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Specialty grand challenge frontiers in bacteriology: Pathogenesis, vaccines, and immunity of bacterial infections

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Introduction

This specialty section covers pathogenesis, vaccines, and immunity to bacterial infections. All three focus areas are interconnected and understanding the mechanisms of bacterial pathogenicity and the immune response to infection informs the development of new vaccines and antimicrobials.

Bacterial pathogenesis

Bacteria are known to cause a huge number of different infections of humans and animals, ranging from asymptomatic to symptomatic to varying degrees. Infection occurs when a microorganism invades a host and multiplies on or in host tissues; multiplication can be contained at the site of infection, for example through granuloma formation, or disseminate and become fulminant. The consequences of infection to the host depend on the interplay between the pathogen and the host immune response, and this interplay can result in the disruption of normal cellular and organ homeostasis. This interplay can be relatively simple to understand, for example in toxin-mediated infections where toxin molecules can interact with host cell receptors and disrupt normal cellular hemostasis, leading to symptoms characteristic of the bacterial infection. These can range from simple released toxins to complicated type secretory systems that can deliver bacterial molecules directly into the host cell. Or the interplay can be more complex, for example infections that involve different life cycle stages, with bacteria moving from an extracellular existence to cellular invasion, immune avoidance, persistence, and dormancy (Wilson et al., 2019).

In this section, we encourage articles that seek to provide new insights into the varieties of human/animal-bacteria interactions, bacterial virulence – the measure of the pathogenicity of an organism - and new experimental vertebrate and invertebrate models of infection. Information about disease pathologies is also a critical need. New mechanisms of bacterial pathogenesis to be explored include survival in external

environments, colonization (adherence, motility, chemotaxis, secretory systems, and biofilm formation), barrier penetration and invasion, nutrient acquisition, and evasion of innate immunity. Virulence regulation and genetic modification is also important, e.g. how bacteria acquire new virulence traits, and how genetic change and diversification is affected through mutation, phase and antigenic variation, and transformation. New developments in restriction-modification systems and the CRISPR-Cas systems of bacterial adaptive immunity (Barrangou et al., 2007) are also important for understanding pathogenesis and CRISPR interference could be used for functional analyses of specific genes in pathogens (Zhang et al., 2021). Other key challenges include the identification of bacterial virulence factors and host factors required for infection and models to measure them, including *ex vivo* cell and organ culture models, and animal transgenic models of infection and controlled human infection models (CHIMs). The latter are available for *Streptococcus pneumoniae, S. pyogenes, Neisseria gonorrhoeae* and *N. lactamica*, enterotoxigenic *Escherichia coli* (ETEC), *Salmonella typhi, Vibrio cholerae* and *Mycobacterium tuberculosis* (BCG surrogate) (Pollard et al., 2020). Identifying host factors required for infection, profiled using comparative genomics, transcriptomics, proteomics, and metabolomics is also needed for drug and vaccine development.

Developed countries and many middle-income countries have lists of notifiable bacterial diseases of humans and animals, which are required by law to be reported to government health authorities. Notifications are important to monitor the emergence of new diseases and/or vaccine-escape mutants and provide an 'early warning system' for epidemics and indeed pandemics. On a global level, the World Health Organization (WHO) no longer has a specific list for human pathogens (originally only restricted to cholera, plague and smallpox) and leaves notifications to member countries (Table 1). The World Organization for Animal Health, conversely, does monitor specific animal diseases globally and the important bacteria are shown in Table 2. It is fair to say that our understanding of how many of these pathogens cause disease is incomplete and a major obstacle to developing effective targeted treatments and prophylactic vaccines.

For this section, we also encourage research articles on emerging bacterial pathogens, which the National Institute of Allergy and Infectious Diseases (NIAID) classifies into three categories, whose membership are under continual review (https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens). The NIAID defines emerging infectious diseases as those that have 'newly appeared in a population or have existed but are rapidly increasing in incidence or geographic range' and naturally many are of concern for biodefense reasons. The characteristics of the bacterial pathogens belonging to each category are shown in Table 3, and they are accompanied with an additional list of emerging infectious diseases/pathogens.

Bacterial vaccines

The history of the development of bacterial vaccines for animals and humans is a rich one (Plotkin and Plotkin, 2011). Figure 1 shows a timeline starting from the 1880s for the introduction of vaccines for major bacterial infections of humans. Many of these vaccines have made an enormous impact on reducing morbidity and mortality from bacterial infections over the past century. Vaccines such as the diphtheria, tetanus, and pertussis (DTP) triple vaccine, the many meningitis vaccines (HiB, meningococcal and pneumococcal) have helped to increase life expectancy by alleviating childhood mortality globally. Today, the WHO estimates that 2-3 million human deaths are prevented every year through immunization against diphtheria, tetanus and pertussis (and measles). Despite their success, global vaccination rates are still insufficient, and the WHO and United Nations International Children's Emergency Fund (UNICEF) also note that 23 million children missed out on basic vaccines through routine immunization services in 2020, a consequence of the COVID-19 pandemic. Reductions in vaccine uptake will impact on herd immunity and could lead to resurgent diseases. The challenge is not only to increase uptake of tried and tested vaccines, but also to develop vaccines for many still intractable bacterial infections and emerging and re-emerging pathogens (Williamson and Westlake, 2019). A complication for many infections is their zoonotic provenance and interrupting the life cycle of several important pathogens may require vaccines for both animals and humans. Zoonotic transmission of bacteria is important, and we encourage research articles into zoonotic infections, as our understanding of animals as reservoirs for emerging and re-emerging bacterial pathogens is wholly incomplete. Furthermore, the WHO priority list of bacteria with anti-microbial resistance contains many challenging organisms for whom no vaccines are currently licensed (Table 4). However, there are a total of 94 confirmed active preclinical candidates and a total of 61 vaccine candidates in active clinical development (WHO, 2022). Worryingly, pathogens rated as a critical or high priority (Table 4) tended to have fewer candidates in clinical development than the pathogens categorized as medium priority.

Historically, the development of important animal vaccines has tended to mirror the development of human vaccines. The major challenges in this sector are the need for new vaccines for zoonotic and chronic diseases of both domestic and companion animals, and a desire to move away from the overuse of antibiotics (Hoelzer et al., 2018a; Hoelzer et al., 2018b). Common technologies used for human and animal vaccine development include live-attenuated, inactivated (killed whole cell), toxoid, recombinant vaccines, glyco-conjugate and DNA/viral vector vaccines (Ghattas et al., 2021). Most of the newer viral-vector and DNA-based technologies have been used to

TABLE 1 Notifiable human bacterial pathogens.

Bacterium	Disease
Anaplasma phagocytophilum	Human granulocytic anaplasmosis
Bacillus anthracis	Anthrax
Bacillus cereus	Food poisoning
Bordetella pertussis	Whooping cough
Borrelia burgdorferi	Lyme disease
Brucella spp.	Brucellosis
Campylobacter spp.	Food poisoning
Chlamydia spp.	Sexually transmitted disease, trachoma, psittacosis, pneumonitis
Clostridium botulinum	Botulism
Clostridium perfringens	Food poisoning
Clostridium tetani	Tetanus
Corynebacterium diphtheriae	Diphtheria
Coxiella burnetii	Q fever
Escherichia coli serogroup 0111	Epidemic diarrhoea of the newborn
Escherichia coli O157:H7	Food poisoning; haemolytic uraemic syndrome (HUS)
Ehrlichia ewingii, chaffeensis	Ehrlichiosis
Francisella tularensis	Tularemia
Haemophilus ducreyi	Chancroid
Haemophilus influenzae	Pneumonia, otitis media, epiglottitis, eye infections, sepsis, meningitis, cellulitis, infectious arthritis
Klebsiella granulomatis	Donovanosis
Legionella pneumophila	Legionellosis
Leptospira interrogans	Leptospirosis (Weil's disease)
Listeria monocytogenes	Listeriosis
Mycobacterium leprae	Leprosy (Hansen's disease)
Mycobacterium tuberculosis	Tuberculosis
Neisseria gonorrhoeae	Gonorrhoea
Neisseria meningitidis	Meningitis, sepsis
Rickettsia spp.	Spotted fevers (Rocky Mountain, rickettsialpox, Boutonneuse fever, Siberian tick fever, Australian tick typhus, oriental spotted fever); typhus group (rickettsia typhi, Louse-borne typhus and Brill-Zinsser disease); scrub typhus (tsutsugamushi disease)
Salmonella typhi	Typhoid fever
Salmonella enterica	Paratyphoid fever
Salmonella spp.	Salmonellosis
Shigella	Shigellosis dysentery
Staphylococcus aureus	Pemphigus neonatorum
Staphylococcus aureus (vancomycin-intermediate (VISA) and Vancomycin-resistant (VRSA))	skin infections, abscess, pneumonia, infection of the heart valves, bones, or blood
Streptococcus agalactiae	Group B streptococcal neonatal infection
Streptococcus pneumoniae	Neonatal infection (sepsis, pneumonia, meningitis), adult skin and soft-tissue infections
Streptococcus pyogenes	Group A streptococcal scarlet fever, invasive infections, erysipelas
Treponema pallidum	Syphilis
Vibrio cholerae	Cholera
Yersinia pestis	Plague

Bacteria are compiled from the notifiable lists from Australia, Brazil, Canada, France, Hong Kong, India, Malaysia, United Kingdom, and United States.

develop vaccines for viral infections of animals (Aida et al., 2021), whereas bacterial vaccines have tended to be killed, live, avirulent and bacterin/toxoids. For example, interrogating the comprehensive list of veterinary vaccines licensed by the United States Department of Agriculture gives an idea of the types of licensed bacterial vaccines for animals (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/ct_vblicensed_products) and also the many mixed vaccines (viral-

TABLE 2 Bacterial diseases notifiable to the World Organization for Animal Health.

	Disease	Bacterium
Multiple species diseases	Anthrax	*Bacillus anthracis*
	Brucellosis	*Brucella abortus, Brucella melitensis, Brucella suis*
	Heartwater	*Ehrlichia (formerly Cowdria) ruminantium*
	Leptospirosis	*Leptospira spp*
	Paratuberculosis	*Mycobacterium avium subspecies paratuberculosis*
	Q fever	*Coxiella burnetii*
	Tularemia	*Francisella tularensis*
Cattle diseases	Bovine anaplasmosis	*Anaplasma marginale*
	Bovine genital campylobacteriosis	*Campylobacter fetus venerealis or C fetus fetus*
	Bovine tuberculosis	*Mycobacterium bovis*
	Contagious bovine pleuropneumonia	*Mycoplasma mycoides subsp. Mycoides*
	Haemorrhagic septicaemia	*Pasteurella multicoda*
Sheep and goat diseases	Contagious agalactia	*Mycoplasma* spp.
	Contagious caprine pleuropneumonia	*Mycoplasma capricolum subsp. Capripneumoniae*
	Enzootic abortion of ewes (ovine chlamydiosis)	*Chlamydophila abortus*
	Salmonellosis	*S. abortusovis*
	Ovine epididymitis	*Brucella ovis*
Equine diseases	Contagious equine metritis	*Taylorella equigenitalis*
	Glanders	*Burkholderia mallei*
Avian diseases	Avian chlamydiosis	*Chlamydia psittaci*
	Avian mycoplasmosis	*Mycoplasma gallisepticum, M. synoviae*
	Fowl cholera	*Pasteurella multicoda*
	Fowl typhoid	*Salmonella gallinarum and S. pullorum*
	Pullorum disease	*Salmonella enterica pullorum*
Bee diseases	American foulbrood of honeybees	*Paenibacillus larvae*
	European foulbrood of honeybees	*Melissococcus plutonius*
Mollusc diseases	Infection with	*Xenohaliotis californiensis*
Fish diseases	Bacterial kidney disease	*Renibacterium salmoninarum*
	Gyrodactylosis	*Gyrodactylus salaris*

bacterial) available (Supplementary Table 1). Given the crude nature of many of these bacterin vaccines, the challenge is to develop modern and more effective vaccines for agriculture, with less toxicity and better immunogenicity.

In this section, we encourage research articles on the broadest scope of human and animal vaccinology, which address many of the challenges we face. With the rapid introduction of the COVID-19 vaccines (underpinned of course by decades of funded pre-clinical studies to develop the platforms), are we entering a new age of vaccine development, with transferable technologies? The application of mRNA and adenoviral-vector based platforms for COVID-19 vaccines may see translation to bacterial vaccine development with defined antigens, though the apparent short-term humoral immunity that necessitates repeated vaccination against SARS-CoV2 may not be appealing for bacterial vaccines compared with more traditional approaches. Many challenges still remain for bacterial vaccines in the C21st: they include the need for 1) new state-of-the-art vaccine platforms; 2) a One Health approach to combat zoonoses; 3) new and safe adjuvant and delivery systems to enhance immunogenicity; 4) vaccines inducing mucosal immunity and obviating parenteral administration; 5) identifying vaccine antigens for pathogens, e.g. from *in silico* studies through to interrogating the proteome; 6) defining the immunological bases of protection against infection and determining correlates of protection; 7) developing vaccines for pathogens that have multiple serotypes and serogroups; even if target antigens are identified, these too may show hypervariability that necessitates developing multiple serotype vaccines to ensure broad coverage of circulating infective strains; and 8) testing vaccines in animal models to demonstrate protection and moving towards using human challenge models

TABLE 3 NIAID Infectious Diseases/ Bacterial Pathogens.

Category	Characteristics	Bacteria
A	•pose the highest risks to national security and to public health •Easily disseminated or transmitted from person to person •high mortality rates •potential for major public health impact •Might cause public panic and social disruption •Special actions required for public health preparedness	*Bacillus anthracis* (anthrax) *Clostridium botulinum* toxin (botulism) *Yersinia pestis* (plague) *Francisella tularensis* (tularemia)
B	•Moderately easy to disseminate •Moderate morbidity, low mortality rates •Diagnostic and disease surveillance enhancement needed	*Burkholderia pseudomallei* (melioidosis) *Coxiella burnetii* (Q fever) *Brucella species* (brucellosis) *Burkholderia mallei* (glanders) *Chlamydia psittaci* (Psittacosis) *Clostridium perfringens* Epsilon toxin *Staphylococcus* enterotoxin B (SEB) *Rickettsia prowazekii* (Typhus fever) Diarrheagenic *E. coli* Pathogenic *Vibrios* *Shigella* species *Salmonella* *Listeria monocytogenes* *Campylobacter jejuni* *Yersinia enterocolitica*
C	•Could be engineered for mass dissemination •Easily available •Easily produced and disseminated •Potentially high morbidity and mortality	Tuberculosis, including drug-resistant TB Other *Rickettsias* Antimicrobial resistance (but excluding research on sexually transmitted organisms, unless the resistance is newly emerging)
Additional emerging bacterial diseases/pathogens		*Anaplasma phagocytophilum* (Anaplasmosis) *Bartonella henselae* *Bordetella pertussis* *Borrelia mayonii* *Borrelia miyamotoi* *Ehrlichia spp* (Ehrlichiosis) *Leptospira interrogans* (Leptospirosis) *Streptococcus*, Group A (*S. pyogenes)*

of infection for vaccine trials. Also, establishing the way science and government respond to the risk of bioterrorism with completely new pathogens is a real challenge.

Immunity to bacterial infections

The mammalian immune response is critical to understanding how bacterial infections develop and how they can be controlled using antimicrobials or prevented by vaccination. There are considerable knowledge gaps to our understanding of immunity to infection, and more knowledge is needed on how the host defends itself from bacterial infection, how the normal microbiota protects against pathogen occupation, and conversely how pathogens perturb the microbiota to establish colonization. What are the molecular and cellular processes that the skin and exposed mucosae of the gastrointestinal, urogenital, and respiratory tracts present as first lines of defense against infection? New *in vitro* and *in vivo* models are needed to study how pathogens breach barriers. In addition, new knowledge is needed on how pathogens interact with the innate immune system, how the latter recognizes pathogens and the molecular and cellular mechanisms involved in the interactions of immune effector cells in aiding pathogen clearance. A deeper understanding of the role of autophagy, complement and immune response mediators (e.g. cytokines and chemokines) in host defense is needed, and also how up- and dysregulated innate immune responses are deleterious to the host. Conversely, the ability of some pathogens to survive within immune cells and enter latency is a challenging biological phenomenon for the development of new vaccines.

We also need to better understand how the innate and adaptive immune responses to bacterial pathogens are linked.

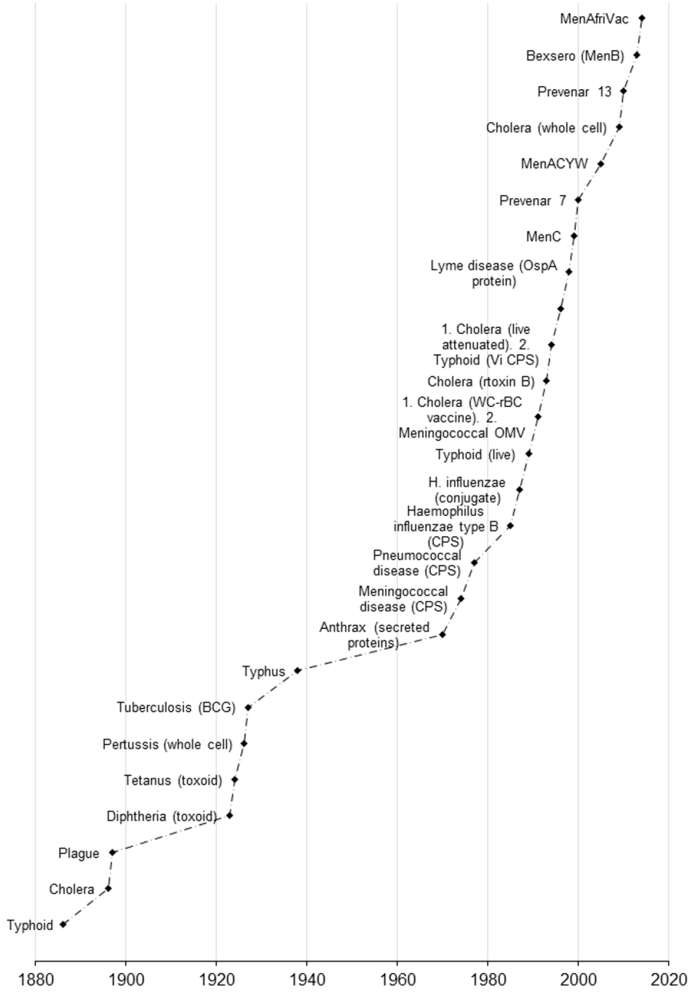

FIGURE 1
Timeline for the introduction of bacterial vaccines.

TABLE 4 World Health Organization priority list of AMR pathogens.

Priority	Bacterium	Vaccines licensed for human use
Critical	*Acinetobacter baumannii*, carbapenem-resistant	No
	Pseudomonas aeruginosa, carbapenem-resistant	No
	Enterobacteriaceae, carbapenem-resistant, extended spectrum beta-lactamase-producing	No
High	*Enterococcus faecium*, vancomycin-resistant	No
	Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant	No
	Helicobacter pylori, clarithromycin-resistant	No
	Campylobacter spp., fluoroquinolone-resistant	No
	Salmonella spp., fluoroquinolone-resistant	No
	Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant	No
Medium	*Streptococcus pneumoniae*, penicillin-non-susceptible	Yes
	Haemophilus influenzae, ampicillin-resistant	Yes
	Shigella spp., fluoroquinolone-resistant	No

In this section, we encourage articles describing new findings on adaptive immune responses against bacterial infections, including how pathogens and antigens are processed and neutralized, and the increasingly important role of Th1/Th2/Th17 cell mediated immunity. Linking these together with the definition of correlates of protection is fundamental to the development of successful vaccines.

Conclusions

The 'golden age of microbiology', that period from the 1880 to 1920s, saw the discovery and first culture of many agents causing different infectious diseases, with notable bacteria including *N. menigitidis* and *N. gonorrhoeae, H. influenzae, S. pneumoniae, S. pyogenes, S. agalactiae, S. aureus, L. monocytogenes, P. aeruginosa, Salmonella* spp., *Klebsiella, Escherichia, Treponema, Leptospira, M. tuberculosis* (Christodoulides, 2013). The introduction of vaccines for many of these pathogens (Figure 1) and of antibiotics since the 1940s, have been two major factors that have helped increase life expectancy globally. Despite our success in controlling many of these major infections, there remain significant challenges for an increasingly interconnected and mobile global population, with the spectre of emerging diseases of concern. More investment into understanding how bacteria cause infections and on developing new vaccines and treatments is needed, to maintain the gains of the last century and to raise the quality of life for people living in the least developed and low-to-middle income countries. In this specialty section, our goal is to present our readership with articles of the highest quality on bacterial pathogenesis and virulence, immunity to infection and vaccines that will have positive impacts on global ill-health and inequalities.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fbrio.2022.1049307/full#supplementary-material

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