *et al.* A novel mouse model of Campylobacter jejuni enteropathy and diarrhea. *PLoS Pathog.* **14,** e1007083 (2018).

82. Flores-Mireles, A. L., Walker, J. N., Caparon, M. & Hultgren, S. J. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat. Rev. Microbiol.* **13,** 269–284 (2015).

83. Rodríguez, J. M. *et al.* The composition of the gut microbiota throughout life, with an emphasis on early life. *Microb. Ecol. Health Dis.* **2,** 26050 (2015).

84. Infections due to Serratia species - UpToDate. Available at: https://www.uptodate.com/contents/infections-due-to-serratia-species. (Accessed: 1st August 2018)

85. Davin-Regli, A. & Pagès, J.-M. Enterobacter aerogenes and Enterobacter cloacae; versatile bacterial pathogens confronting antibiotic treatment. *Front. Microbiol.* **6,** 392 (2015).

86. Schaffer, J. N. & Pearson, M. M. Proteus mirabilis and Urinary Tract Infections. *Microbiol. Spectr.* **3,** (2015).

87. Wie, S.-H. Clinical significance of Providencia bacteremia or bacteriuria. *Korean J. Intern. Med.* **30,** 167–9 (2015).

88. Singla, N., Kaistha, N., Gulati, N. & Chander, J. Morganella morganii could be an important Intensive Care Unit pathogen. *Indian J. Crit. Care Med.* **14,** 154–5 (2010).

89. Epidemiology, pathogenesis, microbiology, and diagnosis of hospital-acquired and ventilator-associated pneumonia in adults - UpToDate. Available at: https://www.uptodate.com/contents/epidemiology-pathogenesis-microbiology-and-diagnosis-of-hospital-acquired-and-ventilator-associated-pneumonia-in-adults. (Accessed: 1st August 2018)

90. Complications of abdominal surgical incisions - UpToDate. Available at: https://www.uptodate.com/contents/complications-of-abdominal-surgical-incisions. (Accessed: 1st August 2018)

91. Clinical manifestations and evaluation of adults with suspected native valve endocarditis - UpToDate. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-evaluation-of-adults-with-suspected-native-valve-endocarditis. (Accessed: 1st August 2018)

92. Clinical features and diagnosis of acute bacterial meningitis in adults - UpToDate. Available at: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-acute-bacterial-meningitis-in-adults. (Accessed: 1st August 2018)

93. Septic arthritis in adults - UpToDate. Available at: https://www.uptodate.com/contents/septic-arthritis-in-adults. (Accessed: 1st August 2018)

94. Manning, M. Lou, Archibald, L. K., Bell, L. M., Banerjee, S. N. & Jarvis, W. R. Serratia marcescens transmission in a pediatric intensive care unit: A multifactorial occurrence. *Am. J. Infect. Control* **29,** 115–119 (2001).

95. Jha, P. *et al.* Transmission of Enterobacter aerogenes septicemia in healthcare workers. *Springerplus* **5,** 1397 (2016).

96. Treatment of hospital-acquired and ventilator-associated pneumonia in adults - UpToDate. Available at: https://www.uptodate.com/contents/treatment-of-hospital-acquired-and-ventilator-associated-pneumonia-in-adults. (Accessed: 17th July 2018)

97. Overview of carbapenemase-producing gram-negative bacilli - UpToDate. Available at: https://www.uptodate.com/contents/overview-of-carbapenemase-producing-gram-negative-bacilli. (Accessed: 1st August 2018)

98. Brumbaugh, A. R. & Mobley, H. L. Preventing urinary tract infection: progress toward an effective Escherichia coli vaccine. *Expert Rev. Vaccines* **11,** 663–676 (2012).

99. Ahmad, T. A. *et al.* Development of immunization trials against Klebsiella pneumoniae. *Vaccine* **30,** 2411–2420 (2012).

100. Nielubowicz, G. R., Smith, S. N. & Mobley, H. L. T. Outer membrane antigens of the uropathogen Proteus mirabilis recognized by the humoral response during experimental murine urinary tract infection. *Infect. Immun.* **76,** 4222–31 (2008).

101. O'Hara, C. M., Brenner, F. W. & Miller, J. M. Classification, identification, and clinical significance of Proteus, Providencia, and Morganella. *Clin. Microbiol. Rev.* **13,** 534–46 (2000).

102. Aucken, H. M., Wilkinson, S. G. & Pitt, T. L. Identification of capsular antigens in Serratia marcescens. *J. Clin. Microbiol.* **35,** 59–63 (1997).

103. Ovchinnikova, O. G., Rozalski, A., Liu, B. & Knirel, Y. A. O-antigens of bacteria of the genus Providencia: Structure, serology, genetics, and biosynthesis. *Biochem.* **78,** 798–817 (2013).

104. Asad, Y., Ahmad, S., Rungrotmongkol, T., Ranaghan, K. E. & Azam, S. S. Immuno-informatics driven proteome-wide investigation revealed novel peptide-based vaccine targets against emerging multiple drug resistant Providencia stuartii. *J. Mol. Graph. Model.* **80,** 238–250 (2018).

105. Gaston, M. A., Strickland, M. A., Ayling-Smith, B. A. & Pitt, T. L. Epidemiological typing of Enterobacter aerogenes. *J. Clin. Microbiol.* **27,** 564–5 (1989).

106. Vörös, S. & Senior, B. W. New O antigens of Morganella morganii and the relationships between haemolysin production. O antigens and morganocin types of strains. *Acta Microbiol. Hung.* **37,** 341–9 (1990).

107. Chen, Y.-T. *et al.* Whole-genome sequencing and identification of Morganella morganii KT pathogenicity-related genes. *BMC Genomics* **13,** S4 (2012).

108. Haouzi, P. Murine models in critical care research. *Crit. Care Med.* **39,** 2290–2293 (2011).

109. Witteveen, E. *et al.* Assessment of intensive care unit-acquired weakness in young and old mice: An E. coli septic peritonitis model. *Muscle Nerve* **53,** 127–33 (2016).

110. Conover, M. S., Flores-Mireles, A. L., Hibbing, M. E., Dodson, K. & Hultgren, S. J. Establishment and Characterization of UTI and CAUTI in a Mouse Model. *J. Vis. Exp.* e52892 (2015). doi:10.3791/52892

111. Melo, L. D. R. *et al.* Development of a Phage Cocktail to Control Proteus mirabilis Catheter-associated Urinary Tract Infections. *Front. Microbiol.* **7,** 1024 (2016).

112. Fei, N. & Zhao, L. An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice. *ISME J.* **7,** 880–884 (2013).

113. Henry, J. N., Gelfand, E. W. & Hinchey, E. J. Gram-negative endotoxin shock due to Serratia marcescens. *Can. Med. Assoc. J.* **102,** 45–8 (1970).

114. Hidron, A. I. *et al.* Antimicrobial-Resistant Pathogens Associated With Healthcare-Associated Infections: Annual Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect. Control Hosp. Epidemiol.* **29,** 996–1011 (2008).

115. Murdoch, D. R. *et al.* Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century. *Arch. Intern. Med.* **169,** 463 (2009).

116. Crank, C. & O'Driscoll, T. Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management. *Infect. Drug Resist.* **8,** 217 (2015).

117. Guzman Prieto, A. M. *et al.* Global Emergence and Dissemination of Enterococci as Nosocomial Pathogens: Attack of the Clones? *Front. Microbiol.* **7,** 788 (2016).

118. Acute simple cystitis in women - UpToDate. Available at: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2018.3627. (Accessed: 18th July 2018)

119. Antimicrobial therapy of native valve endocarditis - UpToDate. Available at: https://www.uptodate.com/contents/antimicrobial-therapy-of-native-valve-endocarditis. (Accessed: 18th July 2018)

120. Treatment of enterococcal infections - UpToDate. Available at: https://www.uptodate.com/contents/treatment-of-enterococcal-infections. (Accessed: 18th July 2018)

121. Balli, E. P., Venetis, C. A. & Miyakis, S. Systematic review and meta-analysis of linezolid versus daptomycin for treatment of vancomycin-resistant enterococcal bacteremia. *Antimicrob. Agents Chemother.* **58,** 734–9 (2014).

122. Sava, I. G., Heikens, E. & Huebner, J. Pathogenesis and immunity in enterococcal infections. *Clin Microbiol Infect* **16,** 533–540 (2010).

123. Kodali, S. *et al.* A Vaccine Approach for the Prevention of Infections by Multidrug-resistant Enterococcus faecium. *J. Biol. Chem.* **290,** 19512–19526 (2015).

124. MODULE 2 – Immunizing the immunocompromised - WHO Vaccine Safety Basics. Available at: http://vaccine-safety-training.org/immunizing-the-immunocompromised.html. (Accessed: 27th July 2018)

125. Dalhoff, A. Global fluoroquinolone resistance epidemiology and implictions for clinical use. *Interdiscip. Perspect. Infect. Dis.* **2012,** 976273 (2012).

126. Cagnacci, S., Gualco, L., Debbia, E., Schito, G. C. & Marchese, A. European emergence of ciprofloxacin-resistant Escherichia coli clonal groups O25:H4-ST 131 and O15:K52:H1 causing community-acquired uncomplicated cystitis. *J. Clin. Microbiol.* **46,** 2605–12 (2008).

127. Seidman, J. C. *et al.* Longitudinal Comparison of Antibiotic Resistance in Diarrheagenic and Non-pathogenic Escherichia coli from Young Tanzanian Children. *Front. Microbiol.* **7,** 1420 (2016).

128. Zhang, S., Wu, Q., Zhang, J., Lai, Z. & Zhu, X. Prevalence, genetic diversity, and antibiotic resistance of enterotoxigenic Escherichia coli in retail ready-to-eat foods in China. *Food Control* **68,** 236–243 (2016).

129. López-Gigosos, R. *et al.* Effectiveness of the WC/rBS oral cholera vaccine in the prevention of traveler's diarrhea. *Hum. Vaccin. Immunother.* **9,** 692–698 (2013).

130. FAQs | DUKORAL® – Oral Vaccine for ETEC Diarrhea. Available at: https://www.dukoralcanada.com/faqs. (Accessed: 25th July 2018)

131. Pathogenic Escherichia coli associated with diarrhea - UpToDate. (2018). Available at: https://www.uptodate.com/contents/pathogenic-escherichia-coli-associated-with-diarrhea. (Accessed: 24th July 2018)

132. CDC - Centers for Disease Control and. Questions and Answers | E.coli. (2018). Available at: https://www.cdc.gov/ecoli/general/index.html. (Accessed: 24th July 2018)

133. Svennerholm, A.-M. & Tobias, J. Vaccines against enterotoxigenic Escherichia coli. *Expert Rev. Vaccines* **7,** 795–804 (2014).

134. Qadri, F., Svennerholm, A.-M., Faruque, A. S. G. & Sack, R. B. Enterotoxigenic Escherichia coli in developing countries: epidemiology, microbiology, clinical features, treatment, and prevention. *Clin. Microbiol. Rev.* **18,** 465–83 (2005).

135. Approach to the adult with acute diarrhea in resource-rich settings - UpToDate. (2018). Available at: https://www.uptodate.com/contents/approach-to-the-adult-with-acute-diarrhea-in-resource-rich-settings. (Accessed: 24th July 2018)

136. Urban, C., Tiruvury, H., Mariano, N., Colon-Urban, R. & Rahal, J. J. Polymyxin-resistant clinical isolates of Escherichia coli. *Antimicrob. Agents Chemother.* (2011). doi:10.1128/AAC.01088-10

137. Adefisoye, M. A. & Okoh, A. I. Identification and antimicrobial resistance prevalence of pathogenic Escherichia coli strains from treated wastewater effluents in Eastern Cape, South Africa. *Microbiologyopen* (2016). doi:10.1002/mbo3.319

138. Konaté, A. *et al.* Epidemiology and antibiotic resistance phenotypes of diarrheagenic Escherichia coli responsible for infantile gastroenteritis in Ouagadougou, Burkina Faso. *Eur. J. Microbiol. Immunol.* **7,** 168–175 (2017).

139. Travelers' diarrhea: Clinical manifestations, diagnosis, and treatment - UpToDate. (2018). Available at: https://www.uptodate.com/contents/travelers-diarrhea-clinical-manifestations-diagnosis-and-treatment. (Accessed: 24th July 2018)

140. Travelers' diarrhea: Microbiology, epidemiology, and prevention - UpToDate. Available at: https://www.uptodate.com/contents/travelers-diarrhea-microbiology-epidemiology-and-prevention. (Accessed: 7th August 2018)

141. Bourgeois, A. L., Wierzba, T. F. & Walker, R. I. Status of vaccine research and development for enterotoxigenic Escherichia coli. *Vaccine* **34,** 2880–2886 (2016).

142. Wolf, M. K. Occurrence, distribution, and associations of O and H serogroups, colonization factor antigens, and toxins of enterotoxigenic Escherichia coli. *Clin. Microbiol. Rev.* **10,** 569–84 (1997).

143. Lundgren, A. *et al.* Safety and immunogenicity of an improved oral inactivated multivalent enterotoxigenic Escherichia coli (ETEC) vaccine administered alone and together with dmLT adjuvant in a double-blind, randomized, placebo-controlled Phase I study. *Vaccine* **32,** 7077–7084 (2014).

144. Klemm, P. Fimbrial adhesions of Escherichia coli. *Rev. Infect. Dis.* **7,** 321–40

145. Kaslow, D. C. *Product Development for Vaccines Advisory Committee (PDVAC): Vaccine development highlights from 2016/17*. (2017).

146. PATH. *The Case for Investment in Enterotoxigenic Escherichia coli Vaccines*. (2011).

147. Burki, T. Typhoid conjugate vaccine gets WHO prequalification. *Lancet Infect. Dis.* **18,** 258 (2018).

148. Feasey, N. A. & Levine, M. M. Typhoid vaccine development with a human challenge model. *Lancet* **390,** 2419–2421 (2017).

149. Xu, Z. & Moyle, P. M. Bioconjugation Approaches to Producing Subunit Vaccines Composed of Protein or Peptide Antigens and Covalently Attached Toll-Like Receptor Ligands. *Bioconjug. Chem.* **29,** 572–586 (2018).

150. Hosangadi, D., Smith, P. G., Kaslow, D. C. & Giersing, B. K. WHO consultation on ETEC and Shigella burden of disease, Geneva, 6–7th April 2017: Meeting report. *Vaccine* (2018). doi:10.1016/J.VACCINE.2017.10.011

151. Méndez, Y. *et al.* Multicomponent polysaccharide-protein bioconjugation in the development of antibacterial glycoconjugate vaccine candidates. *Chem. Sci.* **9,** 2581–2588 (2018).

152. Huttner, A. *et al.* Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women. *JAMA* **319,** 1781 (2018).

153. Terlizzi, M. E., Gribaudo, G. & Maffei, M. E. UroPathogenic Escherichia coli (UPEC) Infections: Virulence Factors, Bladder Responses, Antibiotic, and Non-antibiotic Antimicrobial Strategies. ***Front. Microbiol.*** **8,** 1566 (2017).

154. Dale, A. P. & Woodford, N. Extra-intestinal pathogenic Escherichia coli (ExPEC): Disease, carriage and clones. *J. Infect.* **71,** 615–626 (2015).

155. Marrs, C. F., Zhang, L. & Foxman, B. Escherichia coli mediated urinary tract infections: are there distinct uropathogenic E. coli (UPEC) pathotypes? *FEMS Microbiol. Lett.* **252,** 183–90 (2005).

156. Salvatore, S. *et al.* Urinary tract infections in women. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **156,** 131–136 (2011).

157. Foxman, B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect. Dis. Clin. North Am.* **28,** 1–13 (2014).

158. Nguyen-Van-Tam, S. E., Nguyen-Van-Tam, J. S., Myint, S. & Pearson, J. C. Risk factors for hospital-acquired urinary tract infection in a large English teaching hospital: a case-control study. *Infection* **27,** 192–7

159. Stamm, W. E. & Norrby, S. R. Urinary Tract Infections: Disease Panorama and Challenges. *J. Infect. Dis.* **183,** S1–S4 (2001).

160. Colpan, A. *et al.* Escherichia coli Sequence Type 131 (ST131) Subclone H30 as an Emergent Multidrug-Resistant Pathogen Among US Veterans. *Clin. Infect. Dis.* **57,** 1256–1265 (2013).

161. Huttner, A. *et al.* Safety, immunogenicity, and preliminary clinical efficacy of a vaccine against extraintestinal pathogenic Escherichia coli in women with a history of recurrent urinary tract infection: a randomised, single-blind, placebo-controlled phase 1b trial. *Lancet Infect. Dis.* **17,** 528–537 (2017).

162. Dobbelsteen, G. P. J. M. Van Den *et al.* Immunogenicity and safety of a tetravalent E . coli O-antigen bioconjugate vaccine in animal models. *Vaccine* **34,** 4152–4160 (2016).

163. Inoue, M. *et al.* Safety, tolerability and immunogenicity of the ExPEC4V (JNJ-63871860) vaccine for prevention of invasive extraintestinal pathogenic *Escherichia coli* disease: A phase 1, randomized, double-blind, placebo-controlled study in healthy Japanese participants. *Hum. Vaccin. Immunother.* 1–8 (2018). doi:10.1080/21645515.2018.1474316

164. Al-Badr, A. & Al-Shaikh, G. Recurrent Urinary Tract Infections Management in Women: A review. *Sultan Qaboos Univ. Med. J.* **13,** 359–67 (2013).

165. Sivick, K. E. & Mobley, H. L. T. Waging war against uropathogenic Escherichia coli: winning back the urinary tract. *Infect. Immun.* **78,** 568–85 (2010).

166. Hannan, T. J., Mysorekar, I. U., Hung, C. S., Isaacson-Schmid, M. L. & Hultgren, S. J. Early Severe Inflammatory Responses to Uropathogenic E. coli Predispose to Chronic and Recurrent Urinary Tract Infection. *PLoS Pathog.* **6,** e1001042 (2010).

167. Wiles, T. J., Kulesus, R. R. & Mulvey, M. A. Origins and virulence mechanisms of uropathogenic Escherichia coli. *Exp. Mol. Pathol.* **85,** 11–9 (2008).

168. Poolman, J. T. & Wacker, M. Extraintestinal Pathogenic *Escherichia coli* , a Common Human Pathogen: Challenges for Vaccine Development and Progress in the Field. *J. Infect. Dis.* **213,** 6–13 (2016).

169. Hung, C.-S., Dodson, K. W. & Hultgren, S. J. A murine model of urinary tract infection. *Nat. Protoc.* **4,** 1230–1243 (2009).

170. Hopkins, W. J. & Uehling, D. T. Vaccine development for the prevention of urinary tract infections. *Curr. Infect. Dis. Rep.* **4,** 509–513 (2002).

171. Evans, T. G., Schrager, L. & Thole, J. Status of vaccine research and development of vaccines for tuberculosis. *Vaccine* **34,** 2911–2914 (2016).

172. Fiuk, J. V, Holland, B. C., Dynda, D. I. & Alanee, S. R. Antibiotics prophylaxis before prostate biopsy in practice: Review of online clinical guidelines. *Urol. Ann.* **7,** 279–80 (2015).

173. Wagenlehner, F., Wullt, B., Ballarini, S., Zingg, D. & Naber, K. G. Social and economic burden of recurrent urinary tract infections and quality of life: a patient web-based study (GESPRIT). *Expert Rev. Pharmacoecon. Outcomes Res.* **18,** 107–117 (2018).

174. Nicolle, L. E. Catheter associated urinary tract infections. *Antimicrob. Resist. Infect. Control* **3,** 23 (2014).

175. Young, V. B. The role of the microbiome in human health and disease: an introduction for clinicians. *BMJ* **356,** j831 (2017).

176. Clapp, M. *et al.* Gut microbiota's effect on mental health: The gut-brain axis. *Clin. Pract.* **7,** 987 (2017).

177. Hays, M. P., Ericsson, A. C., Yang, Y. & Hardwidge, P. R. Vaccinating with conserved Escherichia coli antigens does not alter the mouse intestinal microbiome. *BMC Res. Notes* **9,** 401 (2016).

178. ECDC. ECDC Factsheet about Invasive Haemophilus influenzae disease. Available at: https://ecdc.europa.eu/en/invasive-haemophilus-influenzae-disease/facts. (Accessed: 2nd August 2018)

179. Rubach, M. P. *et al.* Increasing incidence of invasive Haemophilus influenzae disease in adults, Utah, USA. *Emerg. Infect. Dis.* **17,** 1645–50 (2011).

180. Van Eldere, J., Slack, M. P. E., Ladhani, S. & Cripps, A. W. Non-typeable Haemophilus influenzae, an under-recognised pathogen. *Lancet. Infect. Dis.* **14,** 1281–92 (2014).

181. WHO Factsheet on immunisation coverage. Available at: http://www.who.int/news-room/fact-sheets/detail/immunization-coverage. (Accessed: 2nd August 2018)

182. Jackson, C., Mann, A., Mangtani, P. & Fine, P. Effectiveness of Haemophilus influenzae Type b Vaccines Administered According to Various Schedules. *Pediatr. Infect. Dis. J.* **32,** 1261–1269 (2013).

183. Giufrè, M. *et al.* Ten years of Hib vaccination in Italy: Prevalence of non-encapsulated Haemophilus influenzae among invasive isolates and the possible impact on antibiotic resistance. *Vaccine* **29,** 3857–3862 (2011).

184. Epidemiology, clinical manifestations, and treatment of Haemophilus influenzae - UpToDate. Available at: https://www.uptodate.com/contents/epidemiology-clinical-manifestations-and-treatment-of-haemophilus-influenzae. (Accessed: 2nd August 2018)

185. King, P. Haemophilus influenzae and the lung (Haemophilus and the lung). *Clin. Transl. Med.* **1,** 10 (2012).

186. Langereis, J. D. & de Jonge, M. I. Invasive Disease Caused by Nontypeable Haemophilus influenzae. *Emerg. Infect. Dis.* **21,** 1711–8 (2015).

187. WHO. WHO Disease and epidemiology - Haemophilus influenzae type B. Available at: http://www.emro.who.int/health-topics/haemophilus-influenzae-type-b/disease-and-epidemiology.html. (Accessed: 2nd August 2018)

188. Pneumonia Symptoms - WebMD. Available at: https://www.webmd.com/lung/understanding-pneumonia-symptoms#1. (Accessed: 2nd August 2018)

189. CDC - Centers for Disease Control and. CDC Haemophilus influenzae - Types of Infection and Causes. Available at: https://www.cdc.gov/hi-disease/about/types-infection.html. (Accessed: 2nd August 2018)

190. Haemophilus influenzae. Available at: https://www.infectiousdiseaseadvisor.com/infectious-diseases/haemophilus-influenzae/article/609450/. (Accessed: 2nd August 2018)

191. WHO. *The Immunological Basis for Immunization Series: Module 9: Haemophilus influenzae type b*. (2007).

192. CDC - Centers for Disease Control and. CDC Haemophilus influenzae - Causes and Transmission. Available at: https://www.cdc.gov/hi-disease/about/causes-transmission.html. (Accessed: 2nd August 2018)

193. Allali, S., Chalumeau, M., Launay, O., Ballas, S. K. & de Montalembert, M. Conjugate Haemophilus influenzae type b vaccines for sickle cell disease. *Cochrane Database Syst. Rev.* (2016). doi:10.1002/14651858.CD011199.pub2

194. *Meningitis Research Foundation: Hib (Haemophilus Influenzae Type B) vaccine*.

195. Adegbola, R. A. *et al.* Elimination of Haemophilus influenzae type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study. *Lancet* **366,** 144–150 (2005).

196. Treatment of bacterial meningitis caused by specific pathogens in adults - UpToDate. Available at: https://www.uptodate.com/contents/treatment-of-bacterial-meningitis-caused-by-specific-pathogens-in-adults. (Accessed: 2nd August 2018)

197. Treatment of community-acquired pneumonia in adults in the outpatient setting - UpToDate. Available at: https://www.uptodate.com/contents/treatment-of-community-acquired-pneumonia-in-adults-in-the-outpatient-setting. (Accessed: 2nd August 2018)

198. Safety, Reactogenicity and Immunogenicity of GlaxoSmithKline (GSK) Biologicals' Non-typeable Haemophilus Influenzae (NTHI) Vaccine - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01657526. (Accessed: 6th August 2018)

199. Siegrist, C. A. Neonatal and early life vaccinology. *Vaccine* **19,** 3331–46 (2001).

200. Kelly, D. F., Moxon, E. R. & Pollard, A. J. Haemophilus influenzae type b conjugate vaccines. *Immunology* **113,** 163–74 (2004).

201. Hamidi, A., Verdijk, P. & Kreeftenberg, H. Preclinical evaluation of a Haemophilus influenzae type b conjugate vaccine process intended for technology transfer. *Hum. Vaccin. Immunother.* **10,** 2691–6 (2014).

202. Akeda, Y. *et al.* Comparison of serum bactericidal and antibody titers induced by two Haemophilus influenzae type b conjugate vaccines: A phase III randomized double-blind study. *Vaccine* **36,** 1528–1532 (2018).

203. WHO. *WHO 27th September 2013 Weekly epidemiology record. Position paper on Hib vaccination*.

204. WHO. *The Vaccines Monovalent Hib vaccine Factsheet*. (2012).

205. CDC - Centers for Disease Control and. CDC Haemophilus Influenza Type B (Hib) Vaccine Safety. Available at: https://www.cdc.gov/vaccinesafety/vaccines/hib-vaccine.html. (Accessed: 2nd August 2018)

206. Infanrix IPV - Summary of Product Characteristics (SmPC) - (eMC). Available at: https://www.medicines.org.uk/emc/product/5535/smpc#STORAGE. (Accessed: 2nd August 2018)

207. Howie, S. R. C. Global Hib vaccination: reasons to cheer and fear. *Lancet Glob. Heal.* **4,** e142–e143 (2016).

208. Gavi support for the Haemophilus influenzae type b vaccine. Available at: https://www.gavi.org/support/nvs/hib/. (Accessed: 2nd August 2018)

209. Yeh, S. Prevention of Haemophilus influenzae type b infection. Available at: https://www.uptodate.com/contents/prevention-of-haemophilus-influenzae-type-b-infection?search=hib coverage&source=search_result&selectedTitle=6~150&usage_type=default&display_rank=6. (Accessed: 2nd August 2018)

210. Plotkin, S. A., Orenstein, W. A. & Offit, P. A. *Plotkin's vaccines*. (2017).

211. Wan Sai Cheong, J. *et al.* Trends in the epidemiology of invasive Haemophilus influenzae disease in Queensland, Australia from 2000 to 2013: what is the impact of an increase in invasive non-typable H. influenzae (NTHi)? *Epidemiol. Infect.* **143,** 2993–3000 (2015).

212. Ladhani, S. N., Ramsay, M. & Slack, M. P. E. The Impact of Haemophilus influenzae Serotype B Resurgence on the Epidemiology of Childhood Invasive Haemophilus influenzae Disease in England and Wales. *Pediatr. Infect. Dis. J.* **30,** 893–895 (2011).

213. Whittaker, R. *et al.* Epidemiology of Invasive Haemophilus Influenzae Disease, Europe, 2007–2014. *Emerg. Infect. Dis.* **23,** 396–404 (2017).

214. Hooi, J. K. Y. *et al.* Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. *Gastroenterology* **153,** 420–429 (2017).

215. Testerman, T. L. & Morris, J. Beyond the stomach: an updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. *World J. Gastroenterol.* **20,** 12781–808 (2014).

216. Salih, B. A. Helicobacter pylori infection in developing countries: the burden for how long? *Saudi J. Gastroenterol.* **15,** 201–7 (2009).

217. H. Pylori Transmission and Spread of Infection | Mel and Enid Zuckerman College of Public Health. Available at: https://publichealth.arizona.edu/outreach/health-literacy-awareness/hpylori/transmission. (Accessed: 31st July 2018)

218. Lahner, E., Carabotti, M. & Annibale, B. Treatment of Helicobacter pylori infection in atrophic gastritis. *World J. Gastroenterol.* **24,** 2373–2380 (2018).

219. Ford, A., Delaney, B., Forman, D. & Moayyedi, P. Eradication therapy for peptic ulcer disease in Helicobacter pylori positive patients. in *Cochrane Database of Systematic Reviews* (ed. Ford, A.) CD003840 (John Wiley & Sons, Ltd, 2003). doi:10.1002/14651858.CD003840.pub2

220. *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*. (2013).

221. Cardaropoli, S., Rolfo, A. & Todros, T. Helicobacter pylori and pregnancy-related disorders. *World J. Gastroenterol.* **20,** 654–64 (2014).

222. Li, L. *et al.* Helicobacter pylori Infection Is Associated with an Increased Risk of Hyperemesis Gravidarum: A Meta-Analysis. *Gastroenterol. Res. Pract.* **2015,** 278905 (2015).

223. Zamani, M. *et al.* Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection. *Aliment. Pharmacol. Ther.* **47,** 868–876 (2018).

224. Grooten, I. J. *et al.* Helicobacter pylori infection: a predictor of vomiting severity in pregnancy and adverse birth outcome. *Am. J. Obstet. Gynecol.* **216,** 512.e1-512.e9 (2017).

225. Crowe, S. Treatment regimens for Helicobacter pylori - UpToDate. Available at: https://www.uptodate.com/contents/treatment-regimens-for-helicobacter-pylori. (Accessed: 30th July 2018)

226. Chey, W. D., Leontiadis, G. I., Howden, C. W. & Moss, S. F. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *Am. J. Gastroenterol.* **112,** 212–239 (2017).

227. Thung, I. *et al.* Review article: the global emergence of Helicobacter pylori antibiotic resistance. *Aliment. Pharmacol. Ther.* **43,** 514–533 (2016).

228. Nayar, D. S. Current eradication rate of Helicobacter pylori with clarithromycin-based triple therapy in a gastroenterology practice in the New York metropolitan area. *Infect. Drug Resist.* **11,** 205–211 (2018).

229. Malaty, H. M. *et al.* Natural History of Helicobacter pylori Infection in Childhood: 12-Year Follow-up Cohort Study in a Biracial Community. *Clin. Infect. Dis.* **28,** 279–282 (1999).

230. Sutton, P. & Boag, J. M. Status of vaccine research and development for Helicobacter pylori. *Vaccine* 1–5 (2018). doi:10.1016/j.vaccine.2018.01.001

231. Aebischer, T. *et al.* Correlation of T cell response and bacterial clearance in human volunteers challenged with Helicobacter pylori revealed by randomised controlled vaccination with Ty21a-based Salmonella vaccines. *Gut* **57,** 1065–1072 (2008).

232. Zeng, M. *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* **386,** 1457–1464 (2015).

233. Graham, D. Y. *et al.* Challenge model for Helicobacter pylori infection in human volunteers. *Gut* **53,** 1235–1243 (2004).

234. Phase 1a/b Study on Safety of IMX101 in H. Pylori-negative and H. Pylori-infected Healthy Volunteers - Full Text View - ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03270800. (Accessed: 31st July 2018)

235. Herrera, V. & Parsonnet, J. Helicobacter pylori and gastric adenocarcinoma. **15,** 971–6 (2009).

236. Cheung, K. S. *et al.* Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. *Gut* **67,** 28–35 (2018).

237. Wan, Q.-Y., Wu, X.-T., Li, N., Du, L. & Zhou, Y. Long-term proton pump inhibitors use and risk of gastric cancer: a meta-analysis of 926 386 participants. *Gut* gutjnl-2018-316416 (2018). doi:10.1136/gutjnl-2018-316416

238. Rupnow, M. F. T., Chang, A. H., Shachter, R. D., Owens, D. K. & Parsonnet, J. Cost-Effectiveness of a Potential Prophylactic Helicobacter pylori Vaccine in the United States. *J. Infect. Dis.* **200,** 1311–1317 (2009).

239. Alkim, H., Koksal, A. R., Boga, S., Sen, I. & Alkim, C. Role of Bismuth in the Eradication of Helicobacter pylori. *Am. J. Ther.* **24,** e751–e757 (2017).

240. Venerito, M., Krieger, T., Ecker, T., Leandro, G. & Malfertheiner, P. E-Mail Meta-Analysis of Bismuth Quadruple Therapy versus Clarithromycin Triple Therapy for Empiric Primary Treatment of Helicobacter pylori Infection. *Digestion* **88,** 33–45 (2013).

241. Alba, C., Blanco, A. & Alarcón, T. Antibiotic resistance in Helicobacter pylori. *Curr. Opin. Infect. Dis.* **30,** 489–497 (2017).

242. Clinical features, diagnosis, and treatment of Klebsiella pneumoniae infection - UpToDate. Available at: https://www.uptodate.com/contents/clinical-features-diagnosis-and-treatment-of-klebsiella-pneumoniae-infection. (Accessed: 7th August 2018)

243. CDC - Centers for Disease Control and. Klebsiella pneumoniae in Healthcare Settings | HAI. Available at: https://www.cdc.gov/hai/organisms/klebsiella/klebsiella.html. (Accessed: 7th August 2018)

244. ECDC. *Healthcare-associated infections acquired in intensive care units - Annual Epidemiological Report for 2015*.

245. Meatherall, B. L., Gregson, D., Ross, T., Pitout, J. D. D. & Laupland, K. B. Incidence, Risk Factors, and Outcomes of Klebsiella pneumoniae Bacteremia. *Am. J. Med.* **122,** 866–873 (2009).

246. Gupta, K. *et al.* International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin. Infect. Dis.* **52,** e103-20 (2011).

247. van Duin, D. & Doi, Y. The global epidemiology of carbapenemase-producing Enterobacteriaceae. *Virulence* **8,** 460–469 (2017).

248. Paterson, D. L. *et al.* International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. *Ann. Intern. Med.* **140,** 26–32 (2004).

249. Morrill, H. J., Pogue, J. M., Kaye, K. S. & LaPlante, K. L. Treatment Options for Carbapenem-Resistant Enterobacteriaceae Infections. *Open forum Infect. Dis.* **2,** ofv050 (2015).

250. Lundberg, U., Senn, B. M., Schüler, W., Meinke, A. & Hanner, M. Identification and characterization of antigens as vaccine candidates against Klebsiella pneumoniae. *Hum. Vaccin. Immunother.* **9,** 497–505 (2013).

251. Follador, R. *et al.* The diversity of Klebsiella pneumoniae surface polysaccharides. *Microb. Genomics* **2,** e000073 (2016).

252. Lavender, H., Jagnow, J. J. & Clegg, S. Klebsiella pneumoniae type 3 fimbria-mediated immunity to infection in the murine model of respiratory disease. *Int. J. Med. Microbiol.* **295,** 153–159 (2005).

253. Fung, C.-P. *et al.* Immune response and pathophysiological features of Klebsiella pneumoniae liver abscesses in an animal model. *Lab. Investig.* **91,** 1029–1039 (2011).

254. Benincasa, M. *et al.* Biofilms from Klebsiella pneumoniae: Matrix Polysaccharide Structure and Interactions with Antimicrobial Peptides. *Microorganisms* **4,** (2016).

255. Pletzer, D., Mansour, S. C., Wuerth, K., Rahanjam, N. & Hancock, R. E. W. New Mouse Model for Chronic Infections by Gram-Negative Bacteria Enabling the Study of Anti-Infective Efficacy and Host-Microbe Interactions. *MBio* **8,** e00140-17 (2017).

256. TB is now the World's Leading Infectious Killer | TB Alliance. Available at: https://www.tballiance.org/news/tb-now-worlds-leading-infectious-killer. (Accessed: 24th July 2018)

257. Tuberculosis is now the world's deadliest infectious disease - KNCV. Available at: https://www.kncvtbc.org/en/2015/10/28/tuberculose-nu-dodelijkste-infectieziekte-wereldwijd/. (Accessed: 24th July 2018)

258. Roy, A. *et al.* Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. *BMJ* **349,** g4643 (2014).

259. Mangtani, P. *et al.* Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials. *Clin. Infect. Dis.* **58,** 470–480 (2014).

260. Tuberculosis. Available at: http://textbookofbacteriology.net/tuberculosis.html. (Accessed: 25th July 2018)

261. Lee, J. Y. Diagnosis and treatment of extrapulmonary tuberculosis. *Tuberc. Respir. Dis. (Seoul).* **78,** 47–55 (2015).

262. CDC - Centers for Disease Control and. TB Risk Factors. *https://www.cdc.gov/tb/topic/basics/risk.htm. (Accessed: 30th July 2018)*

263. USAID. Intersecting Epidemics: An Overview of the Causes of Maternal Death and Infectious Diseases WHERE ARE MOTHERS DYING? REGIONAL BURDENS OF DISEASE. **2,** (2014).

264. Gamez-Gonzalez, L. B., Hamada, H., Llamas-Guillen, B. A., Ruiz-Fernandez, M. & Yamazaki-Nakashimada, M. BCG and Kawasaki disease in Mexico and Japan. *Hum. Vaccin. Immunother.* **13,** 1091–1093 (2017).

265. WHO. *WHO Global tuberculosis report 2017. World Health Organization Press* (2017). doi:ISBN 978 92 4 156539 4

266. TB in Children | Kids, getting, diagnosing & preventing TB. Available at: https://www.tbfacts.org/tb-children/. (Accessed: 23rd July 2018)

267. Tuberculosis - Diagnosis and treatment - Mayo Clinic. Available at: https://www.mayoclinic.org/diseases-conditions/tuberculosis/diagnosis-treatment/drc-20351256. (Accessed: 23rd July 2018)

268. WHO. WHO | Tuberculosis vaccine development. *WHO* (2018).

269. Huang, L. & Russell, D. G. Protective immunity against tuberculosis: what does it look like and how do we find it? *Curr. Opin. Immunol.* **48,** 44–50 (2017).

270. Urdahl, K. Understanding the Immune Response to M. tuberculosis. *Nature Education* (2015). Available at: https://www.nature.com/scitable/topicpage/understanding-the-immune-response-to-m-tuberculosis-132624401.

271. Houben, R. M. G. J. & Dodd, P. J. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLOS Med.* **13,** e1002152 (2016).

272. Karp, C. L., Wilson, C. B. & Stuart, L. M. Tuberculosis vaccines: barriers and prospects on the quest for a transformative tool. *Immunol. Rev.* **264,** 363–381 (2015).

273. Zhan, L., Tang, J., Sun, M. & Qin, C. Animal Models for Tuberculosis in Translational and Precision Medicine. *Front. Microbiol.* **8,** 717 (2017).

274. Minassian, A. M. *et al.* A human challenge model for Mycobacterium tuberculosis using Mycobacterium bovis bacille Calmette-Guerin. *J. Infect. Dis.* **205,** 1035–42 (2012).

275. Croucher, K., Kershaw, F. & Rick, T. Challenges in Conducting Tuberculosis Clinical Trials in Developing Countries: Lessons Learned. *J. Clin. Stud.* **5,** (2013).

276. Kaufmann, S. H. E., Weiner, J. & Maertzdorf, J. Accelerating tuberculosis vaccine trials with diagnostic and prognostic biomarkers. *Expert Rev. Vaccines* **16,** 845–853 (2017).

277. Viewpoint - Is the universal BCG vaccination necessary? | GPonline. Available at: https://www.gponline.com/viewpoint-universal-bcg-vaccination-necessary/infections-and-infestations/immunisation/article/906355. (Accessed: 20th July 2018)

278. G-FINDER - Public Search Tool. Available at: https://gfinder.policycuresresearch.org/PublicSearchTool/search. (Accessed: 6th August 2018)

279. Gonorrhea. Available at: https://emedicine.medscape.com/article/218059-overview (Accessed: 21st September 2018).

280. Jerse, A. E., Bash, M. C. & Russell, M. W. Vaccines against gonorrhea: Current status and future challenges. *Vaccine* **32,** 1579–1587 (2014).

281. Miller, K. E. Diagnosis and Treatment of Neisseria gonorrhoeae Infections. *Am. Fam. Physician* **73,** (2006).

282. Vincent, L. R. & Jerse, A. E. Biological feasibility and importance of a gonorrhea vaccine for global public health. *Vaccine* (2018). doi:10.1016/j.vaccine.2018.02.081

283. Plummer, F. A. *et al.* Antibodies to opacity proteins (Opa) correlate with a reduced risk of gonococcal salpingitis. *J. Clin. Invest.* **93,** 1748–1755 (1994).

284. Fox, K. K. *et al.* Longitudinal evaluation of serovar-specific immunity to Neisseria gonorrhoeae. *Am. J. Epidemiol.* **149,** 353–8 (1999).

285. Petousis-Harris, H. *et al.* Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet* **390,** 1603–1610 (2017).

286. ECDC: first detected cases of extensively drug-resistant gonorrhoea threaten future treatment. Available at: https://ecdc.europa.eu/en/news-events/ecdc-first-detected-cases-extensively-drug-resistant-gonorrhoea-threaten-future (Accessed: 21st September 2018)

287. Mlisana, K. *et al.* Symptomatic Vaginal Discharge Is a Poor Predictor of Sexually Transmitted Infections and Genital Tract Inflammation in High-Risk Women in South Africa. *J. Infect. Dis.* **206,** 6–14 (2012).

288. Mullick, S., Watson-Jones, D. & Beksinska, M. Sexually transmitted infections in pregnancy: prevalence, impact on pregnancy outcomes, and approach to treatment in developing countries. *Sex. Transm. Infect.* **81,** 294–302

289. Treatment of uncomplicated Neisseria gonorrhoeae infections - UpToDate.

290. Plummer, F. A. ***et al.*** Epidemiologic evidence for the development of serovar-specific immunity after gonococcal infection. *J. Clin. Invest.* **83,** 1472–6 (1989).

291. Broutet, N., Fruth, U., Deal, C., Gottlieb, S. L. & Rees, H. Vaccines against sexually transmitted infections : The way forward. *Vaccine* **32,** 1630–1637 (2014).

292. Fruth, U., Broutet, N., Deal, C., Dodet, B. & Meheus, A. Vaccines for sexually transmitted infections : Past , present and future. *Vaccine* **32,** 1525–1526 (2014).

293. WHO. *Scientists warn that antibiotic-resistant gonorrhea is on the rise.* (2017).

294. The Value of Vaccines in the Avoidance of Antimicrobial Resistance Royal Society.

295. CDC. https://www.cdc.gov/std/gonorrhea/stdfact-gonorrhea-detailed.htm.

296. Epidemiology, microbiology, and pathogenesis of Pseudomonas aeruginosa infection - UpToDate. (2018). Available at: https://www.uptodate.com/contents/epidemiology-microbiology-and-pathogenesis-of-pseudomonas-aeruginosa-infection. (Accessed: 25th July 2018)

297. CDC - Centers for Disease Control and. Pseudomonas aeruginosa in Healthcare Settings | HAI | CDC. (2018). Available at: https://www.cdc.gov/hai/organisms/pseudomonas.html. (Accessed: 25th July 2018)

298. Clifton, I. J. & Peckham, D. G. Defining routes of airborne transmission of *Pseudomonas aeruginosa* in people with cystic fibrosis. *Expert Rev. Respir. Med.* **4,** 519–529 (2010).

299. Treepong, P. *et al.* Global emergence of the widespread Pseudomonas aeruginosa ST235 clone. *Clin. Microbiol. Infect.* **24,** 258–266 (2018).

300. Elborn, J. S. Cystic fibrosis. *Lancet* **388,** 2519–2531 (2016).

301. Angrill, J. *et al.* Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. *Thorax* **57,** 15–9 (2002).

302. Engler, K. *et al.* Colonisation with Pseudomonas aeruginosa and antibiotic resistance patterns in COPD patients. *Swiss Med. Wkly.* **142,** w13509 (2012).

303. Murray, T. S., Egan, M. & Kazmierczak, B. I. Pseudomonas aeruginosa chronic colonization in cystic fibrosis patients. *Curr. Opin. Pediatr.* **19,** 83–88 (2007).

304. Pseudomonas aeruginosa infections of the eye, ear, urinary tract, gastrointestinal tract, and central nervous system - UpToDate. Available at: https://www.uptodate.com/contents/pseudomonas-aeruginosa-infections-of-the-eye-ear-urinary-tract-gastrointestinal-tract-and-central-nervous-system. (Accessed: 25th July 2018)

305. Pseudomonas aeruginosa pneumonia - UpToDate. Available at: https://www.uptodate.com/contents/pseudomonas-aeruginosa-pneumonia?topicRef=3142&source=see_link. (Accessed: 25th July 2018)

306. Gellatly, S. L. & Hancock, R. E. W. Pseudomonas aeruginosa : new insights into pathogenesis and host defenses. *Pathog. Dis.* **67,** 159–173 (2013).

307. Lelong, E. *et al.* Evolution of Pseudomonas aeruginosa virulence in infected patients revealed in a Dictyostelium discoideum host model. *Clin. Microbiol. Infect.* **17,** 1415–1420 (2011).

308. Yordanov, D. & Strateva, T. Pseudomonas aeruginosa – a phenomenon of bacterial resistance. *J. Med. Microbiol.* **58,** 1133–1148 (2009).

309. Yordanov, D. & Strateva, T. Pseudomonas aeruginosa – a phenomenon of bacterial resistance. *J. Med. Microbiol.* **58,** 1133–1148 (2009).

310. Principles of antimicrobial therapy of Pseudomonas aeruginosa infections - UpToDate. Available at: https://www.uptodate.com/contents/principles-of-antimicrobial-therapy-of-pseudomonas-aeruginosa-infections. (Accessed: 25th July 2018)

311. Lavoie, E. G., Wangdi, T. & Kazmierczak, B. I. Innate immune responses to Pseudomonas aeruginosa infection. *Microbes Infect.* **13,** 1133–45 (2011).

312. Cigana, C. *et al.* Tracking the immunopathological response to Pseudomonas aeruginosa during respiratory infections. *Sci. Rep.* **6,** 21465 (2016).

313. Pitt, T. L. Cross infection of cystic fibrosis patients with Pseudomonas aeruginosa. *Thorax* **57,** 921 (2002).

314. Gellatly, S. L. & Hancock, R. E. W. *Pseudomonas aeruginosa* : new insights into pathogenesis and host defenses. *Pathog. Dis.* **67,** 159–173 (2013).

315. Lelong, E. *et al.* Evolution of Pseudomonas aeruginosa virulence in infected patients revealed in a Dictyostelium discoideum host model. *Clin. Microbiol. Infect.* **17,** 1415–1420 (2011).

316. Winstanley, C., O'Brien, S. & Brockhurst, M. A. Pseudomonas aeruginosa Evolutionary Adaptation and Diversification in Cystic Fibrosis Chronic Lung Infections. *Trends Microbiol.* **24,** 327–337 (2016).

317. Goldberg, J. B. & Pier, G. B. The role of the CFTR in susceptibility to Pseudomonas aeruginosa infections in cystic fibrosis. *Trends Microbiol.* **8,** 514–20 (2000).

318. Priebe, G. P. & Goldberg, J. B. Vaccines for Pseudomonas aeruginosa: a long and winding road. *Expert Rev. Vaccines* **13,** 507–519 (2014).

319. Bielen, K. *et al.* Animal models of hospital-acquired pneumonia: current practices and future perspectives. *Ann. Transl. Med.* **5,** 132 (2017).

320. Rello, J. *et al.* A randomized placebo-controlled phase II study of a Pseudomonas vaccine in ventilated ICU patients. *Crit. Care* **21,** 22 (2017).

321. Gagneux-Brunon, A., Lucht, F., Launay, O., Berthelot, P. & Botelho-Nevers, E. Vaccines for healthcare-associated infections: present, future, and expectations. *Expert Rev. Vaccines* **17,** 421–433 (2018).

322. Teresa Aguado, M. *et al.* Report on WHO meeting on immunization in older adults: Geneva, Switzerland, 22–23 March 2017. *Vaccine* **36,** 921–931 (2018).

323. Lavelle, G. M., White, M. M., Browne, N., McElvaney, N. G. & Reeves, E. P. Animal Models of Cystic Fibrosis Pathology: Phenotypic Parallels and Divergences. *Biomed Res. Int.* **2016,** 1–14 (2016).

324. About Cystic Fibrosis | CF Foundation. Available at: https://www.cff.org/What-is-CF/About-Cystic-Fibrosis/. (Accessed: 25th July 2018)

325. Cystic fibrosis: Company urged to lower cost of life-changing drug - BBC News. Available at: https://www.bbc.co.uk/news/uk-43849586. (Accessed: 25th July 2018)

326. Polverino, E., Cacheris, W., Spencer, C. & Operschall, E. Global burden of non-cystic fibrosis bronchiectasis: A simple epidemiological analysis. *Eur. Respir. J.* **40,** (2012).

327. Redondo, M., Keyt, H., Dhar, R. & Chalmers, J. D. Global impact of bronchiectasis and cystic fibrosis. *Breathe (Sheffield, England)* **12,** 222–235 (2016).

328. Fisher, J. T., Zhang, Y. & Engelhardt, J. F. Comparative Biology of Cystic Fibrosis Animal Models. in *Methods in molecular biology (Clifton, N.J.)* **742,** 311–334 (2011).

329. Ward, C., Rydell-Törmänen, K., Westergren-Thorsson, G., Eriksson, L. T. & Walters, H. Infection and remodelling: a 21st century model of bronchiectasis? *Eur. Respir. J.* **38,** 758–60 (2011).

330. Chalmers, J. D., Loebinger, M. & Aliberti, S. Challenges in the development of new therapies for bronchiectasis. *Expert Opin. Pharmacother.* **16,** 833–850 (2015).

331. Tennant, S. M., Maclennan, C. A., Simon, R., Martin, L. B. & Khan, M. I. Nontyphoidal salmonella disease : Current status of vaccine research and development. *Vaccine* **34,** 2907–2910 (2016).

332. Morpeth, S. C., Ramadhani, H. O. & Crump, J. A. Invasive non-Typhi Salmonella disease in Africa. *Clin. Infect. Dis.* **49,** 606–11 (2009).

333. Kingsley, R. A. *et al.* Epidemic multiple drug resistant Salmonella Typhimurium causing invasive disease in sub-Saharan Africa have a distinct genotype. *Genome Res.* (2009). doi:10.1101/gr.091017.109

334. CDC - Centers for Disease Control and. Signs & Symptoms | Multistate Outbreak of Salmonella I 4,[5],12:b:- Infections Linked to Kratom | February 2018 | Salmonella | CDC. Available at: https://www.cdc.gov/salmonella/kratom-02-18/signs-symptoms.html. (Accessed: 28th July 2018)

335. Mayoclinic. Typhoid fever. Available at: https://www.mayoclinic.org/diseases-conditions/typhoid-fever/symptoms-causes/syc-20378661.

336. WHO. Salmonella (non-typhoidal). Available at: http://www.who.int/news-room/fact-sheets/detail/salmonella-(non-typhoidal). (Accessed: 31st July 2018)

337. Feasey, N. A., Dougan, G., Kingsley, R. A., Heyderman, R. S. & Gordon, M. A. Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa. *Lancet (London, England)* **379,** 2489–2499 (2012).

338. Nontyphoidal Salmonella bacteremia - UpToDate. Available at: https://www.uptodate.com/contents/nontyphoidal-salmonella-bacteremia#H9. (Accessed: 30th July 2018)

339. Tacconelli, E. *et al.* Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet. Infect. Dis.* **18,** 318–327 (2018).

340. Gibani, M. M., Jin, C., Darton, T. C. & Pollard, A. J. Control of Invasive Salmonella Disease in Africa: Is There a Role for Human Challenge Models? *Clin. Infect. Dis.* **61,** S266–S271 (2015).

341. Leslie, T. *et al.* Overdiagnosis and mistreatment of malaria among febrile patients at primary healthcare level in Afghanistan: observational study. *BMJ* **345,** e4389–e4389 (2012).

342. Martin, L. B. *et al.* Status of paratyphoid fever vaccine research and development. *Vaccine* **34,** 2900–2902 (2016).

343. Paratyphoid Fever | Encyclopedia.com. Available at: https://www.encyclopedia.com/medicine/diseases-and-conditions/pathology/paratyphoid-fever. (Accessed: 28th July 2018)

344. Khosla, S. N., Jain, N. & Khosla, A. Gastric acid secretion in typhoid fever. *Postgrad. Med. J.* **69,** 121–3 (1993).

345. Bhutta, Z. A. Typhoid Fever. *Infect. Dis. Clin. Pract.* **14,** 266–272 (2006).

346. Treatment and prevention of enteric (typhoid and paratyphoid) fever - UpToDate. Available at: https://www.uptodate.com/contents/treatment-and-prevention-of-enteric-typhoid-and-paratyphoid-fever?search=paratyphoid fever&source=search_result&selectedTitle=2~88&usage_type=default&display_rank=2. (Accessed: 27th July 2018)

347. Zuckerman, J. N., Hatz, C. & Kantele, A. Expert Review of Vaccines Review of current typhoid fever vaccines , cross- protection against paratyphoid fever , and the European guidelines. *Expert Rev. Vaccines* **16,** 1029–1043 (2017).

348. Capeding, M. R. *et al.* Safety and immunogenicity of a Vi-DT typhoid conjugate vaccine: Phase I trial in Healthy Filipino adults and children. *Vaccine* **36,** 3794–3801 (2018).

349. WHO. *Status of Vaccine Research and Development for Paratyphoid Fever Prepared for WHO PD-VAC*. (2014).

350. Higginson, E. E., Simon, R. & Tennant, S. M. Animal Models for Salmonellosis: Applications in Vaccine Research. *Clin. Vaccine Immunol.* **23,** 746–56 (2016).

351. McCullagh, D. *et al.* Understanding paratyphoid infection: study protocol for the development of a human model of Salmonella enterica serovar Paratyphi A challenge in healthy adult volunteers. *BMJ Open* **5,** e007481–e007481 (2015).

352. World Health Organization. Typhoid vaccines: WHO position paper, March 2018 – Recommendations. *Vaccine* (2018). doi:10.1016/j.vaccine.2018.04.022

353. Enteric fevers: migrant health guide - GOV.UK. Available at: https://www.gov.uk/guidance/enteric-fevers-migrant-health-guide. (Accessed: 2nd August 2018)

354. CDC - Centers for Disease Control and. Typhoid Fever | Disease Directory | Travelers' Health | CDC. Available at: https://wwwnc.cdc.gov/travel/diseases/typhoid. (Accessed: 2nd August 2018)

355. Klemm, E. J. *et al.* Emergence of an extensively drug-resistant Salmonella enterica serovar typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *MBio* (2018). doi:10.1128/mBio.00105-18

356. Jin, C. *et al.* Efficacy and immunogenicity of a Vi-tetanus toxoid conjugate vaccine in the prevention of typhoid fever using a controlled human infection model of Salmonella Typhi: a randomised controlled, phase 2b trial. *Lancet* **390,** 2472–2480 (2017).

357. Bharat Biotech; Gates Foundation; The Clinton Healt Access initiative; Oxford University; PATH. Typbar TCV® from Bharat Biotech, World's First Typhoid Conjugate Vaccine Prequalified by WHO. *2018* Available at: http://www.who.int/medicines/news/2017/Bharat-Biotech-TypbarTCV-WHO-PQ-Press-Release-Global-Final.pdf.

358. Mohan, V. K. *et al.* Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study. *Clin. Infect. Dis.* **61,** 393–402 (2015).

359. Mohan, V. K. *et al.* Safety and Immunogenicity of a Vi Polysaccharide–Tetanus Toxoid Conjugate Vaccine (Typbar-TCV) in Healthy Infants, Children, and Adults in Typhoid Endemic Areas: A Multicenter, 2-Cohort, Open-Label, Double-Blind, Randomized Controlled Phase 3 Study. *Clin. Infect. Dis.* **61,** 393–402 (2015).

360. Vaccination | Typhoid Fever | CDC. Available at: https://www.cdc.gov/typhoid-fever/typhoid-vaccination.html. (Accessed: 25th July 2018)

361. Typhoid fever - NHS.UK. Available at: https://www.nhs.uk/conditions/typhoid-fever/. (Accessed: 2nd August 2018)

362. GAVI Alliance Approves $85 Million for Typhoid Conjugate Vaccines | News | PND. Available at: https://philanthropynewsdigest.org/news/gavi-alliance-approves-85-million-for-typhoid-conjugate-vaccines. (Accessed: 2nd August 2018)

363. Mani, S., Wierzba, T. & Walker, R. I. Status of vaccine research and development for Shigella. *Vaccine* **34,** 2887–2894 (2016).

364. Kotloff, K. L. *et al.* Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* **382,** 209–222 (2013).

365. Questions & Answers | Shigella – Shigellosis | CDC. Available at: https://www.cdc.gov/shigella/general-information.html. (Accessed: 23rd July 2018)

366. Shigellosis - Chapter 3 - 2018 Yellow Book | Travelers' Health | CDC. Available at: https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/shigellosis. (Accessed: 23rd July 2018)

367. Sources of Infection & Risk Factors | Shigella – Shigellosis | CDC. Available at: https://www.cdc.gov/shigella/infection-sources.html. (Accessed: 25th July 2018)

368. Kotloff, K. L. *et al.* Global burden of Shigella infections: implications for vaccine development and implementation of control strategies. *Bull. World Health Organ.* **77,** 651–66 (1999).

369. Kotloff, K. L. *et al.* Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* **382,** 209–222 (2013).

370. Shigella infection: Treatment and prevention in adults - UpToDate. Available at: https://www.uptodate.com/contents/shigella-infection-treatment-and-prevention-in-adults. (Accessed: 25th July 2018)

371. Rahman, M. *et al.* Emergence of Extensively Drug-resistant Shigella sonnei in Bangladesh. *Immunol. Infect. Dis.* **5,** 1–9 (2017).

372. Bodhidatta, L. *et al.* Establishment of a Shigella sonnei human challenge model in Thailand. *Vaccine* **30,** 7040–5 (2012).

373. Black, R. E. *et al.* Prevention of shigellosis by a Salmonella typhi-Shigella sonnei bivalent vaccine. *J. Infect. Dis.* **155,** 1260–5 (1987).

374. Herrington, D. A. *et al.* Studies in volunteers to evaluate candidate Shigella vaccines: further experience with a bivalent Salmonella typhi-Shigella sonnei vaccine and protection conferred by previous Shigella sonnei disease. *Vaccine* **8,** 353–7 (1990).

375. Munoz, C. *et al.* Characteristics of Shigella sonnei infection of volunteers: signs, symptoms, immune responses, changes in selected cytokines and acute-phase substances. *Am. J. Trop. Med. Hyg.* **53,** 47–54 (1995).

376. Kaslow, D. C. Presentation: The concept and status of Full Public Health Value Propositions (FPHVP) for Vaccines. (2018).

377. Typhoid fever - Vaccination - NHS.UK. Available at: https://www.nhs.uk/conditions/typhoid-fever/vaccination/. (Accessed: 25th July 2018)

378. Lee, E. C., Viboud, C., Simonsen, L., Khan, F. & Bansal, S. Detecting signals of seasonal influenza severity through age dynamics. *BMC Infect. Dis.* **15,** 587 (2015).

379. Baorto, E. & Baorto, D. Staphylococcus Aureus Infection Treatment Management. *Medscape* (2017). Available at: https://emedicine.medscape.com/article/971358-treatment. (Accessed: 17th July 2018)

380. Pray, L. Antibiotic Resistance, Mutation Rates and MRSA. *Nat. Educ.* **1,** (2008).

381. Tong, S. Y. C., Davis, J. S., Eichenberger, E., Holland, T. L. & Fowler, V. G. Staphylococcus aureus Infections: Epidemiology, Pathophysiology, Clinical Manifestations, and Management. *Clin. Microbiol. Rev.* **28,** 603–661 (2015).

382. Epidemiology of Staphylococcus aureus bacteremia in adults - UpToDate. Available at: https://www.uptodate.com/contents/epidemiology-of-staphylococcus-aureus-bacteremia-in-adults. (Accessed: 17th July 2018)

383. Schaumburg, F., Alabi, A. S., Peters, G. & Becker, K. New epidemiology of Staphylococcus aureus infection in Africa. *Clin. Microbiol. Infect.* **20,** 589–596 (2014).

384. Lee, B. Y. *et al.* Staphylococcus aureus vaccine for orthopedic patients : An economic model and analysis. *Vaccine* **28,** 2465–2471 (2010).

385. Epidemiology, risk factors, and microbiology of infective endocarditis - UpToDate. Available at: https://www.uptodate.com/contents/epidemiology-risk-factors-and-microbiology-of-infective-endocarditis. (Accessed: 26th July 2018)

386. Giersing, B. K., Dastgheyb, S. S., Modjarrad, K. & Moorthy, V. Status of vaccine research and development of vaccines for Staphylococcus aureus. *Vaccine* **34,** 2962–2966 (2016).

387. FDA. *Vaccines and Related Biological Products Advisory Committee Meeting Clinical Development Plan for Pfizer's Investigational Staphylococcus aureus Vaccine (SA4Ag) Intended for Pre-Surgical Prophylaxis in Elective Orthopedic Surgical Po*. (2017).

388. Hiramatsu, K. *et al.* Methicillin-resistant Staphylococcus aureus clinical strain with reduced vancomycin susceptibility. *J. Antimicrob. Chemother.* **40,** 135–6 (1997).

389. Liu, C. & Chambers, H. F. Staphylococcus aureus with heterogeneous resistance to vancomycin: epidemiology, clinical significance, and critical assessment of diagnostic methods. *Antimicrob. Agents Chemother.* **47,** 3040–5 (2003).

390. David, M. Z. & Daum, R. S. Community-associated methicillin-resistant Staphylococcus aureus: epidemiology and clinical consequences of an emerging epidemic. *Clin. Microbiol. Rev.* **23,** 616–87 (2010).

391. Staphylococcus aureus bacteremia with reduced susceptibility to vancomycin - UpToDate. Available at: https://www.uptodate.com/contents/staphylococcus-aureus-bacteremia-with-reduced-susceptibility-to-vancomycin. (Accessed: 17th July 2018)

392. Marty, F. M. *et al.* Emergence of a clinical daptomycin-resistant Staphylococcus aureus isolate during treatment of methicillin-resistant Staphylococcus aureus bacteremia and osteomyelitis. *J. Clin. Microbiol.* **44,** 595–7 (2006).

393. Skiest, D. J. Treatment failure resulting from resistance of Staphylococcus aureus to daptomycin. *J. Clin. Microbiol.* **44,** 655–6 (2006).

394. Fowler, V. G. *et al.* Effect of an Investigational Vaccine for Preventing Staphylococcus aureus Infections After Cardiothoracic Surgery. *JAMA* **309,** 1368 (2013).

395. Six reasons we lack an S. aureus vaccine. Available at: https://www.healio.com/pediatrics/mrsa/news/print/infectious-diseases-in-children/%7Bf3140a44-b05d-4963-800b-a1347980459a%7D/six-reasons-we-lack-an-s-aureus-vaccine. (Accessed: 31st July 2018)

396. Foster, T. J. Immune evasion by staphylococci. *Nat. Rev. Microbiol.* **3,** 948–958 (2005).

397. Montgomery, C. P. *et al.* Protective immunity against recurrent Staphylococcus aureus skin infection requires antibody and interleukin-17A. *Infect. Immun.* **82,** 2125–34 (2014).

398. Brown, A. F., Leech, J. M., Rogers, T. R. & McLoughlin, R. M. Staphylococcus aureus Colonization: Modulation of Host Immune Response and Impact on Human Vaccine Design. *Front. Immunol.* **4,** 507 (2014).

399. Parker, D. Humanized Mouse Models of Staphylococcus aureus Infection. *Front. Immunol.* **8,** 512 (2017).

400. McNeely, T. B. *et al.* Mortality among recipients of the Merck V710 Staphylococcus aureus vaccine after postoperative S. aureus infections: an analysis of possible contributing host factors. *Hum. Vaccin. Immunother.* **10,** 3513–6 (2014).

401. Frenck, R. W. *et al.* Safety, tolerability, and immunogenicity of a 4-antigen Staphylococcus aureus vaccine (SA4Ag): Results from a first-in-human randomised, placebo-controlled phase 1/2 study. *Vaccine* **35,** 375–384 (2017).

402. NovaDigm initiates Phase IIa trial of NDV-3A for S. aureus - Drug Development Technology. Available at: https://www.drugdevelopment-technology.com/news/novadigm-initiates-phase-iia-trial-ndv-3a-s-aureus/. (Accessed: 22nd July 2018)

403. Sanicas, M. Can we find a vaccine for Staph aureus? | World Economic Forum. *World Economic Forum* (2016). Available at: https://www.weforum.org/agenda/2016/02/can-we-find-a-vaccine-for-staph-aureus/. (Accessed: 17th July 2018)

404. Pneumococcal vaccine support - Gavi, the Vaccine Alliance. Available at: https://www.gavi.org/support/nvs/pneumococcal/. (Accessed: 25th July 2018)

405. van der Linden, M., Falkenhorst, G., Perniciaro, S., Fitzner, C. & Imöhl, M. Effectiveness of Pneumococcal Conjugate Vaccines (PCV7 and PCV13) against Invasive Pneumococcal Disease among Children under Two Years of Age in Germany. *PLoS One* **11,** e0161257 (2016).

406. Bonten, M. J. M. *et al.* Polysaccharide Conjugate Vaccine against Pneumococcal Pneumonia in Adults. *N. Engl. J. Med.* **372,** 1114–1125 (2015).

407. Esposito, S. & Principi, N. Impacts of the 13-Valent Pneumococcal Conjugate Vaccine in Children. *J. Immunol. Res.* 1–6 (2015). doi:10.1155/2015/591580

408. Farooqui, H. H., Zodpey, S., Chokshi, M. & Thacker, N. Estimates on state-specific Pneumococcal Conjugate Vaccines (PCV) coverage in the private sector in the year 2012: Evidence from PCV utilization data. *Indian J. Public Health* **60,** 145–9 (2016).

409. Boulton, M. L., Ravi, N. S., Sun, X., Huang, Z. & Wagner, A. L. Trends in childhood pneumococcal vaccine coverage in Shanghai, China, 2005–2011: a retrospective cohort study. *BMC Public Health* **16,** 109 (2015).

410. Gavi. Pneumococcal Vaccine Supply and Procurement Roadmap. (2017). doi:10.1016/S1068-607X(00)00070-6

411. Serum Institute Of India. Available at: https://www.seruminstitute.com/product_horizon.php. (Accessed: 25th July 2018)

412. Regev-Yochay, G. *et al.* Nasopharyngeal Carriage of Streptococcus pneumoniae by Adults and Children in Community and Family Settings. *Clin. Infect. Dis.* **38,** 632–639 (2004).

413. Pneumococcal pneumonia in children - UpToDate. Available at: https://www.uptodate.com/contents/pneumococcal-pneumonia-in-children. (Accessed: 25th July 2018)

414. Hill, P. C. *et al. Nasopharyngeal Carriage of Streptococcus pneumoniae in Gambian Villagers*. *Pneumococcal Carriage in Gambians • CID* (2006).

415. Gray, B. M., Converse, G. M. & Dillon, H. C. Epidemiologic studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first 24 months of life. *J. Infect. Dis.* **142,** 923–33 (1980).

416. Turner, P. *et al.* A Longitudinal Study of Streptococcus pneumoniae Carriage in a Cohort of Infants and Their Mothers on the Thailand-Myanmar Border. *PLoS One* **7,** e38271 (2012).

417. Wahl, B. *et al.* Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Global Health 697):e744-e757 (2018). doi:10.1016/S2214-109X(18)30247-X

418. Ngo, C. C., Massa, H. M., Thornton, R. B. & Cripps, A. W. Predominant Bacteria Detected from the Middle Ear Fluid of Children Experiencing Otitis Media: A Systematic Review. *PLoS One* **11,** (2016).

419. Berical, A. C., Harris, D., Dela Cruz, C. S. & Possick, J. D. Pneumococcal Vaccination Strategies. An Update and Perspective. *Ann. Am. Thorac. Soc.* **13,** 933–44 (2016).

420. Pneumococcal pneumonia in adults - UpToDate. Available at: https://www.uptodate.com/contents/pneumococcal-pneumonia-in-adults. (Accessed: 8th August 2018)

421. Resistance of Streptococcus pneumoniae to beta-lactam antibiotics - UpToDate. Available at: https://www.uptodate.com/contents/resistance-of-streptococcus-pneumoniae-to-beta-lactam-antibiotics. (Accessed: 25th July 2018)

422. Normark, B. H. *et al.* Clinical Isolates of Streptococcus pneumoniae That Exhibit Tolerance of Vancomycin. *Clin. Infect. Dis.* **32,** 552–558 (2001).

423. Domínguez, Á. *et al.* Effectiveness of the 13-valent pneumococcal conjugate vaccine in preventing invasive pneumococcal disease in children aged 7-59 months. A matched case-control study. *PLoS One* **12,** e0183191 (2017).

424. Su, L.-H. *et al.* Evolving pneumococcal serotypes and sequence types in relation to high antibiotic stress and conditional pneumococcal immunization. *Sci. Rep.* **5,** 15843 (2015).

425. Wilson, R. Natural adaptive immunity to Streptococcus pneumoniae lung infection. *Dr. thesis, UCL (University Coll. London).* (2014).

426. Wilson, R. *et al.* Protection against Streptococcus pneumoniae lung infection after nasopharyngeal colonization requires both humoral and cellular immune responses. *Mucosal Immunol.* **8,** 627–639 (2015).

427. Wilson, R. *et al.* Naturally Acquired Human Immunity to Pneumococcus Is Dependent on Antibody to Protein Antigens. *PLoS Pathog.* **13,** (2017).

428. Daniels, C. C., Rogers, P. D. & Shelton, C. M. A Review of Pneumococcal Vaccines: Current Polysaccharide Vaccine Recommendations and Future Protein Antigens. *J. Pediatr. Pharmacol. Ther.* **21,** 27–35 (2016).

429. Bröker, M., Berti, F., Schneider, J. & Vojtek, I. Polysaccharide conjugate vaccine protein carriers as a "neglected valency" – Potential and limitations. *Vaccine* **35,** 3286–3294 (2017).

430. Bogaert, D., Hermans, P. W. ., Adrian, P. ., Rümke, H. . & de Groot, R. Pneumococcal vaccines: an update on current strategies. *Vaccine* **22,** 2209–2220 (2004).

431. Chiavolini, D., Pozzi, G. & Ricci, S. Animal Models of Streptococcus pneumoniae Disease. *Clin. Microbiol. Rev.* **21,** 666–685 (2008).

432. Giebink, G. S. Otitis Media: The Chinchilla Model. *Microb. Drug Resist.* **5,** 57–72 (1999).

433. Parra, A. *et al.* Optimal dose of amoxicillin in treatment of otitis media caused by a penicillin-resistant pneumococcus strain in the gerbil model. *Antimicrob. Agents Chemother.* **46,** 859–62 (2002).

434. van der Ven, L. T. *et al.* A new rat model of otitis media caused by Streptococcus pneumoniae: conditions and application in immunization protocols. *Infect. Immun.* **67,** 6098–103 (1999).

435. Cunningham, A. L. *et al.* Vaccine development: From concept to early clinical testing. *Vaccine* **34,** 6655–6664 (2016).

436. Collins, A. M. *et al.* First Human Challenge Testing of a Pneumococcal Vaccine. Double-Blind Randomized Controlled Trial. *Am. J. Respir. Crit. Care Med.* **192,** 853–858 (2015).

437. Voysey, M. *et al.* Serotype-Specific Correlates of Protection for Pneumococcal Carriage: An Analysis of Immunity in 19 Countries. *Clin. Infect. Dis.* **66,** 913–920 (2018).

438. Andrews, N. J. *et al.* Serotype-specifi c eff ectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine : a postlicensure indirect cohort study. *Lancet Infect. Dis.* **14,** 839–846 (2014).

439. WHO. *WHO position paper on pneumococcal vaccines 2012*. (2012). Available at: http://www.who.int/immunization/position_papers/PP_pneumococcal_April_2012_summary.pdf (Accessed: 21st September 2018)

440. Gavi. *Advance market commitment for pneumococcal vaccines. Annual Report*. (2016). Available at: https://www.gavi.org/library/gavi.../amc/2016-pneumococcal-amc-annual-report/ (Accessed: 21st September 2018)

441. Pneumococcal AMC - Gavi, the Vaccine Alliance. Available at: https://www.gavi.org/funding/pneumococcal-amc/. (Accessed: 25th July 2018)

442. 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.* **14,** 1003–1012 (2018).

443. *Factors associated with pneumococcal conjugate and rotavirus vaccines uptake among infants: Evidence from the Africa Centre*. (2013).

444. *Global Pneumococcal Vaccine Market - Forecasts from 2018 to 2023*. https://www.researchandmarkets.com/reports/4518596/global-pneumococcal-vaccine-market-forecasts (Accessed: 21st September 2018)

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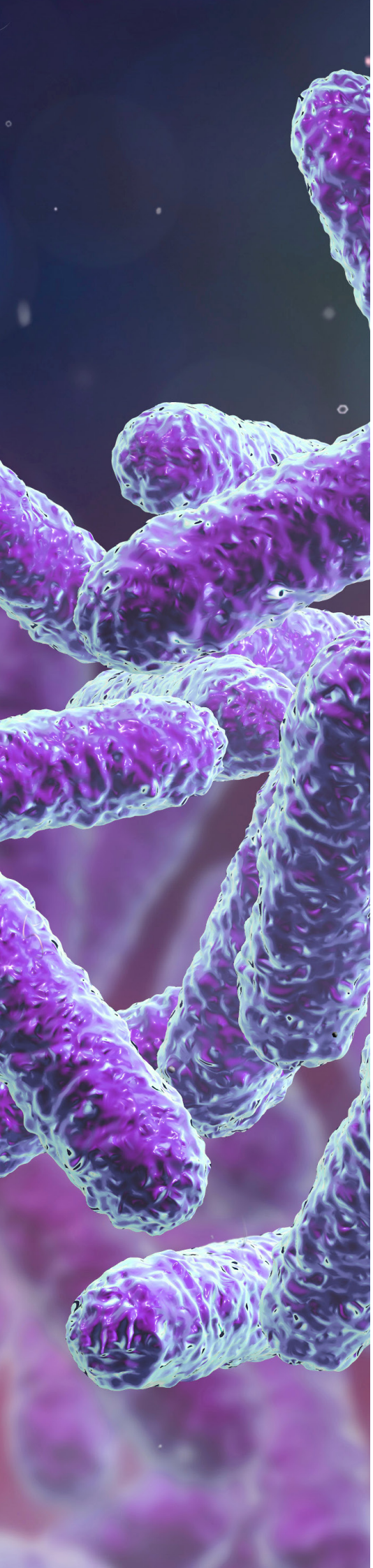


Appendix

Detailed Methodology

Introduction

This chapter lays out the detailed methodology, data sources and scoring system behind the scorecard assessment made for each pathogen. Also discussed is the scope of this project and how pathogens listed by the WHO were further sub-divided for the purposes of this report.

Scope of this project

The scope of this project was limited to the pathogens on the WHO global priority list of antibiotic resistant pathogens. Although ***M. tuberculosis*** is not included on the WHO priority list, the WHO have already established ***M. tuberculosis*** to be "a globally established priority for which innovative new treatments are urgently needed". Therefore, ***M. tuberculosis*** has been included in this assessment.

The WHO priority list was chosen for the scope of this project as it provides a starting point for pathogen comparison and was developed from consultation with a wide range of experts and a thorough review of available data. However, experts highlighted that this list may not be complete and that there are other pathogens – bacterial, viral and parasitic – that contribute significantly to AMR. The WHO list was also designed with a different purpose in mind – guiding the R&D of new therapeutics rather than vaccines.

Recognising the potential need to expand the scope of this project at a later stage, the scorecard system has been designed to be durable to cover additional pathogens as required.

Sub-division of pathogens

The following pathogens listed by the WHO were further sub-divided for the purpose of this report:

Enterobacteriaceae: This group was defined by the WHO as including *K. pneumoniae*, *E. coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., and *Providencia* spp., *Morganella* spp.

This group was split into three parts - ***K. pneumoniae***, ***E. coli*** and other ***Enterobacteriaceae*** to reflect the greater health impact of ***K. pneumoniae*** and ***E. coli*** compared to the rest of the group and also reflects the paucity of data on the other pathogens in this group.

E. coli: *E. coli* can be divided into multiple different subtypes with significant differences in epidemiology, clinical importance and R&D implications. Recognised subtypes include Enterotoxigenic (ETEC), Enteropathogenic (EPEC), Enteroinvasive (EIEC), Enterohaemorrhagic (EHEC), Enteroaggerative (EAEC), and Uropathogenic (UPEC) ***E. coli***.

To facilitate a useful comparison two ***E. coli*** groupings were created – ***E. coli*** (enteric) representing those subtypes causing enteric infections (ETEC, EPEC, EIEC, EHEC and EAEC) and ***E. coli*** (urinary) representing UPEC infections.

Research and development efforts for enteric and urinary subtypes are clearly delineated by different target antigens and therefore vaccine design – for example, enteric ***E. coli*** may be targeted by a toxoid vaccine but this approach would not be effective for urinary ***E. coli*** infections.

Whilst ***E. coli*** is also a cause of neonatal infections, data on the role of ***E. coli*** in the global burden of these infections is very limited and their health impact is likely much lower than the impact of enteric or urinary ***E. coli*** infections – for this reason, neonatal infections caused by ***E. coli*** were excluded from the current analysis.

Salmonella: *Salmonella* species encompass multiple different serotypes with significant differences in epidemiology, clinical importance and research and development implications**.** Serotypes are commonly divided into those which are typhoidal and non-typhoidal. Typhoidal serotypes included Typhi and Paratyphi which cause distinct clinical syndromes and have distinct epidemiology. Non-typhoidal serotypes generally cause enteric infections ("Salmonellosis") but can in some regions also cause invasive disease (invasive non-typhoidal salmonella).

To facilitate a useful comparison, three ***Salmonella*** groupings were created – ***S.*** Typhi, ***S.*** Paratyphi and non-typhoidal salmonella.

Non-typhoidal ***Salmonella*** was not further subdivided into invasive and non-invasive subtypes as the majority of cases are not invasive and global estimates of disease burden often do not make this further subdivision.

Research and development efforts for these different groups are also clearly delineated by different target antigens and therefore vaccine design – for example, ***S.*** Typhi contains a Vi capsular antigen that is targeted by current vaccines but this antigen is absent from ***S.*** Paratyphi.

Approach to data collection

Data collection focused on collating high-quality, robust assessments whilst also making these assessments consistent across pathogens. To achieve this, wherever possible data was sourced from well recognised global datasets, primarily the IHME, WHO, Evaluate Pharma, and PharmaProjects, which ensured a high quality and consistency across pathogens.

Where global datasets were not available large, multi-pathogen review articles or meta-analyses were favoured. Only when data was not available in the above formats were individual articles in the research literature considered.

Similarly, when conducting expert interviews, several measures were taken to ensure high quality and consistency. All experts were provided with the same information at the start of the interview and a structured interview guide was used to ensure consistency in questioning.

Expert interviews were conducted in three discrete rounds. The first round involved structured interviews with a wide range of experts spanning the global health community – including organisations such as the WHO and The Gates Foundation, regulatory bodies such as the EMA, and industry representatives from large pharmaceutical companies as well as a number of smaller biotechnology companies. The second round included more detailed interviews with pathogen experts to confirm the outcomes of the assessments and the preliminary recommendations for each pathogen. The third round was focused on validating preliminary findings with interviewees and collecting feedback on findings and insights.

The scorecard

To facilitate cross-pathogen comparisons, a balanced scorecard was deployed, assessing pathogens on impact, probability of R&D success and probability of uptake:

Fields not scored represent qualitative assessments included for extra information and detail.

PATHOGEN SCORECARD

Health impact:

Direct health impact

- Global mortality associated with pathogen
- Global morbidity associated with pathogen

Impact on AMR reduction

- Antibiotic use currently associated with pathogen
- Urgency of AMR threat

Secondary health impact

- Benefits of vaccination not directly related to pathogen mortality and morbidity (e.g. cross protection)

Sub-population benefits

- Benefits of particular importance to certain populations (e.g. pregnant women, children)

Alternative interventions

- List of any alternative interventions

Probability of R&D success:

Pipeline robustness

- Quantitative and qualitative assessment of pipeline strength

Pathogen biology

- Existence of natural immunity
- Knowledge of vaccine targets

Pre-clinical and clinical R&D

- Ease of pre-clinical programme
- Ease of clinical programme (incl. regulatory success)

Combination potential

- Potential to combine with other vaccines

Acceleration potential

- Identification of definitive moves to accelerate development

Major barriers to development

- Identification of scientific or other barriers

Probability of uptake:

Commercial attractiveness

- Likelihood of successful market strategy

Expected policy stance

- Strength of policy recommendations to address threat

Payer, government or Gavi support

- Likelihood of support in low-income countries, mid-income countries and high-income countries based on cost-effectiveness assessment and Gavi priorities

Barriers to uptake

- Influence of cultural factors, need for new vaccination touchpoint and new clinician behaviours

Who needs the vaccine / Potential vaccination strategy

- Identification of those who will benefit from the vaccine
- Likely vaccination strategy

Potential health impact

Incidence, Morbidity and Mortality

IHME data was used where available as it provided a high level of granularity for the pathogens in this report. Wherever possible this was cross-checked against WHO data and any discrepancies explored during expert interviews. Based on expert opinion, WHO data for TB mortality was selected over IHME data for this pathogen. IHME and WHO use a defined methodology and their data is accepted in the global health community.

Where pathogen data was not reported in the IHME or WHO datasets, the literature was searched for review articles and meta-analyses providing estimates of disease burden at a global level. These sources are generally viewed with a lower confidence compared to IHME or WHO datasets.

Where the above data sources were not available, global disease burden was estimated by combining estimates of global disease from clinical conditions (for example, cellulitis, pneumonia, endocarditis, and others) with estimates of global causative organism splits for each condition. Data on global disease burden from clinical conditions was generally taken from IHME datasets. As a simplification, causative organism splits for incidence were then used to attribute morbidity and mortality of a clinical condition to the pathogen of interest.

Whilst necessary due to limitations of the available data, this approach produces results of a lower confidence which must be interpreted with caution but likely reflects the correct order of magnitude of pathogen health impact.

The detailed methodology for this estimation is below:

Pathogen	Data source / Assumptions
A. baumannii	▶ Incidence, mortality and morbidity for *A. baumannii* based on data for LRTI from all pathogens listed on 2016 IHME – assumes 1% of this is due to *A. baumannii* based on causative organism incidence reported in Gadsby *et al* 2016, Clinical Infectious Disease
Campylobacter spp.	▶ Mortality and morbidity from 2016 IHME data ▶ Incidence from Havelaar *et al* 2015, PloS Medicine
Enterobacteriaceae	▶ Mortality and morbidity for UTI, LRTI and neonatal sepsis from all pathogens listed on 2016 IHME. Incidence for UTI and LRTI listed on 2016 IHME, incidence for Neonatal sepsis from Fleischmann-Struzek *et al* 2018, The Lancet Respiratory Medicine. Assumes the following split for *Enterobacteriaceae*: – 2% of UTI based on causative organism incidence reported in Flores-Mireles *et al* 2015, Nature Reviews Microbiology – 0.9% of LRTI based on causative organism incidence reported in von Baum *et al* 2010, European Respiratory Journal – 0.3% of neonatal sepsis based on causative organism incidence reported in Simonsen *et al* 2015, Clinical Microbiology Reviews
E. faecium	▶ Incidence, mortality and morbidity for UTI and endocarditis from all pathogens listed on 2016 IHME – assumes the following split for *E. faecium*: – 3% of UTI based on causative organism incidence reported in Flores-Mireles *et al* 2015, Nature Reviews Microbiology and Hidron *et al* 2008, Infection Control Hospital Epidemiology – 4% of endocarditis based on causative organism incidence reported in Murdoch *et al* 2009, Archives of Internal Medicine and Hidron *et al* 2008, Infection Control Hospital Epidemiology
E. coli	▶ Mortality and morbidity for enteric *E. coli* based on EPEC and ETEC from 2016 IHME data ▶ Incidence for enteric *E. coli* based on EPEC and ETEC from Havelaar *et al* 2015, PloS Medicine ▶ Incidence, mortality and morbidity for urinary *E. coli* based on data for UTI from all pathogens listed on 2016 IHME – assumes 70% of this is due to *E. coli* based on causative organism incidence reported in Flores-Mireles *et al* 2015, Nature Reviews Microbiology
H. influenzae	▶ Incidence, mortality and morbidity for *H. influenzae* b meningitis from 2016 IHME data ▶ Mortality and morbidity for *H. influenzae* b pneumonia from 2016 IHME data. Incidence for pneumonia from Watt *et al* 2009, The Lancet
H. pylori	▶ Incidence, mortality and morbidity for PUD and gastric cancer listed on 2016 IHME – assumes *H. pylori* is responsible for: – 70% of all mortality and morbidity from PUD based on Ford *et al* 2016, Cochrane Database of Systematic Reviews – 78% of all mortality and morbidity from gastric cancer based on IARC working group report 2014
K. pneumoniae	▶ Incidence, mortality and morbidity for UTI and LRTI from all pathogens listed on 2016 IHME – assumes the following split for *K. pneumoniae*: – 7% of UTI based on causative organism incidence reported in Flores-Mireles *et al* 2015, Nature Reviews Microbiology – 4% of LRTI based on causative organism incidence reported in Gadsby *et al* 2016, Clinical Infectious Diseases

Pathogen	Data source / Assumptions
M. tuberculosis	▶ Mortality from 2016 WHO data ▶ Incidence and morbidity from 2016 IHME data ▶ Mortality and morbidity data includes *M. tuberculosis* infections in the context of concurrent HIV infection
N. gonorrhoeae	▶ Mortality taken from 2016 WHO data ▶ Incidence and morbidity from 2016 IHME data
P. aeruginosa	▶ Mortality and morbidity for UTI, LRTI and neonatal sepsis from all pathogens listed on 2016 IHME. Incidence for UTI and LRTI listed on 2016 IHME, incidence for Neonatal sepsis from Fleischmann-Struzek *et al* 2018, The Lancet Respiratory Medicine. Assumes the following split for *P. aeruginosa*: – 2% of UTI based on causative organism incidence reported in Flores-Mireles *et al* 2015, Nature Reviews Microbiology – 3% of LRTI based on causative organism incidence reported in Gadsby *et al* 2016, Clinical Infectious Disease – 0.2% of neonatal sepsis based on causative organism incidence reported in Simonsen *et al* 2015, Clinical Microbiology Reviews
Salmonella spp.	▶ Incidence, mortality and morbidity for *S.* Typhi and *S.* Paratyphi from 2016 IHME data ▶ Incidence, mortality and morbidity for non-typhoidal salmonella from Havelaar *et al* 2015, PloS Medicine, includes both invasive and diarrhoeal disease
Shigella spp.	▶ Mortality and morbidity from 2016 IHME data ▶ Incidence from Havelaar *et al* 2015, PloS Medicine
S. aureus	▶ Incidence, mortality and morbidity for cellulitis, endocarditis, meningitis and pneumonia from all pathogens listed on 2016 IHME – assumes the following split for *S. aureus*: – 30% of cellulitis based on causative organism incidence reported in Lee *et al* 2015, BMC Infectious Diseases – 31% of endocarditis based on causative organism incidence reported in UptoDate, Epidemiology, risk factors, and microbiology of infective endocarditis – 3% of meningitis based on causative organism incidence reported in Tong *et al* 2015, Clinical Microbiology Review and BMJ Best Practice for bacterial/viral split – 10% of pneumonia based on causative organism incidence reported in Gadsby *et al* 2016, Clinical Infectious Diseases
S. pneumoniae	▶ Incidence, mortality and morbidity for *S. pneumoniae* meningitis from 2016 IHME data ▶ Mortality and morbidity for *S. pneumoniae* pneumonia from 2016 IHME data. Incidence for pneumonia from all pathogens listed on 2016 IHME - assumes 36% of all cases are due to *S. pneumoniae* based on causative organism incidence reported in Gadsby *et al* 2016, Clinical Infectious Diseases ▶ Morbidity for AOM from all pathogens listed on 2016 IHME – assumes 27% of all mortality and morbidity from AOM is due to *S. pneumoniae* based on causative organism incidence reported in Ngo *et al* 2016, PLOS One

The estimated global mortality and morbidity was then scored on the following system with thresholds set based upon observed clustering of data:

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Mortality	<0.05M global deaths (0 pts) OR 0.05-0.1M global deaths (0.5 pts)	0.1 – 1M global deaths	>1M global deaths
Morbidity	<0.25M years lived with disability	0.25 – 0.45M years lived with disability	>0.45M years lived with disability

Urgency of AMR threat

- Assessment of this indicator was based on four factors:
  - The CDC "Biggest Threats" list
  - The WHO Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics
  - Literature review for evidence of resistance / tolerance to last line antibiotics
  - Expert opinion

The pathogens were then scored on the following system:

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Urgency of AMR threat	Pathogen still sensitive to a range of agents OR only on one of the CDC/ WHO priority lists	Strains requiring last-line therapy reported OR second highest level on either CDC/WHO priority lists	Resistance to last-line therapy reported OR highest level on either CDC/WHO priority list

Finally the assessment was discounted by one point on the scorecard where resistance to last-line therapies had been reported but this had not had a significant impact on clinical practice. Whilst all the pathogens evaluated in this report are on the WHO priority list for AMR, some received a score of 0 on this indicator. This is a score given in relation to the other pathogens evaluated and does not indicate that the pathogen poses no AMR threat.

Antibiotic use

The aim of this assessment was to create an initial, order of magnitude assessment of antibiotic uses associated with the pathogen. To this end, for each major clinical condition or infection associated with the pathogen, the incidence of this clinical condition or infection was multiplied by the standard length of treatment. The assessment assumed that:

- All infections are treated
- Treatment is with a single completed course
- Antibiotic choice is for pathogen that has a "normal" level of AMR
- Antibiotic choice is based on recommendations in resource-intensive settings

The estimated global antibiotic use was then colour-coded on the following system with thresholds set based upon observed clustering of data:

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Antibiotic use	<100M antibiotic days	100M -1B antibiotic days	>1B antibiotic days

A key point in the cross-cutting activities chapter is focused on increasing the robustness of this assessment.

Secondary health impact

This indicator is an assessment of vaccine impact beyond morbidity and mortality for the pathogen of interest, for example cross-protection from other pathogens or reduction in disease risk for conditions not directly associated with infection.

The assessment is based on literature review and expert opinions and although not scored, was included in the scorecard to give a more detailed assessment of the potential health impact of a vaccine.

Sub-population benefits

This indicator is an assessment of sub-populations at particularly high risk of pathogen infection or high impact if infection occurs.

The assessment is based on literature review and expert opinions and although not scored, was included in the scorecard to give a more detailed assessment of the potential health impact of a vaccine.

Alternative interventions

This indicator is an assessment of potential alternative treatment or prevention strategies if AMR rendered current antibiotics ineffective

The assessment is based on literature review and expert opinions and although not scored, was included in the scorecard to give more information about the pathogen.

Probability of R&D success

Pipeline robustness

Vaccine candidates for each pathogen were collated based on searches in the following databases and literature:

- Evaluate Pharma
- PharmaProjects
- Review of major pharmaceutical websites
- Recent literature reviews (from 2013 onwards). Vaccine candidates were included when found to be in active development (confirmed by scientific results published since 2013).

Duplicates were then removed and the data grouped by development phase based on the following groupings:

- Pre-clinical: Academic research, Research project, Pre-clinical
- Phase I: Phase I
- Phase II: Phase II
- Phase III: Phase III, Filed
- Marketed: Approved, Marketed, Phase IV

Points were attributed to each vaccination programme in the pipeline depending on their progress and added up to a final score:

- 1 pt: Research/Pre-clinical
- 2 pts: in Phase I
- 3 pts: in Phase II
- 4 pts: in Phase III
- 5 pts: Marketed
- 1 extra point each for commercially driven vaccination programmes

The results were scored based on the following system:

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Pipeline robustness	Pipeline robustness 0-25 points	Pipeline robustness 25 – 100 points	Pipeline robustness > 100 points

Finally the assessment was supplemented (+/- up to 0.5 points on scorecard) by a qualitative assessment of the developmental pipeline, taking into account:

- Qualitative assessment of vaccine candidate quality
- Expert opinions/assessments
- Knowledge of pathogen from the same family / genus

This methodology ensures a comprehensive view on the current pipeline; however, it might not be entirely comprehensive given that the literature review was in depth, but not completely exhaustive.

Pathogen biology

Pathogen biology was assessed by looking at the existence of natural immunity, cross-strain immunity and knowledge of vaccine targets.

This was based on literature review and expert opinions and scored based on the following system:

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Pathogen biology	Two reds (0 pts) OR One red, one amber (0.5 pts) in sub-scores below	One red, one green (1 pt) OR Two amber (1 pt) in sub-scores below	One green, one amber (1.5 pts) in sub-scores below OR Two greens (2 pts)
Existence of natural immunity/ cross-strain immunity?	▶ Almost non-existent immunity post natural infection ▶ No cross-strain immunity	▶ Partial immunity post natural infection ▶ OR partial cross-strain immunity	▶ Protective immunity post natural infection ▶ OR cross-strain immunity
Knowledge of vaccine targets	▶ Pathogen biology still largely unknown ▶ No good vaccine targets identified yet	▶ Pathogen biology fairly well-understood ▶ Conserved & immunogenic targets identified	▶ Pathogen biology largely understood ▶ OR protective target antigens defined

Pre-clinical and clinical R&D

Pre-clinical and clinical R&D was assessed by looking at the ease of pre-clinical and clinical programmes.

This was based on literature review and expert opinions and scored based on the following system:

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Pre-clinical and clinical R&D	Two reds (0 pts) OR One red, one amber (0.5 pts) in sub-scores below	One red, one green (1 pt) OR Two amber (1 pt) in sub-scores below	One green, one amber (1.5 pts) in sub-scores below OR Two greens (2 pts)
Ease of pre-clinical programme	No appropriate animal (or in vitro) models in place	Animal (or in vitro) models in place, relevance often unclear	Appropriate animal (or in vitro) models in place that reliably predict results in humans
Ease of clinical programme	Low, based on ▶ Possibility of simple efficacy trials (correlates, challenges) ▶ Trial infrastructure; trial set-up ▶ Diagnostics etc.	Middle, based on ▶ Possibility of simple efficacy trials (correlates, challenges) ▶ Trial infrastructure; trial set-up ▶ Diagnostics etc.	High, based on : ▶ Possibility of simple efficacy trials (correlates, challenges) ▶ Trial infrastructure; trial set-up ▶ Diagnostics etc.

Combination potential

Combination potential captures policy or scientific support for creating a combination vaccine.

This qualitative assessment is based on literature review and expert opinions – it does not form part of the score for probability of R&D success but is included in the scorecard to give additional information.

Acceleration potential

Acceleration potential identifies key areas where additional focus and investment could accelerate bringing a vaccine to market.

This qualitative assessment is based on literature review and expert opinions – it does not form part of the score for probability of R&D success but is included in the scorecard to give additional information.

Major barriers to development

Major barriers to development describes the common themes from experts and the literature of barriers currently preventing successful vaccine development.

This qualitative assessment is based on literature review and expert opinions – it does not form part of the score for probability of R&D success but is included in the scorecard to give additional information.

Probability of uptake

Who needs the vaccine and potential vaccination strategy

Who needs the vaccine refers to the population who would benefit from a vaccine whereas potential vaccination strategy describes the likely initial target population for a new vaccine. This takes into account epidemiology, likely vaccine product profile, implementation challenges and cost.

It is important to note that for this assessment, the target population described by the likely vaccination strategy may only be a small subsection of the total population that could benefit from a vaccine. This reflects the different commercial routes to market for a new vaccine. For example, whilst there is a large population world-wide who could benefit from a vaccine against certain hospital-acquired infections, the likely vaccination strategy may be to concentrate – at least initially – solely on high risk patients in high-resource settings.

Subsequent sections of the scorecard were assessed in reference to this target population rather than the total population described by "who needs the vaccine".

This qualitative assessment is based on literature review and expert opinions – it does not form part of the score for probability of uptake but is included in the scorecard to give additional information and as a guide to interpreting later scores in this section.

Expected policy stance

Expected policy stance refers to the likelihood of the relevant policy body supporting vaccination of the target population identified in the potential vaccination strategy above.

This assessment is based on literature review and expert opinions including:

- Incidence, morbidity and mortality assessed in impact section of scorecard
- WHO, SAGE, and PDVAC reports
- Chatham House report
- Expert opinion
- Analogous, currently licensed vaccines

Payer, government or Gavi support

Payer, government or Gavi support refers to the likelihood of the relevant funder supporting vaccination of the target population identified in the potential vaccination strategy above.

This assessment is based on literature review and expert opinions taking into account analogous, currently licensed vaccines, and scored on the following system depending on the likely target population:

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Payer, government or Gavi support	Likely target population falls into one of the categories below	Likely target population falls into one of the categories below	Likely target population falls into one of the categories below
Likely target pop. in Gavi country	Mortality too low for Gavi support	Mortality borderline for Gavi support	Mortality within range for Gavi support
Likely target pop. in HIC/MIC	Unlikely to be cost-effective in target population OR Little/no support from bodies representing target population	May be cost-effective in target population OR Some support from bodies representing target population	Likely to be cost-effective in target population OR Likely support from bodies representing target population

Gavi sets priorities for vaccine support programmes every five years through their vaccine investment strategy process. Previous frameworks used in the prioritisation of vaccines have placed a large emphasis on the potential impact of a vaccine on mortality and on the cost-effectiveness of vaccines (cost per death averted).

The funding decisions of governments and payers are informed by cost-effectiveness calculations. These calculations aim to quantify the gains associated with a particular intervention or policy relative to the cost. Gains are often measured in disability-adjusted life years (DALYs), which represented a weighted combination of the mortality and morbidity effects of an intervention. Other possible measures include quality-adjusted life years (QALYs), life years or years of life saved.

Barriers to uptake

Barriers to uptake refers to the potential barriers that would prevent vaccine uptake in the target population identified in the potential vaccination strategy above

This assessment is based on literature review and expert opinions and scored on the following system:

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Barriers to uptake	Extensive challenges with a new vaccination touchpoint required and high level of clinician judgement/ clinical engagement	New vaccination touchpoint required OR Cultural barriers, negative patient perceptions OR Evidence of low uptake for marketed vaccine	Well defined target population with likelihood of high acceptability OR Well defined target population with likelihood of high acceptability, but possible difficulties in infrastructure for vaccination OR Evidence of high uptake for marketed vaccine

Green assessment can be discounted by 0.5 points to reflect possible need to invest in infrastructure to enable high uptake of likely vaccine strategy.

A Green assessment was discounted by 0.5 points where the literature and expert opinions suggested significant investment in infrastructure may be required to support uptake.

Commercial attractiveness

This qualitative assessment is based on literature review and expert opinions taking into account the size and location of the target population and the role of Gavi in funding a vaccination programme. It does not form part of the score for probability of uptake but is included in the scorecard to give additional information.

	Thresholds		
Indicator	**0 / 0.5 points**	**1 point**	**1.5 / 2 points**
Commercial attractiveness	Poorly defined target population OR Small target populations predominately in developing markets OR Unlikely to be supported by Gavi	Difficulty defining target population in developed markets OR Large target populations distributed predominately in developing markets with potential Gavi support	Well defined target population in developed markets OR Large target populations distributed across developed and developing markets

Weighting of scores and matrix assessment

In order to facilitate cross-pathogen comparisons, each score on the scorecard was weighted with each of the three sections totalling to a score of 100:

Section	Indicator	Weighting
Health impact	Mortality	50%
	Morbidity	20%
	Urgency of AMR threat	30%
Probability of R&D success	Pipeline robustness	40%
	Pre-clinical and clinical R&D	30%
	Pathogen biology	30%
Probability of uptake	Expected policy stance	30%
	Payer, government or Gavi support	50%
	Barriers to uptake	20%

These weighted scores were then used to create the matrix of Impact vs. Probability of R&D success shown in the Executive summary.

Vaccine Pipeline Information

PATHOGEN PIPELINE SUMMARY TABLE

Pathogen name	Research / Preclinical	Phase I	Phase II	Phase III	Marketed	Total
Acinetobacter baumannii	0	0	0	0	0	0
Campylobacter	3	1	0	0	0	4
Enterobacteriaceae	0	0	0	0	0	0
Enterococcus faecium	0	0	0	0	0	0
Escherichia coli (enteric)	11	2	3	1	1	18
Escherichia coli (urinary)	1	1	1	0	0	3
Haemophilus influenzae	8	1	2	3	46	60
Helicobacter pylori	9	1	0	0	0	10
Klebsiella pneumoniae	3	0	0	0	0	3
Mycobacterium. tuberculosis	25	4	8	2	13	52
Neisseria gonorrhoeae	4	0	0	0	0	4
Pseudomonas aeruginosa	4	0	0	0	0	4
Salmonella (non-typhoidal)	5	0	0	0	0	5
Salmonella Paratyphi	2	1	0	1	0	4
Salmonella Typhi	6	2	2	2	20	32
Shigella	15	2	2	0	0	19
Staphylococcus aureus	23	2	2	0	0	27
Streptococcus pneumoniae	31	7	8	3	7	56

Pathogen	Product	Developer	Category	Phase	Source
Campylobacter	Campylobactor/ ETEC Vaccines	Immuron	Commercial	Research / Preclinical	EvaluatePharma
Campylobacter	Campylobacter Research Program	Vir Biotechnology	Commercial	Research / Preclinical	EvaluatePharma
Campylobacter	Campylobacter jejuni capsule conjugate	US Department of Defense	Academic	Phase I	Riddle et al., 2016, Vaccine
Campylobacter	PEB1 DNA prime/ protein boost	Shandong Medical College	Academic	Research / Preclinical	Riddle et al., 2016, Vaccine
Escherichia coli (enteric)	Dukoral	Johnson & Johnson	Commercial	Marketed	PharmaProjects
Escherichia coli (enteric)	ETEC & Shigella vaccine	University of Maryland	Academic	Phase I	EvaluatePharma
Escherichia coli (enteric)	Etvax	Scandinavian Biopharma	Commercial	Phase II	EvaluatePharma
Escherichia coli (enteric)	ETEC vaccine	Eubiologics	Commercial	Phase III	PharmaProjects
Escherichia coli (enteric)	E. coli (LT) Vaccine	U.S. Army Medical	Academic	Research / Preclinical	EvaluatePharma
Escherichia coli (enteric)	Bacterial diarrhoea vaccine	Prokarium	Commercial	Research / Preclinical	EvaluatePharma
Escherichia coli (enteric)	E. coli Vaccine Program	Syntiron	Commercial	Research / Preclinical	EvaluatePharma
Escherichia coli (enteric)	ETEC vaccine	Hilleman Laboratories	Commercial	Research / Preclinical	PharmaProjects
Escherichia coli (enteric)	E. coli vaccine	Mucosis	Commercial	Research / Preclinical	PharmaProjects
Escherichia coli (enteric)	CDX-EC	Codagenix	Commercial	Research / Preclinical	PharmaProjects
Escherichia coli (enteric)	ETEC/Cholera vaccine, Valneva; VLA 1701; VLA-1701; VLA1701	Valneva	Commercial	Phase II	PharmaProjects
Escherichia coli (enteric)	Campylobactor/ ETEC Vaccines	Immuron	Commercial	Research / Preclinical	EvaluatePharma
Escherichia coli (enteric)	ACE527	PATH, NVSI, UGA	Academic	Phase II	PATH - Status of Vaccine Development for ETEC (27-Jun-18)
Escherichia coli (enteric)	FTA	PATH, NMRC, Sanofi, IDRI	Commercial	Phase I	PATH - Status of Vaccine Development for ETEC (27-Jun-18)
Escherichia coli (enteric)	Ty21a typhoid vaccine expressing Shigella LPS and MEFA	Protein Potential LLC.	Commercial	Research / Preclinical	PATH - Status of Vaccine Development for ETEC (27-Jun-18)

Pathogen	Product	Developer	Category	Phase	Source
Escherichia coli (enteric)	CVD GuaBA mutants expressing ETEC antigens	UMB, PaxVax	Commercial	Research / Preclinical	PATH - Status of Vaccine Development for ETEC (27-Jun-18)
Escherichia coli (enteric)	MEFA	KSU, JHU, PATH	Academic	Research / Preclinical	PATH - Status of Vaccine Development for ETEC (27-Jun-18)
Escherichia coli (enteric)	LT/ST Fusion/ conjugate	ENTVAC Consortium, PATH	Academic	Research / Preclinical	PATH - Status of Vaccine Development for ETEC (27-Jun-18)
E. coli (urinary)	ExPEC Vaccine	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma
E. coli (urinary)	UPEC Vaccine Program	GlaxoSmithKline	Commercial	Research / Preclinical	EvaluatePharma
E. coli (urinary)	UTI Vaccine Program	Sequoia Sciences	Commercial	Phase I	EvaluatePharma
Haemophilus influenzae	Vaxelis	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Eupenta	LG Chem	Commercial	Phase III	EvaluatePharma
Haemophilus influenzae	Actacel	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	ActHIB	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Bactolisato	Grupo De Laboratorios Leti	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Biohib	Bharat Biotech	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	ComBEfive	Biological E	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Comvax	Merck & Co	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	DTaP-IPV/Act-Hib	Statens Serum Institut	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Easyfive-TT	Panacea Biotec	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Easyfour-TT	Panacea Biotec	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Easysix-TT	Panacea Biotec	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Euforvac-Hib	LG Chem	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Euhib	LG Chem	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Haemophilus Influenzae Type b Conjugate Vaccine	Walvax Biotechnology	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Haemophilus Influenzae Type b Conjugate Vaccine	Biological E	Commercial	Marketed	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Haemophilus influenzae	Haemophilus Influenzae Type b Vaccine	Chongqing Zhifei Biological Products	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Hexacima	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Hib conjugate vaccine	Sun Pharmaceutical Industries	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Hib Vaccine	PT Bio Farma	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	HibACon	Chongqing Zhifei Biological Products	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Hiberix	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	HibTITER	Pfizer	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Infanrix Hep B-IPV/ Hib	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Infanrix Hib	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Infanrix IPV/Hib	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	MenHibrix	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Menitorix	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	NovoHib	Panacea Biotec	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Pediacel	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Pedvax HIB	Merck & Co	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Pentabio	PT Bio Farma	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Pentacel	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	PENTAct-HIB	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Pentavac	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Pentaxin	Center for Research and Production of Vaccines and Biologicals (POLYVAC)	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Provax	Almirall	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Quimi-Hib	VABIOTECH	Commercial	Marketed	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Haemophilus influenzae	Quintanrix	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Quinvaxem	Johnson & Johnson	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Shan Hib	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Shan4	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Shan5	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Sii HibPRO	Serum Institute of India	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	Tetracel	Pfizer	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	TriHIBit	Sanofi	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	TritanrixHB	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Haemophilus influenzae	LBVD	LG Chem	Commercial	Phase I	EvaluatePharma
Haemophilus influenzae	Shan 6	Sanofi	Commercial	Phase II	EvaluatePharma
Haemophilus influenzae	GSK2838497A	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma
Haemophilus influenzae	MT-2355	Mitsubishi Tanabe Pharma	Commercial	Phase III	EvaluatePharma
Haemophilus influenzae	VN-0105	Sanofi	Commercial	Phase III	EvaluatePharma
Haemophilus influenzae	DTcP-Hib Combo Vaccine	Tianjin CanSino Biotechnology	Commercial	Research / Preclinical	EvaluatePharma
Haemophilus influenzae	MCV2-Hib Combo Vaccine	Tianjin CanSino Biotechnology	Commercial	Research / Preclinical	EvaluatePharma
Haemophilus influenzae	ACYW135-Hib Polysaccharide Conjugate Vaccine	Chongqing Zhifei Biological Products	Commercial	Research / Preclinical	EvaluatePharma
Haemophilus influenzae	DTP-Hib Vaccine	Zydus Cadila	Commercial	Research / Preclinical	EvaluatePharma
Haemophilus influenzae	Haemophilus Influenzae Type b Conjugate Vaccine	Wellstat Group	Commercial	Research / Preclinical	EvaluatePharma
Haemophilus influenzae	Liquid Hexavalent Vaccine	Biological E	Commercial	Research / Preclinical	EvaluatePharma
Haemophilus influenzae	Haemophilus influenza vaccine	The University of Iowa	Academic	Research / Preclinical	EvaluatePharma
Haemophilus influenzae	Liquid Hexavalent Vaccine	GlaxoSmithKline	Commercial	Research / Preclinical	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Helicobacter pylori	IMX101	ImevaX	Commercial	Phase I	EvaluatePharma
Helicobacter pylori	Helicobacter pylori vaccine	HeliCure	Commercial	Research / Preclinical	EvaluatePharma
Helicobacter pylori	H. pylori vaccine	EpiVax	Commercial	Research / Preclinical	EvaluatePharma
Helicobacter pylori	H. pylori vaccine	Academy of Military Medical Sciences	Academic	Research / Preclinical	EvaluatePharma
Helicobacter pylori	H. pylori vaccine	ImmunoBiology	Commercial	Research / Preclinical	PharmaProjects
Helicobacter pylori	H. pylori vaccine	ImmBio	Commercial	Research / Preclinical	EvaluatePharma
Helicobacter pylori	Urease epitope vaccine	Sichuan University	Academic	Research / Preclinical	Sutton et al., 2018, Vaccine
Helicobacter pylori	Lp220 vaccine	Southern Medical University	Academic	Research / Preclinical	Sutton et al., 2018, Vaccine
Helicobacter pylori	Probiotic vaccine delivery	China Pharmaceutical University	Academic	Research / Preclinical	Sutton et al., 2018, Vaccine
Helicobacter pylori	Gastric Cancer Vaccine	MCRI (Murdoch Children's Research Institute)	Academic	Research / Preclinical	Sutton et al., 2018, Vaccine
Klebsiella pneumonia	Klebsiella Pneumoniae Vaccine Program	Syntiron	Commercial	Research / Preclinical	EvaluatePharma
Klebsiella pneumonia	Klebsiella pneumonia vaccine	Emergex Vaccines	Commercial	Research / Preclinical	PharmaProjects
Klebsiella pneumonia	Klebsiella pneumonia Vaccine Program	Astrogenetix	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis vaccine	Abera Bioscience	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Ad5Ag85A	Aeras Global TB Vaccine Foundation	Academic	Phase I	EvaluatePharma
Mycobacterium tuberculosis	DAR-901	Aeras Global TB Vaccine Foundation	Academic	Phase II	EvaluatePharma
Mycobacterium tuberculosis	H1-IC31	Aeras Global TB Vaccine Foundation	Academic	Phase II	EvaluatePharma
Mycobacterium tuberculosis	ID93+GLA-SE	Aeras Global TB Vaccine Foundation	Academic	Phase II	EvaluatePharma
Mycobacterium tuberculosis	MTBVAC	Aeras Global TB Vaccine Foundation	Academic	Phase II	EvaluatePharma
Mycobacterium tuberculosis	SSI H56-IC31	Aeras Global TB Vaccine Foundation	Academic	Phase II	EvaluatePharma
Mycobacterium tuberculosis	MVA Vaccine	Aeras Global TB Vaccine Foundation	Academic	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	rCMV	Aeras Global TB Vaccine Foundation	Academic	Research / Preclinical	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Mycobacterium tuberculosis	Ruti Vaccine	Archivel Farma	Commercial	Phase II	EvaluatePharma
Mycobacterium tuberculosis	Antitubercle Vaccine BCG 10	Biomed-Lublin	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	Vaccae	Chongqing Zhifei Biological Products	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis vaccine	Chongqing Zhifei Biological Products	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	TB Vaccine	EpiVax	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis GTU Vaccine Research Project	FIT Biotech	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	GC3107	GC Pharma	Commercial	Phase I	EvaluatePharma
Mycobacterium tuberculosis	BCG Vaccine	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	GSK M72	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis vaccine	GlaxoSmithKline	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	GI-19000	GlobeImmune	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis Research Project	GlobeImmune	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	BCG Vaccine	Green Signal Bio Pharma	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	T-Biovax	ImmBio	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	IMM201	Immodulon Therapeutics	Commercial	Research / Preclinical	PharmaProjects
Mycobacterium tuberculosis	V-5 Immunitor	Immunitor	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	V-7 Immunitor	Immunitor	Commercial	Phase III	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis vaccine	Inovio Pharmaceuticals	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis Vaccine Project	I'rom Group	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Immuvac	Cadila Pharmaceuticals	Commercial	Marketed	PharmaProjects
Mycobacterium tuberculosis	Freeze-Dried BCG Vaccine	Japan BCG Laboratory	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	Freeze-Dried BCG Vaccine	Korea Vaccine	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	Lipovax-Fg115-TB	Lipotek	Commercial	Research / Preclinical	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Mycobacterium tuberculosis	Lipovax-FliC-TB	Lipotek	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis Research Programme	Longhorn Vaccines and Diagnostics	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Ad5Ag85A Aerosol	McMaster University	Academic	Phase I	EvaluatePharma
Mycobacterium tuberculosis	VAC B.C.G.	medac	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	BCG Vaccine	PT Bio Farma	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	TB Vaccine	Recipharm	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	BCG vaccine	Sanofi	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	Aeras-404 (H4:IC31)	Sanofi	Commercial	Phase II	EvaluatePharma
Mycobacterium tuberculosis	VPM1002	Serum Institute of India	Commercial	Phase III	EvaluatePharma
Mycobacterium tuberculosis	BCG Vaccine	SINOPHARM	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	BCG Vaccine	Statens Serum Institut	Commercial	Marketed	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis vaccine	The University of Hawai'i System	Academic	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis Research Project	The University of Melbourne	Academic	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis vaccine	The University of Wisconsin System	Academic	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Therapeutic MDR Tuberculosis Program	Theravectys	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	TB Immunotherapy Program	Transgene	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	TVI-Tuberculosis-1	TVAX Biomedical	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	BCG Aerosol	University of Birmingham	Academic	Phase I	EvaluatePharma
Mycobacterium tuberculosis	MTbuVax	Vaxil BioTherapeutics	Commercial	Research / Preclinical	EvaluatePharma
Mycobacterium tuberculosis	Tuberculosis vaccine, Greffex	Greffex	Commercial	Research / Preclinical	PharmaProjects
Neisseria gonorrhoeae	Gonorrhoea Vaccine Program	Novavax	Commercial	Research / Preclinical	EvaluatePharma
Neisseria gonorrhoeae	Gonorrhoea Vaccine Program	Genocea Biosciences	Commercial	Research / Preclinical	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Neisseria gonorrhoeae	Neisserial Vaccine	The Rockefeller University	Academic	Research / Preclinical	EvaluatePharma
Neisseria gonorrhoeae	Gonorrhoea Vaccine	The University of Iowa	Academic	Research / Preclinical	EvaluatePharma
Pseudomonas aeruginosa	Pseudomonas Vaccine	Wake Forest University	Academic	Research / Preclinical	EvaluatePharma
Pseudomonas aeruginosa	Pseudomonas Aeruginosa Vaccine Program	Syntiron	Commercial	Research / Preclinical	EvaluatePharma
Pseudomonas aeruginosa	Pseudomonas Aeruginosa Vaccine Program	Astrogenetix	Commercial	Research / Preclinical	EvaluatePharma
Pseudomonas aeruginosa	Pseudomonas Aeruginosa Vaccine Program	GlaxoSmithKline	Commercial	Research / Preclinical	EvaluatePharma
Salmonella (non-typhoidal)	NTS Vaccine	University of Maryland	Academic	Research / Preclinical	EvaluatePharma
Salmonella (non-typhoidal)	CVD NTS Project	University of Maryland, Bharat Biotech, Wellcome Trust	Commercial	Research / Preclinical	EvaluatePharma
Salmonella (non-typhoidal)	Bivalent iNTS-GMMA	GlaxoSmithKline (NVGH)	Commercial	Research / Preclinical	Tennant at al., 2016, Vaccine
Salmonella (non-typhoidal)	Bivalent conjugate (O:1,4[5],12-CRM197 + O:1,9,12-CRM197)	GlaxoSmithKline (NVGH)	Commercial	Research / Preclinical	Tennant at al., 2016, Vaccine
Salmonella (non-typhoidal)	OmpD	University of Birmingham	Academic	Research / Preclinical	Tennant at al., 2016, Vaccine
Salmonella Paratyphi	CVD 1902	University of Maryland, Bharat Biotech	Commercial	Phase I	EvaluatePharma
Salmonella Paratyphi	Paratyphoid A conjugate vaccine	Lanzhou Institute	Academic	Phase III	PharmaProjects
Salmonella Paratyphi	O:2,12-DT + Vi-DT [International Vaccine Institute]	International Vaccine Institute (IVI)	Academic	Research / Preclinical	Martin et al., 2016, Vaccine
Salmonella Paratyphi	O:2,12-CRM197 + Vi-CRM197	Biological E	Commercial	Research / Preclinical	Martin et al., 2016, Vaccine
Salmonella Typhi	Typhetec	Prokarium	Commercial	Phase I	EvaluatePharma
Salmonella Typhi	Salmonella Vaccine Project	Affinivax	Commercial	Research / Preclinical	EvaluatePharma
Salmonella Typhi	Ttyphoid vaccine	Microgen	Commercial	Marketed	PharmaProjects
Salmonella Typhi	CVD 909	University of Maryland	Academic	Phase II	EvaluatePharma
Salmonella Typhi	Vi polysaccharide typhoid vaccine	China National Pharmaceutical (Beijing Tiantan Biological)	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Tyvax VI plus	VHB Life Sciences	Commercial	Marketed	PharmaProjects

Pathogen	Product	Developer	Category	Phase	Source
Salmonella Typhi	Ttyphoid vaccine	Zydus Cadila (Zydus Vaccicare)	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Tyrix Vi	SK Holdings	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Shantyph	Sanofi (Shantha Biotechnics)	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Typhim Vi, Typhyvax	Sanofi (Pasteur Mérieux)	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Typhobox, Typhovax	Green Cross	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Typherix	GlaxoSmithKline	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Zerotyph	Boryung	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Peda-Typh	Bio-Med	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Neotyf, Typhoral, Vivotif	Johnson & Johnson	Commercial	Marketed	PharmaProjects
Salmonella Typhi	vax-TyVi	Finlay Institute	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Typhoid-Kovax	Sanofi	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Typbar-TCV	Bharat Biotech	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Hepatyrix	GlaxoSmithKline	Commercial	Marketed	PharmaProjects
Salmonella Typhi	VIVAXIM	Sanofi	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Biovac Typhoid	Wockhardt	Commercial	Marketed	PharmaProjects
Salmonella Typhi	Typho-Vi	Bio-Med	Commercial	Marketed	PharmaProjects
Salmonella Typhi	enteric fever vaccine	Prokarium	Commercial	Phase II	PharmaProjects
Salmonella Typhi	Vi-DT typhoid conjugate vaccine	Bio Farma	Commercial	Phase I	PharmaProjects
Salmonella Typhi	Salmonella typhi + paratyphi vaccine	Prokarium	Commercial	Research / Preclinical	PharmaProjects
Salmonella Typhi	Vi-rEPA	National Health Institute	Academic	Phase III	MacLennan et al., 2014, Human Vaccines & Immunotherapeutics
Salmonella Typhi	Vi-rEPA	Lanzhou Institute (China)	Commercial	Marketed	MacLennan et al., 2014, Human Vaccines & Immunotherapeutics
Salmonella Typhi	Vi-CRM	Biological E	Commercial	Phase III	MacLennan et al., 2014, Human Vaccines & Immunotherapeutics
Salmonella Typhi	Vi conjugated to fusion protein PsaA-PdT	Harvard Medical School	Academic	Research / Preclinical	MacLennan et al., 2014, Human Vaccines & Immunotherapeutics
Salmonella Typhi	Ty21a typhoid vaccine expressing Shigella LPS	Protein Potential LLC.	Commercial	Research / Preclinical	Mani et al., 2016, Vaccine
Salmonella Typhi	O:2,12-DT + Vi-DT [International Vaccine Institute]	International Vaccine Institute (IVI)	Academic	Research / Preclinical	Martin et al., 2016, Vaccine

Pathogen	Product	Developer	Category	Phase	Source
Salmonella Typhi	O:2,12-CRM197 + Vi-CRM197	Biological E	Commercial	Research / Preclinical	Martin et al., 2016, Vaccine
Shigella	SF2a-TT15 vaccine	Institut Pasteur	Academic	Phase I	EvaluatePharma
Shigella	ETEC & Shigella vaccine	University of Maryland	Academic	Phase I	EvaluatePharma
Shigella	Flexyn2a	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma
Shigella	1790GAHB vaccine	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma
Shigella	Bacterial diarrhoea vaccine	Prokarium	Commercial	Research / Preclinical	EvaluatePharma
Shigella	Shigella Vaccine Program	Immuron	Commercial	Research / Preclinical	EvaluatePharma
Shigella	Multivalent Shigella Vaccine	GlaxoSmithKline	Commercial	Research / Preclinical	EvaluatePharma
Shigella	Shigella vaccine	Merck & Co.	Commercial	Research / Preclinical	PharmaProjects
Shigella	Shigella vaccine	Immuron	Commercial	Research / Preclinical	PharmaProjects
Shigella	Shigella vaccine	Chongqing Zhifei Biological	Commercial	Research / Preclinical	PharmaProjects
Shigella	Quadrivalent Shigella Vaccine	University of Maryland	Academic	Research / Preclinical	EvaluatePharma
Shigella	Holotoxoid Vaccine	Uniformed Services University of the Health Sciences	Academic	Research / Preclinical	EvaluatePharma
Shigella	CVD 1208, CVD 1213 and CVD 1215	University of Maryland	Academic	Research / Preclinical	Mani et al., 2016, Vaccine
Shigella	Truncated Shigella	International Vaccine Institute, Seoul, Korea	Academic	Research / Preclinical	Mani et al., 2016, Vaccine
Shigella	Ty21a typhoid vaccine expressing Shigella LPS	Protein Potential LLC.	Commercial	Research / Preclinical	Mani et al., 2016, Vaccine
Shigella	Inactivated trivalent Shigella whole cell	PATH, Washington DC and WRAIR, Silver Spring, Maryland USA	Academic	Research / Preclinical	Mani et al., 2016, Vaccine
Shigella	Heat Killed Multi Serotype Shigella (HKMS) vaccine	NICED, Kolkata, India	Academic	Research / Preclinical	Mani et al., 2016, Vaccine
Shigella	DB Fusion	PATH	Academic	Research / Preclinical	Mani et al., 2016, Vaccine
Shigella	34 kDa OmpA	NICED, Kolkata, India	Academic	Research / Preclinical	Mani et al., 2016, Vaccine
Staphylococcus aureus	STEBVax	Integrated BioTherapeutics	Commercial	Phase I	EvaluatePharma
Staphylococcus aureus	Staph Aureus Vaccine	GlaxoSmithKline	Commercial	Phase I	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Staphylococcus aureus	PF-06290510	Pfizer	Commercial	Phase II	EvaluatePharma
Staphylococcus aureus	NDV-3A	NovaDigm Therapeutics	Commercial	Phase II	EvaluatePharma
Staphylococcus aureus	MRSA Vaccine	Sanofi	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	MVA-BN MRSA Vaccine	Bavarian Nordic	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	IBT-V02	Integrated BioTherapeutics	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Staphylococcus Aureus Vaccine	Syntiron	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	S. aureus vaccine research program	Absynth Biologics	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Bellerophon Project	IMAXIO	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Methicillin-resistant Staphylococcus Aureus (MRSA) Research project	Bharat Biotech	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Superantigen Toxin Vaccine	U.S. Army Medical	Academic	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Staphylococcus Aureus Vaccine	U.S. Army Medical	Academic	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Staphylococcus Aureus Vaccine	University of Minnesota	Academic	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	MRSA Vaccine Program	University of Maryland	Academic	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Serenta-University of Maryland Research Project	University of Maryland	Academic	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	MRSA Vaccine Project	VLP Biotech	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Staphylococcus Aureus Bioconjugate Vaccine Program	GlaxoSmithKline	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Bacterial Vaccine Research Program	Ludwig Maximilians University	Academic	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Staphylococcus aureus vaccine	Abcombi Biosciences	Commercial	Research / Preclinical	PharmaProjects
Staphylococcus aureus	Methicillin-resistant Staphylococcus Aureus (MRSA) Research project	SBI Holdings	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Staphylococcus Aureus Vaccine Program	Astrogenetix	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	Staphylococcal Vaccine	Uniformed Services University of the Health Sciences	Academic	Research / Preclinical	EvaluatePharma

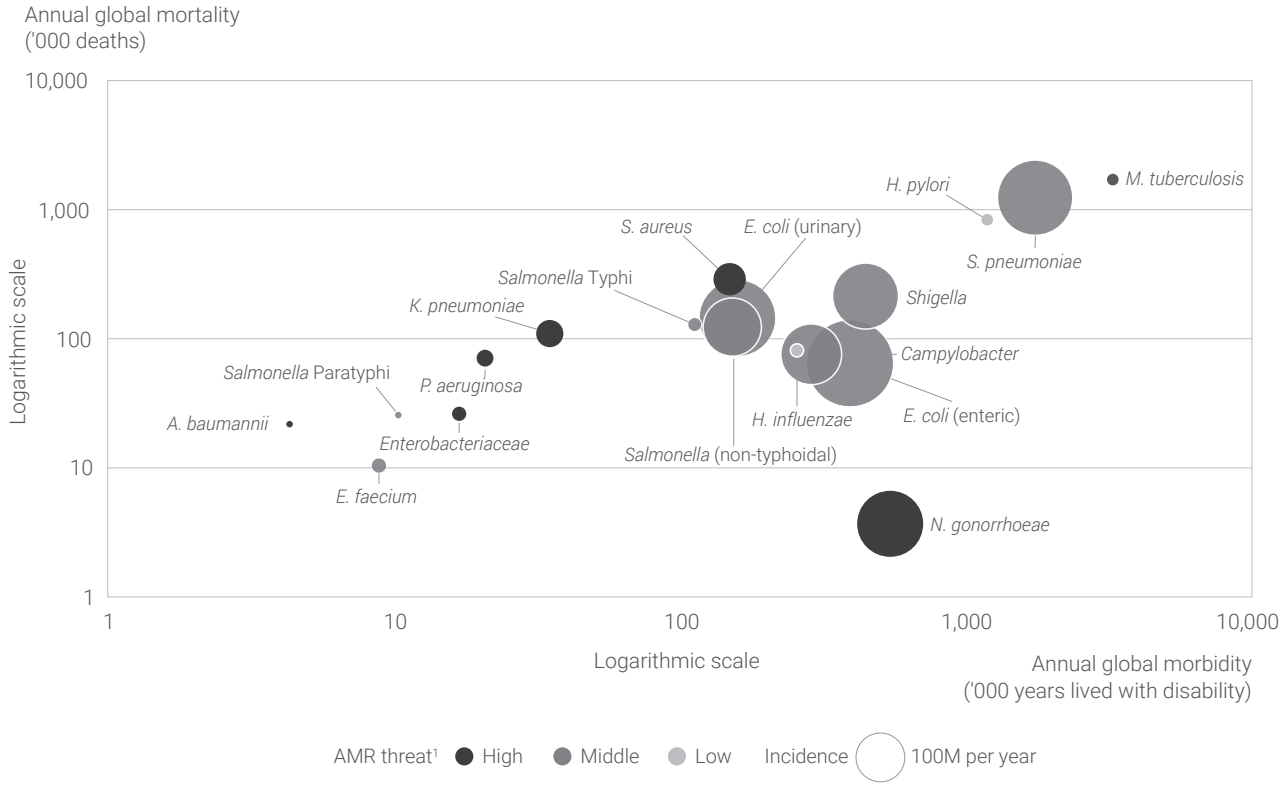
Pathogen	Product	Developer	Category	Phase	Source
Staphylococcus aureus	Staphylococcus Aureus Vaccine Project	Affinivax	Commercial	Research / Preclinical	EvaluatePharma
Staphylococcus aureus	AV-0328; AV0328	Alopexx Vaccine, LLC	Commercial	Phase I	PharmaProjects
Staphylococcus aureus	Staphylococcus aureus infection therapy, Immunartes	ImmunArtes	Commercial	Research / Preclinical	PharmaProjects
Staphylococcus aureus	Staphylococcus aureus vaccine, Astellas	Astellas Pharma	Commercial	Research / Preclinical	PharmaProjects
Staphylococcus aureus	Staphylococcus aureus ghost	Pan Chai University	Academic	Research / Preclinical	Giersing et al., 2016, Vaccine
Streptococcus pneumoniae	Pneumococcal Vaccine	Abera Bioscience	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine	Affinivax	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Streptococcus Pneumoniae Research Project	Affinivax	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine	Astellas Pharma	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Streptococcus pneumonia Vaccine Program	Astrogenetix	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	15 Valent Pneumococcal conjugate Vaccine	Aurobindo Pharma	Commercial	Phase I	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Conjugate Vaccine	Biological E	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Hib Vaccine	BioNet-Asia	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	13-Valent Pneumococcal conjugate Vaccine	Chongqing Zhifei Biological Products	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	23-Valent Pneumococcal conjugate Vaccine	Chongqing Zhifei Biological Products	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine	Eurocine Vaccines	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine	Gamma Vaccines	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	GSK2189242A	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma
Streptococcus pneumoniae	S. Pneumoniae Vaccine Program	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma
Streptococcus pneumoniae	NTHi-Pneumo	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma
Streptococcus pneumoniae	GSK2830929A	GlaxoSmithKline	Commercial	Phase II	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Streptococcus pneumoniae	Synflorix	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Streptococcus pneumoniae	Pneumopur/ Steptopur	GlaxoSmithKline	Commercial	Marketed	EvaluatePharma
Streptococcus pneumoniae	PnuBiovax	ImmBio	Commercial	Phase I	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine Program	Instituto Butantan	Academic	Phase I	EvaluatePharma
Streptococcus pneumoniae	Streptococcus Pneumoniae Vaccine	Integrated BioTherapeutics	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	LBVE	LG Chem	Commercial	Phase II	EvaluatePharma
Streptococcus pneumoniae	Multivalent Pneumococcal Vaccine	Liquidia Technologies	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	V114	Merck & Co	Commercial	Phase III	EvaluatePharma
Streptococcus pneumoniae	Pneumovax	Merck & Co	Commercial	Marketed	EvaluatePharma
Streptococcus pneumoniae	Osaka University-BIKEN Pneumococcal Vaccine	Osaka University	Academic	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Nucovac	Panacea Biotec	Commercial	Phase II	EvaluatePharma
Streptococcus pneumoniae	Pneumo Nexgen Vaccine	Pfizer	Commercial	Phase II	EvaluatePharma
Streptococcus pneumoniae	PF-06482077	Pfizer	Commercial	Phase II	EvaluatePharma
Streptococcus pneumoniae	PF-06842433	Pfizer	Commercial	Phase I	EvaluatePharma
Streptococcus pneumoniae	Prevnar 13	Pfizer	Commercial	Marketed	EvaluatePharma
Streptococcus pneumoniae	Prevnar	Pfizer	Commercial	Marketed	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine TruePatch	Prometheon Pharma	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Conjugate Vaccine	Sanofi	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Streptococcus Pneumoniae Vaccine	Sanofi	Commercial	Phase I	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Polysaccharide Conjugate Vaccine	Serum Institute of India	Commercial	Phase I	EvaluatePharma
Streptococcus pneumoniae	Huiyikang	SINOPHARM	Commercial	Marketed	EvaluatePharma

Pathogen	Product	Developer	Category	Phase	Source
Streptococcus pneumoniae	Pneumococcal 13-valent Conjugate Vaccine (PCV)	Sinovac Biotech	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal 23-valent Polysaccharide Vaccine (PPV)	Sinovac Biotech	Commercial	Phase III	EvaluatePharma
Streptococcus pneumoniae	NBP606	SK Chemicals	Commercial	Phase III	EvaluatePharma
Streptococcus pneumoniae	CBPG Protein	St. Jude Children's Research Hospital	Academic	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Streptococcus Pneumoniae Vaccine	St. Jude Children's Research Hospital	Academic	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Conjugate Vaccine	SutroVax	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine Program	Synergy America	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	15 Valent Pneumococcal conjugate Vaccine	Tergene Biotech	Commercial	Phase I	EvaluatePharma
Streptococcus pneumoniae	Osaka University-BIKEN Pneumococcal Vaccine	The Research Foundation for Microbial Diseases of Osaka University (BIKEN)	Academic	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	GlpO	The University of Adelaide	Academic	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Immunoregulatory Therapy	The University of Newcastle	Academic	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine	The University of Pennsylvania	Academic	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal 13-valent Conjugate Vaccine (PCV)	Tianjin CanSino Biotechnology	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Protein Vaccine	Tianjin CanSino Biotechnology	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Polysaccharide Vaccine	Tianjin CanSino Biotechnology	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Anti-Pneumococcal Vaccine	Vaxxilon	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	Pneumococcal Vaccine Program	Virometix	Commercial	Research / Preclinical	EvaluatePharma
Streptococcus pneumoniae	PPV23	Walvax Biotechnology	Commercial	Marketed	EvaluatePharma
Streptococcus pneumoniae	Pneumococcus Conjugate Vaccine	Wellstat Group	Commercial	Research / Preclinical	EvaluatePharma

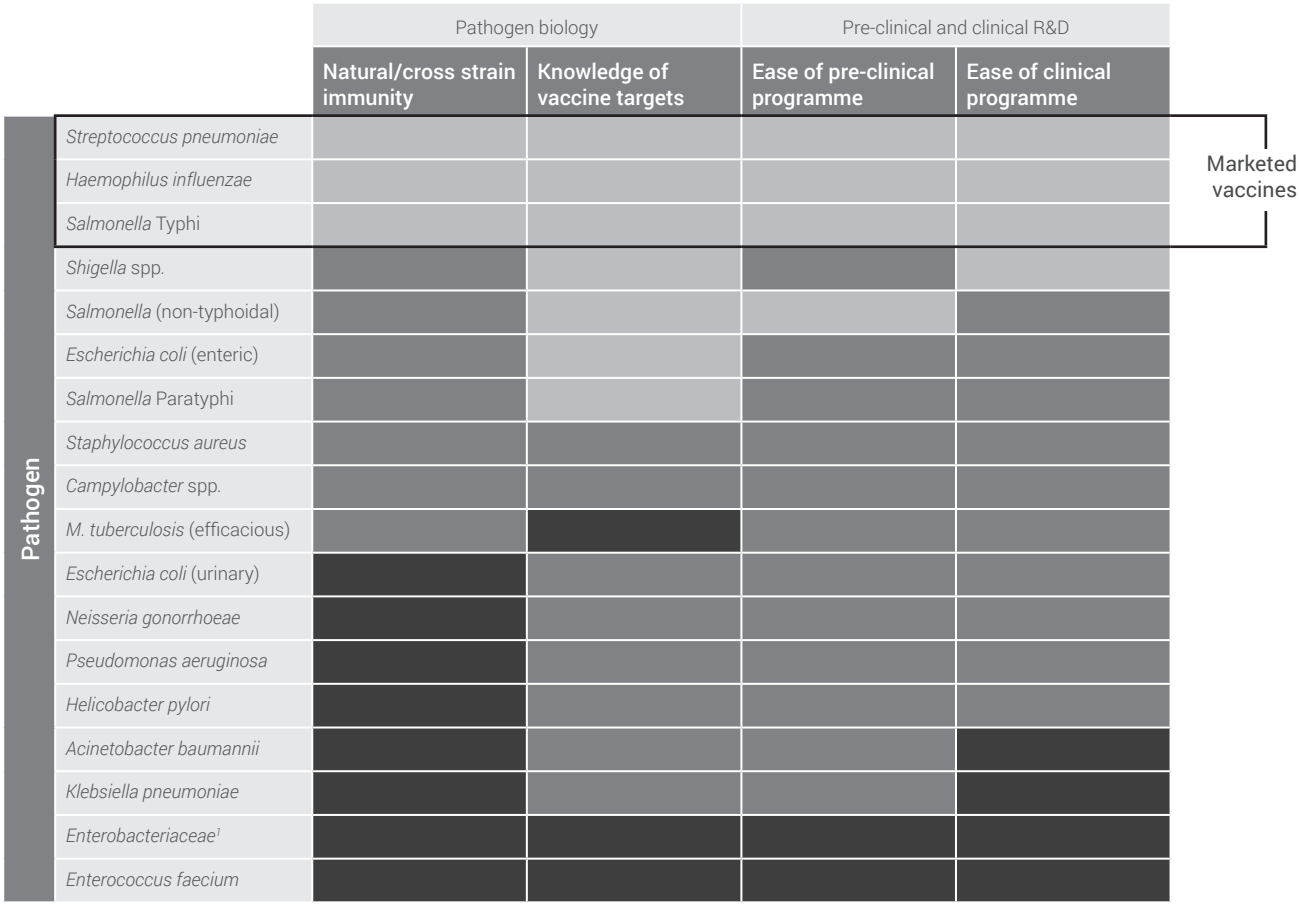
Greyscale versions of exhibits

ORDERS OF MAGNITUDE DIFFERENCES IN INCIDENCE, MORBIDITY, MORTALITY ACROSS PATHOGEN SET



1) Colour code for AMR threat different from pathogen scorecards.
Source: WHO and IHME 2016 global disease burden datasets and literature review – full source list and methodology in appendix.

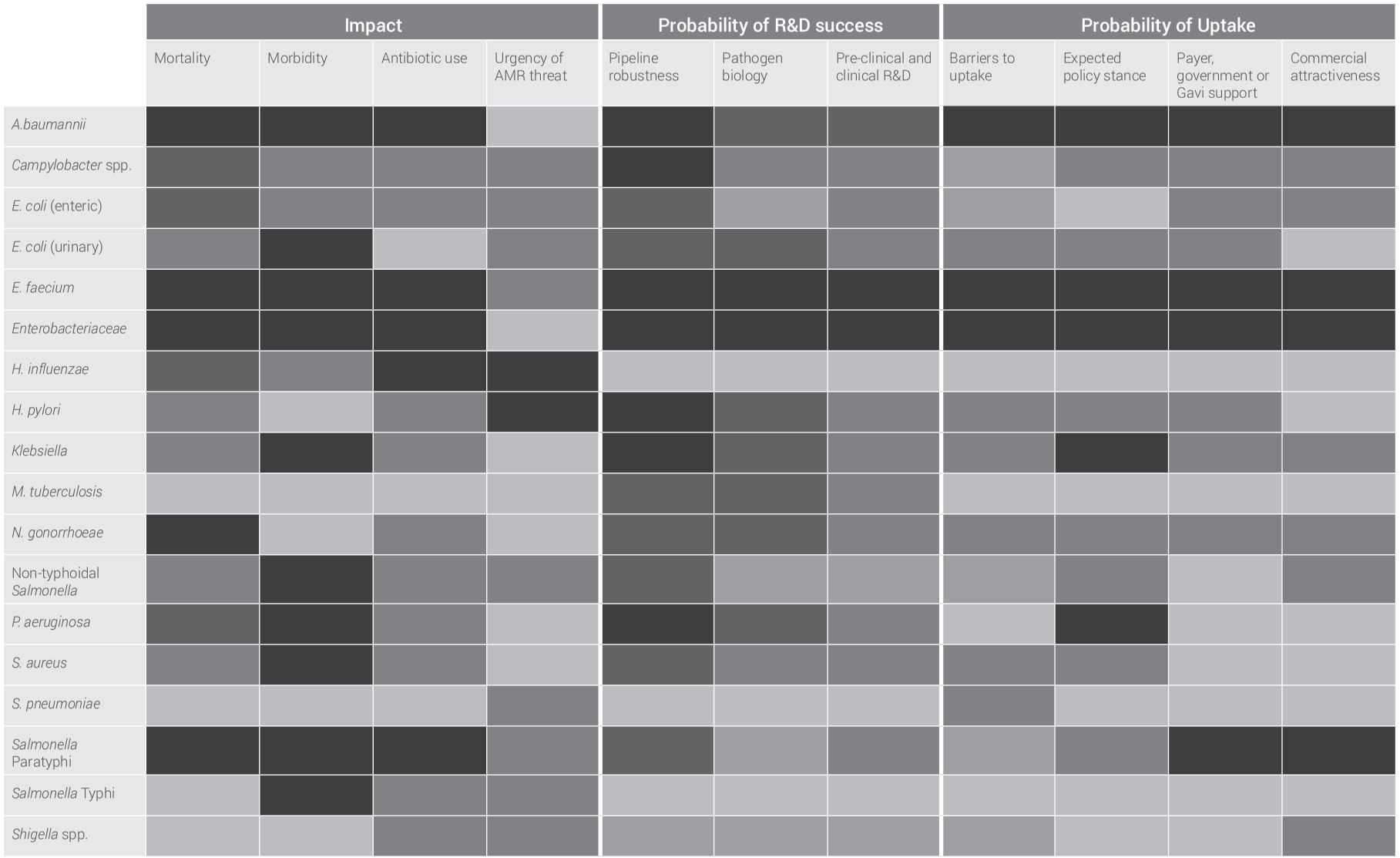
SUMMARY OF TECHNICAL HURDLES



Note: Ordered from lowest to highest in terms of hurdles for dimensions listed in columns. Does not include pipeline robustness measure.

The colour-coding reflects the pathogen's categorisation (low, medium or high) on the variables listed in the columns. Red represents significant hurdles to vaccine development, yellow represent moderate hurdles to vaccine development and green represents low hurdles to vaccine development.

1) Entire family excluding *E. coli* and *K. pneumoniae*; Source: Literature research; expert interviews; BCG analysis.



Note: The colour-coding reflects each pathogen's scorecard score on the variables specified in the columns. Scores range from 0-2. A score of 0 indicates low health impact, probability of R&D success or probability of uptake and is represented in dark red, reflecting low favourability for vaccine development. A score of 2 indicates high health impact, probability of R&D success or probability of uptake and is represented in dark green, reflecting high favourability for vaccine development

The data reflected in this table has varying levels of confidence. In particular, the figures for antibiotic usage are estimates based upon the estimated global incidence of disease caused by the pathogen and standard antibiotic treatment regimens

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