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REVIEW

The impact of human vaccines on bacterial antimicrobial resistance. A review

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Abstract

At present, the dramatic rise in antimicrobial resistance (AMR) among important human bacterial pathogens is reaching a state of global crisis threatening a return to the pre-antibiotic era. AMR, already a significant burden on public health and economies, is anticipated to grow even more severe in the coming decades. Several licensed vaccines, targeting both bacterial (*Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Salmonella enterica* serovar Typhi) and viral (influenza virus, rotavirus) human pathogens, have already proven their anti-AMR benefits by reducing unwarranted antibiotic consumption and antibiotic-resistant bacterial strains and by promoting herd immunity. A number of new investigational vaccines, with a potential to reduce the spread of multidrug-resistant bacterial pathogens, are also in various stages of clinical development. Nevertheless, vaccines as a tool to combat AMR remain underappreciated and unfortunately underutilized. Global mobilization of public health and industry resources is key to maximizing the use of licensed vaccines, and the development of new prophylactic vaccines could have a profound impact on reducing AMR.

Keywords Bacterial vaccine · Viral vaccine · Human vaccination · Herd immunity · Antibiotic resistance · Multidrug resistance

Abbreviations

AMR	Antimicrobial resistance
BCG	Bacillus Calmette Guérin
CARB-X	Combating antibiotic-resistant bacteria biopharmaceutical accelerator
CDC	Centers for disease control and prevention
CRM_{197}	Cross-reactive material 197
EU	European Union
GAVI	Global alliance for vaccines and immunization
GBS	Group B streptococcus
Hib	*Haemophilus influenzae* Type b
HIV	Human immunodeficiency virus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
NDM-1	New Delhi metallo-β-lactamase 1
PCV	Polysaccharide conjugate vaccine
RSV	Respiratory syncytial virus
UK	United Kingdom
U.S.	United States
WHO	World health organization

Introduction

The development of effective vaccines and the discovery of antibiotics, along with improvements in effective sanitation and hygiene practices and nutrition, led to the unprecedented increases in life expectancy seen today (Centers for Disease Control and Prevention 2017). However, antimicrobial resistance (AMR) among important human bacterial pathogens is on the rise, representing an alarming global crisis with threats to return to the pre-antibiotic era and to have a significant adverse effect on public health in the coming decades. Vaccines are effective in preventing infections by induction of a typically broad polyclonal antibody and/or cellular immune responses specifically targeted to the pathogen of concern. Unlike current antibiotics, vaccines cannot cause "bystander" microbial resistance or induce resistance in the pathogens targeted. The present article reviews the

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evidence, rationale, and opportunity for vaccines to reduce and prevent AMR and combat the rise of multidrug-resistant bacterial pathogens. This article is an abridged version of the book chapter published by Jansen et al. (Jansen et al. 2021).

Antimicrobial resistance is an urgent public health threat

Antimicrobial resistance predates the age of humans, as bacteria and the eukaryotic fungi and molds from which many antibiotics have been derived have been engaged in a chemical arms race for millennia as they compete for ecological niches. The introduction of antibiotics in the 1940 and 1950s placed evolutionary pressure on microorganisms to adapt developing AMR. Indeed, introduction of each new antibiotic class since has been reliably met with the expansion of resistance. Moreover, this trend has accelerated over time, with recognition of the shortening of the intervals from introduction of a new antibiotic to first documented cases of resistance (Pray 2008). Molecular mechanisms of resistance to different classes of antibiotics associated with major bacterial pathogens and survival strategies have been reviewed (Walsh 2000) and are schematically shown in Fig. 1a.

AMR spread has been further exacerbated due to globalization that served as a vehicle for rapid transmission of emerging antibiotic-resistant microbial strains and associated resistance plasmids across continents. This phenomenon is illustrated well by the spread of fluoroquinolone-resistant *Clostridioides* (previously known as *Clostridium) difficile* 027 epidemic lineages (He et al. 2013; Peng et al. 2017), as well as methicillin- and fluoroquinolone-resistant *Staphylococcus aureus* strains detected in clinical trial isolates (Holden et al. 2013). The excessive and irresponsible use of antimicrobials in healthcare, agriculture, and the food industry has fueled the dramatic rise of AMR globally (https://www.combatamr.org/amr-review-antimicrobial-resistance). Worldwide, AMR is a significant and growing cause of mortality. It is estimated that at least 700,000 people die of infections with AMR pathogens every year, with up to 50,000 deaths occurring in the U.S. and Europe alone (O'Neill 2014). The mortality rates due to AMR are greater than those due to tetanus, cholera, and measles combined, and not much lower than those caused by common afflictions such as diarrheal disease or diabetes (O'Neill 2016a). With rates of resistance continuing at their current pace, it is estimated that annually, 10 million people worldwide will succumb to an AMR infection by 2050, exceeding the number of deaths from cancer (O'Neill 2016a). AMR also represents a major economic burden on healthcare systems, with an associated cost of over 20 billion U.S. dollars each year in the U.S. alone (Centers for Disease Control and Prevention 2013a; Tufts University 2010). If no action is taken against AMR, the cost in terms of lost global production until 2050 is estimated to be 100 trillion U.S. dollars. AMR is thus an immense global problem with serious implications for public health, healthcare systems, and economies.

In 2013, the United States (U.S.) Centers for Disease Control and Prevention (CDC) published a list of antibiotic-resistant pathogens in the U.S. (Centers for Disease Control and Prevention 2013a), which were stratified into urgent, serious, and concerning threat tiers based on the threat they pose to human health and urgency of the need for new and effective modalities for their treatment and prevention. This list was updated in 2019 (Centers for Disease Control and Prevention 2019) (Table 1). A global priority list of antibiotic-resistant pathogens was also established by the World Health Organization (WHO) in 2017, stratified them into three priority tiers: critical, high, and medium (Table 1) (World Health Organization 2017a). Global antibiotic resistance levels associated with major bacterial pathogens are shown in Fig. 2 (Jansen et al. 2018a). Pathogens of the highest priority on both lists include *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and members of the *Enterobacteriaceae* family (primarily *Klebsiella* spp. and *Escherichia coli*) (Table 1). These ominous public health threats are important causes of hospital based, or nosocomial infections and have demonstrated resistance to a large number of antibiotics, including carbapenems and third-generation cephalosporins (World Health Organization 2017a) (https://www.who.int/en/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed). These highlighted pathogens cause a wide range of diseases, including pneumonia, urinary tract infection, bacteremia, and wound infections (Gaynes et al. 2005). Other pathogens of concern identified by the CDC and WHO include those responsible for diarrheal and enteric illness (*C. difficile*, *Helicobacter pylori*, *Campylobacter*, *Salmonella* spp., *Shigella* spp.) or sexually transmitted disease (*Neisseria gonorrhoeae*) (Table 1). Other notable AMR bacterial pathogens recognized by the CDC and WHO are also listed in Table 1.

Vaccines are an underutilized tool to address the antimicrobial resistance problem

To address the AMR crisis, a number of international organizations, including the WHO, the United Nations General Assembly, the World Bank, the G7, the G20, and the EU, as well as the U.S. and United Kingdom (UK) governments have been urgently developing strategic action plans to address the rising AMR issues (G7 Summit 2015; Tagliabue and Rappuoli 2018). Among the proposed measures against AMR, these organizations emphasize the importance of prudent use of existing antimicrobials, and development

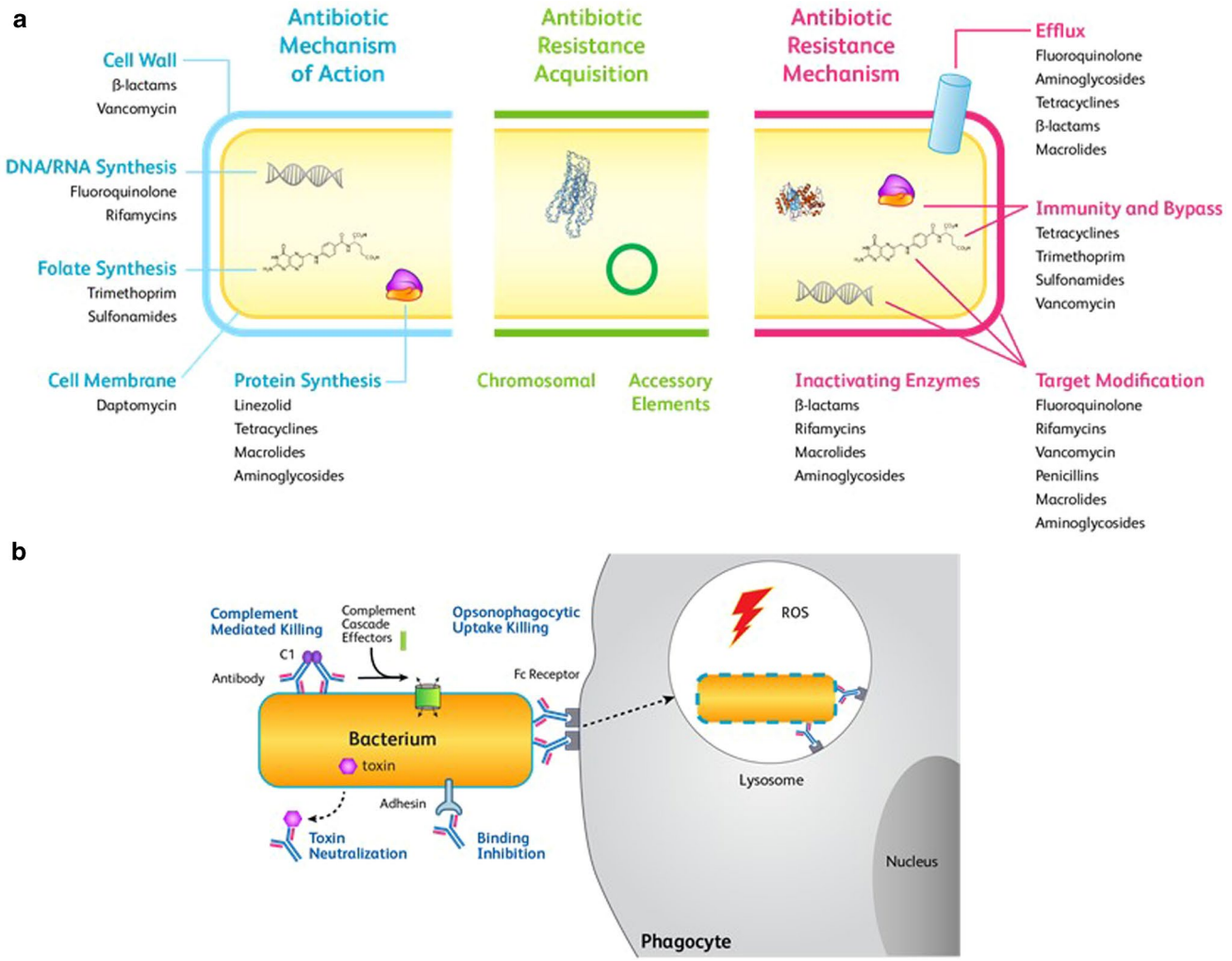

Fig. 1 Molecular mechanisms of action for antibiotics compared to vaccines. **a** Antibiotics either kill bacteria (bactericidal) or stop them from growing (bacteriostatic) by four main mechanisms: preventing DNA/RNA synthesis; preventing folate synthesis, which prevents nucleic acid synthesis; destroying the cell wall/membrane; and targeting ribosomes to prevent protein synthesis. Antibiotic resistance mechanisms neutralize the mechanism of action for the antibiotic. Resistance mechanisms can be acquired through horizontal transfer from plasmids and other genetic elements donated by bacteria that are co-localized with the pathogen. Alternatively, resistance can occur through vertical transmission via chromosomal mutations. These resistance mechanisms include the expression of enzymes such as the β-lactamases which inactivate the antibiotics (β-lactams); the expression or overexpression of efflux pumps which remove the antibiotic from the bacteria; the modification of the target so that it is no longer susceptible to the antibiotic; and using bypass mechanisms to circumvent antibiotic toxicity, including modification of the cell surface to prevent antibiotic entry or direct modification of antibiotics to prevent target engagement (Kohanski et al. 2010; Levy and Marshall 2004). **b** In contrast to antibiotics, vaccines exert their action via immune pathways, eliciting antigen specific polyclonal antibodies that can either neutralize bacterial virulence factors such as toxins or adhesins, or engage effector arms to kill the bacteria through mechanisms including the complement cascade or opsonophagocytic uptake into phagocytes (Forthal 2014). ROS, reactive oxygen species. Copyright [Kathrin U. Jansen, William C. Gruber, Raphael Simon, James Wassil, and Annaliesa S. Anderson] 2021

of new effective antimicrobial medicines and vaccines for human and animals (World Health Organization 2015; Centers for Disease Control and Prevention 2015; National Vaccine Advisory Committee 2016; O'Neill 2016a; Chatham House 2017; Clift and Salisbury 2017). Despite concerted efforts, no new classes of antibiotics have been introduced over the past 15 years and there are few candidates in the pipeline (O'Neill 2016a). Additionally, new antimicrobials are placed on the WHO reserve list, limiting their use. These factors make the development of new antimicrobials commercially unattractive for pharmaceutical companies. On the other hand, the research and development pipelines for prophylactic infectious disease vaccines are on the rise (Shen and Cooke 2019; World Health Organization 2019a), providing valuable opportunities to prevent disease caused by AMR pathogens.

Table 1 Stratification of antibiotic-resistant microbial pathogens according to the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) guidelines

CDC		WHO	
Urgent threats	Carbapenem-resistant *Acinetobacter*	Critical priority	*Acinetobacter baumannii*, carbapenem resistant
	Candida auris		*Pseudomonas aeruginosa*, carbapenem resistant
	Clostridioides difficile		
	Carbapenem-resistant *Enterobacteriaceae*		*Enterobacteriaceae**, carbapenem resistant, 3rd-generation cephalosporin resistant
	Drug-resistant *Neisseria gonorrhoeae*		
Serious threats	Drug-resistant *Campylobacter*	High priority	*Enterococcus faecium*, vancomycin resistant
	Drug-resistant *Candida*		*Staphylococcus aureus*, methicillin resistant, vancomycin intermediate and resistant
	Extended spectrum β-lactamase producing *Enterobacteriaceae*		*Helicobacter pylori*, clarithromycin resistant
	Vancomycin-resistant *Enterococcus*		*Campylobacter*, fluoroquinolone resistant
	Multidrug-resistant *Pseudomonas aeruginosa*		*Salmonella* spp., fluoroquinolone resistant
	Drug-resistant non-typhoidal *Salmonella*		*Neisseria gonorrhoeae*, 3rd-generation cephalosporin resistant, fluoroquinolone resistant
	Drug-resistant *Salmonella* serotype Typhi		
	Drug-resistant *Shigella*		
	Methicillin-resistant *Staphylococcus aureus*		
	Drug-resistant *Streptococcus pneumoniae*		
	Drug-resistant *Mycobacterium tuberculosis*		
Concerning threats	Erythromycin-resistant Group A *Streptococcus*	Medium priority	*Streptococcus pneumoniae*, penicillin nonsusceptible
	Clindamycin-resistant Group B *Streptococcus*		*Haemophilus influenzae*, ampicillin resistant
			Shigella spp., fluoroquinolone resistant
Watch list	Azole-resistant *Aspergillus fumigatus*		
	Drug-resistant *Mycoplasma genitalium*		
	Drug-resistant *Bordetella pertussis*		

**Enterobacteriaceae* include: *Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp, and *Morganella* spp

CDC, Centers for Disease Control and Prevention; WHO, World Health Organization

Adapted from (Centers for Disease Control and Prevention 2019; World Health Organization 2017a)

The mechanisms of action of vaccines and antibiotics are fundamentally different (Fig. 1). Antibiotics classically treat established infections and disease, whereas vaccines classically prevent infections from happening in the first place. The mode of action for antibiotics centers on interference with a pathogen's physiology, addressing usually a single biological target (Kohanski et al. 2010). The broad spectrum action of antibiotics is beneficial when the etiology of the infection is not or cannot be identified; however, antibiotics also kill bystander bacteria and microbial flora, making the patient vulnerable to dysbiosis and outgrowth of resistant disease causing pathogens, as well as promote selection for bacteria to develop AMR. In contrast to antibiotics, prophylactic vaccines are species specific and prevent the infection or disease, thus reducing both antibiotic use and spread of resistant bacterial strains and do not induce antibiotic resistance. Vaccines act through immune pathways, inducing protective immune responses that are pathogen specific and target one or more bacterial virulence factors such as toxins or adhesins, either neutralizing them or engaging the effector arms of the immune system to kill the bacterial pathogen through complement and/or opsonophagocytosis (Forthal 2014). The polyclonal nature of vaccine induced immune responses limits escape mutants. Although vaccine immunity may fade over time due to waning of the specific host immune response (Kennedy and Read 2017), functional immunity can be restored following re-immunization with a booster dose and that can be done repeatedly over one's lifetime.

Vaccination can affect AMR both directly and indirectly. Bacterial vaccines directly reduce antibiotic use through prevention of bacterial infections, and thus selection for AMR strains. Viral vaccines also diminish antibiotic use through avoidance of unwarranted antibiotic prescriptions as well as through prevention of secondary bacterial infections. Additionally, bacterial vaccines decrease circulation of resistant strains in vaccinated populations in regions with adequate vaccine coverage. In such settings, vaccines are known to induce herd immunity, an indirect vaccine

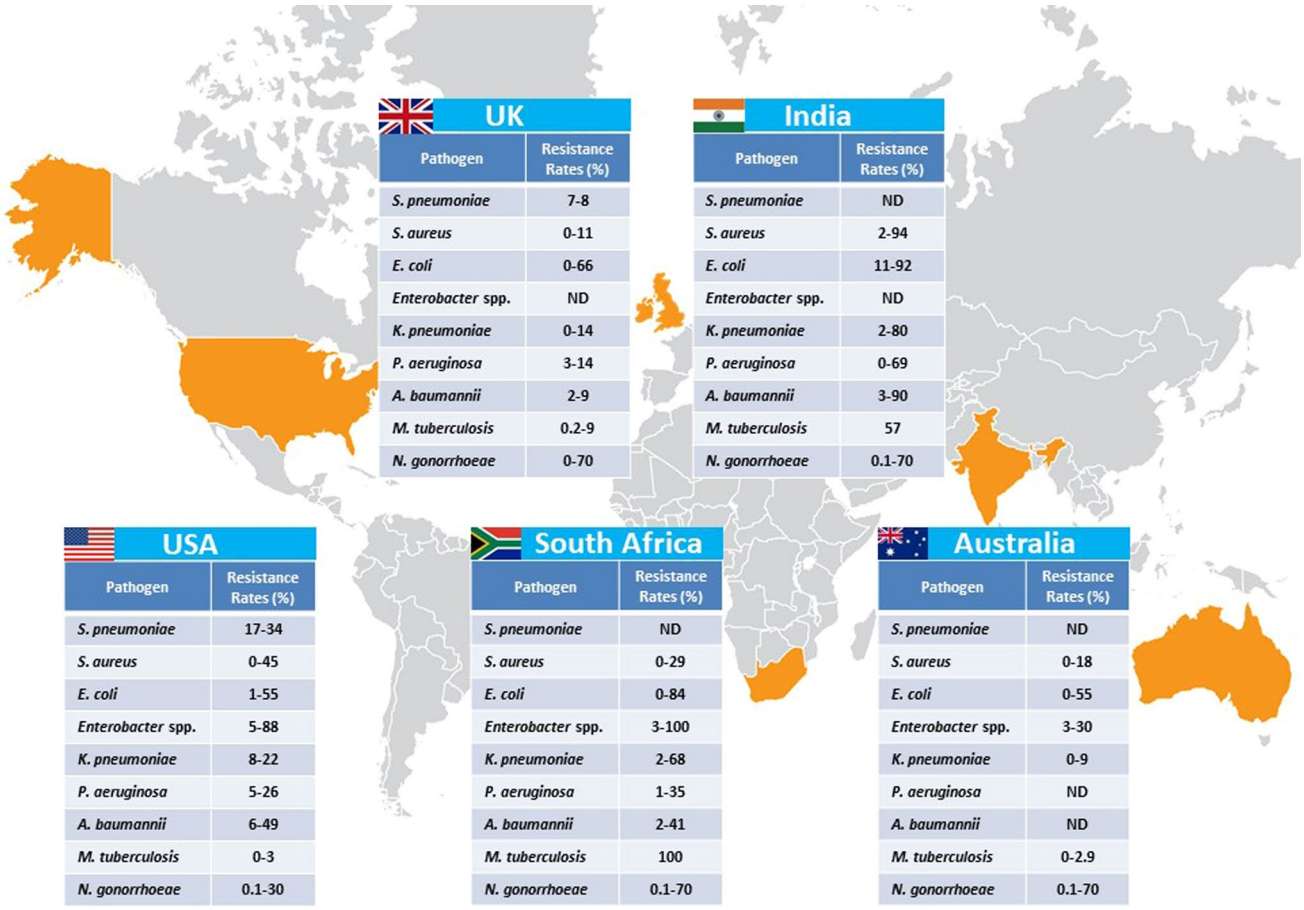

Fig. 2 Antibiotic resistance levels associated with major bacterial pathogens across the globe. Data shown are from 2000 to 2014 and represent the percentage of isolates (the range) tested that are resistant to each antibiotic class used for each pathogen (pathogen specific), not taking into account the proportion of strains that are resistant to more than one antibiotic class. ROS: reactive oxygen species. For all pathogens except *M. tuberculosis* and *N. gonorrhoeae*, data were obtained from the Center for Disease Dynamics, Economics & Policy (https://resistancemap.cddep.org). For *M. tuberculosis*, data were obtained from WHO Drug Resistant TB Surveillance & Response—Supplement: Global Tuberculosis Report 2014 (World Health Organization 2014a). For *N. gonorrhoeae*, data were obtained from the World Health Organization Global Gonococcal Antimicrobial Surveillance Program which covers strains analyzed between 2011 and 2014 (http://www.who.int/reproductivehealth/topics/rtis/gonococcal_resistance/en/). ND, no data provided. Copyright [Kathrin U. Jansen, William C. Gruber, Raphael Simon, James Wassil, and Annaliesa S. Anderson] 2021

phenomenon that leads to protection of even unvaccinated individuals in a vaccinated population. In the following sections of this article, we will discuss examples of proven anti-AMR benefits of licensed vaccines, review the status of new vaccine candidates with potential against AMR, and outline challenges and prospects related to the use of vaccines as a tool to reduce prevent AMR.

Vaccines have reduced incidence and evolution of antimicrobial-resistant bacterial pathogens

There are several well-documented and epidemiologically supported examples whereby both bacterial and viral vaccines have impacted AMR. Additionally, vaccine strategies have been purposefully used to combat the rise of an AMR pathogen.

Vaccines reduce circulating antibiotic-resistant strains and antibiotic use

Haemophilus influenzae type b vaccine

H. influenzae is an invasive bacterial pathogen that can cause severe infection characterized by pneumonia, septicemia, and meningitis, where mortality occurs in up to 5% of infected individuals (https://www.cdc.gov/hi-disease/about/index.html). Prior to the introduction of Hib conjugate vaccines into the routine infant immunization schedule in 1987, first in the U.S. and then globally, Hib was a devastating pathogen in infants and young children. At that time, incidence rates of Hib disease (including bacterial meningitis and other invasive diseases) in children younger than 5 years ranged from 49 to 601 per 100,000 in some populations (Peltola et al. 1990; Ward et al. 1986). In addition, a steady increase in β-lactam resistance among invasive Hib isolates had been observed starting in the early 1970s (Tristram et al. 2007).

The development and deployment of Hib capsular polysaccharide conjugate vaccines (PCV) as part of routine childhood immunizations rapidly reduced the incidence of Hib disease (Adam et al. 2010; Centers for Disease Control and Prevention (CDC) 2002; Peltola et al. 1999). According to the CDC reported Active Bacterial Core Surveillance data from 2014, the invasive Hib disease incidence was 0.19 per 100,000 for children younger than 5 years, the value below the Healthy People 2020 objective of 0.27 per 100,000 (Centers for Disease Control and Prevention 2016), indicating a dramatic reduction in the disease rates due to Hib vaccination. Comparable successes were observed globally (Hargreaves et al. 1996). Moreover, global use of the Hib vaccine turned the tide against growing Hib antibiotic resistance (Heilmann et al. 2005). The impact of Hib conjugate vaccines on AMR strains was also confirmed in studies that have shown a correlation between Hib vaccine use and a reduction in resistance to one or more antibiotics. For example, in a 10-year Italian study, after universal introduction of Hib vaccine in 1999, a 50% decrease in resistance to ampicillin and related antibiotics among clinical isolates across all ages was observed (Giufre et al. 2011).

Pneumococcal conjugate vaccines

S. pneumoniae continues to be a leading global cause of serious illness among unvaccinated children and adults. In 2005, the WHO estimated that 1.6 million deaths were caused by this pathogen annually (http://www.who.int/ith/diseases/pneumococcal/en/). In the 1990s, before the introduction of the 7-valent pneumococcal capsular polysaccharide conjugate vaccine (PCV7, Prevnar®) into the childhood immunization program, ~ 63,000 cases of invasive pneumococcal disease occurred each year in the U.S. (Feldman and Anderson 2016). Importantly, at this time resistance to penicillin and other classes of antibiotics also emerged among *S. pneumoniae* isolates in the U.S. (Breiman et al. 1994; Butler et al. 1996).

Introduction of PCVs, initially covering 7 (PCV7; Wyeth, 2000) and subsequently 13 (PCV13, Prevnar 13®; Pfizer, 2010) pneumococcal serotypes, had a tremendous success in the U.S. with more than 90% efficacy against invasive pneumococcal disease observed in the primary target population of children younger than 5 years (Cohen et al. 2017). Importantly, PCVs protected against both antibiotic-susceptible and antibiotic-resistant isolates. Several studies in the U.S. have analyzed the laboratory confirmed data from the population based Active Bacterial Core Surveillance system to evaluate changes in invasive pneumococcal disease rates following introduction of PCVs. One of those analyses, performed on the data from 1996 to 2004, found that after introduction of PCV7 in the U.S., rates of penicillin nonsusceptible infections with serotypes included in the vaccine fell by 87% (5.0–0.7 cases per 100,000) for any ages, 98% (61.5–1.2 cases per 100,000) for children younger than 2 years, and 79% (12.3–2.6 cases per 100,000) for adults 65 years of age and older. Additionally, the rate of infection with strains of *S. pneumoniae* showing reduced susceptibility to multiple antibiotics dropped by 59% for people of all ages (Kyaw et al. 2006). Prevention of invasive pneumococcal disease caused by the seven serotypes covered by PCV7 (including antibiotic-resistant strains) in children younger than 5 years as well as adults 65 years of age and older was also confirmed in other studies (Pilishvili et al. 2010; Hampton et al. 2012).

A subsequent study on the impact of PCV13 on antibiotic nonsusceptible invasive pneumococcal disease in the U.S. also demonstrated decreased rates of antibiotic nonsusceptible invasive pneumococcal disease caused by serotypes included in PCV13 but not in PCV7 between 2009 (immediately before PCV13 was introduced) and 2013: from 6.7 to 2.2 per 100,000 for all ages, from 6.5 to 0.5 per 100,000 in children younger than 5 years, and from 4.4 to 1.4 per 100,000 in adults 65 years of age and older (Tomczyk et al. 2016) (Fig. 3). Marked decreases were also observed for rates of multidrug nonsusceptible invasive pneumococcal disease. Furthermore, following the introduction of PCV13, the annual incidence of antibiotic nonsusceptible invasive pneumococcal disease in children younger than 5 years in the U.S. was reduced from 2010 through 2013 by a range of 63–83% for strains resistant to macrolides, cephalosporins, tetracyclines, and penicillins, indicating direct impact on circulating AMR strains (Tomczyk et al. 2016). Surveillance studies in other countries have also shown a considerable impact of PCVs on invasive pneumococcal disease rates (von Gottberg et al. 2014; von Gottberg et al. 2016).

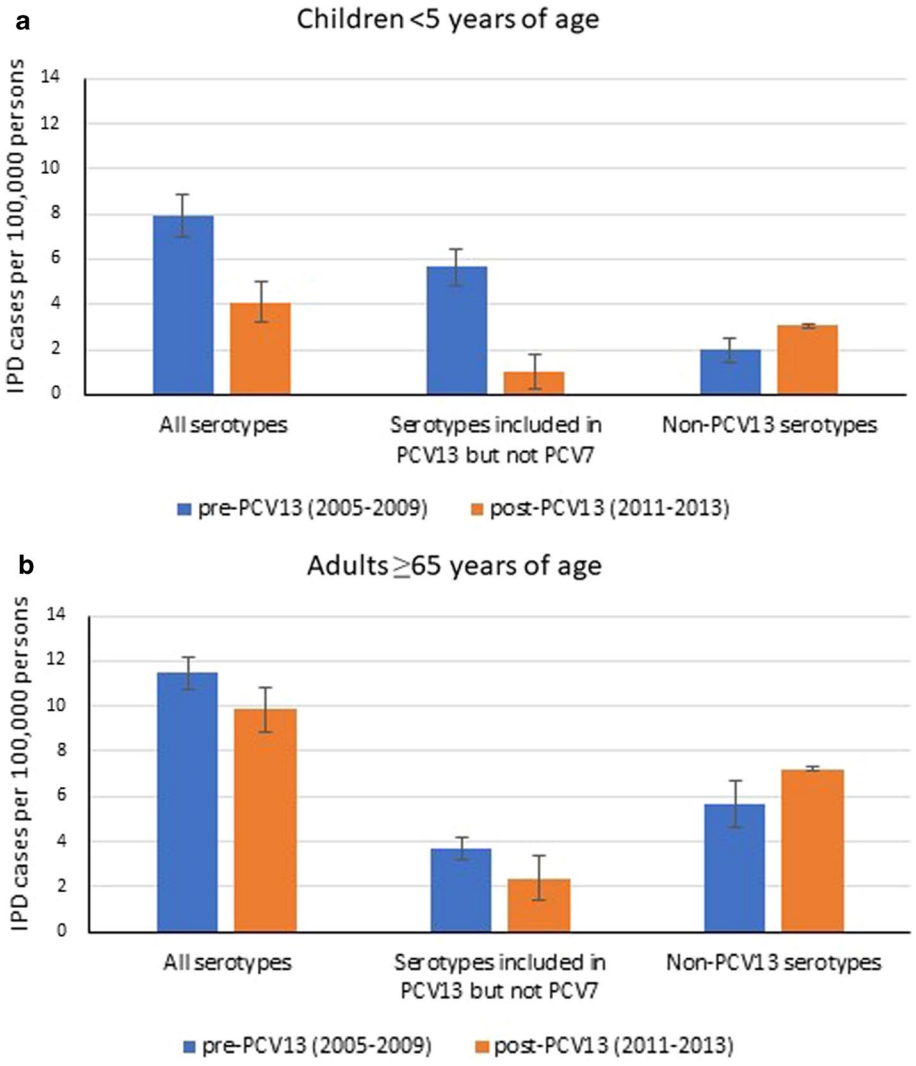

Fig. 3 Reduction of antimicrobial resistance after broad rollout of PCV13. Data presented show average annual rates of antibiotic nonsusceptible invasive pneumococcal disease (IPD) of the vaccine- and non-vaccine type, with standard deviations in (**a**) vaccinated (children younger than 5 years) and (**b**) non-vaccinated (adults 65 years of age and older) populations, prior to (2005–2009) and following (2011–2013) introduction of PCV13 vaccine. Adapted from (Tomczyk et al. 2016). Copyright [Kathrin U. Jansen, William C. Gruber, Raphael Simon, James Wassil, and Annaliesa S. Anderson] 2021

Studies in different countries demonstrate that vaccination with PCV also decreases antibiotic use and reduces pneumonia cases misattributed to respiratory viral infection. For example, with introduction of PCV7 in 2000 in the U.S., antibiotic prescription for acute otitis media in children younger than 2 years fell by 42% from 1997–1999 to 2004 (Zhou et al. 2008). An international group of experts estimated that overall, universal coverage with PCV could avert up to 11.4 million days of antibiotic therapy for pneumonia caused by *S. pneumoniae* annually in children younger than 5 years, a 47% reduction in the 75 countries included in the analysis (Laxminarayan et al. 2016). In a large randomized, placebo-controlled study in South Africa, a 9-valent PCV prevented 31% (95% confidence interval, 15–43%) of pneumonias attributed to influenza A and parainfluenza viruses and respiratory syncytial virus (RSV) in fully immunized infants, with the effect presumed due to otherwise undiagnosed contemporaneous pneumococcal infection (Madhi et al. 2004).

Typhoid conjugate vaccine

Typhoid vaccines also provide a contemporary example of how a vaccine can be used to prevent dissemination of an AMR pathogen. In 2000, *S.* Typhi caused approximately 21.7 million illnesses and 216,000 deaths worldwide (Crump et al. 2004). Typhoid fever remains a common infectious disease in low- and middle-income countries, causing approximately 11.9 million cases and 129,000 deaths in 2010 according to the International Vaccine Institute (Mogasale et al. 2014), although the true disease burden is likely underestimated. The CDC has categorized *S.* Typhi as being of serious concern as an antibiotic resistance threat, as 74% of *S.* Typhi infections had partial or full resistance to ciprofloxacin in 2017, and resistance to other antibiotics was also observed (Centers for Disease Control and Prevention 2019).

The discovery in 2016, in the Sindh province of Pakistan, of an extensively drug-resistant haplotype 58 clone of *S.* Typhi, resistant to first- and second-line antibiotics as

well as third-generation cephalosporins, thus evoked particular alarm (Andrews et al. 2018). Since recognition of its emergence, the ongoing major typhoid outbreak with this clone has affected more than 5,200 people within the Sindh region (https://www.who.int/csr/don/27-december-2018-typhoid-pakistan/en/) (Qamar et al. 2018), and extensively drug-resistant H58 *S.* Typhi has the capacity to cause a global public health crisis (Klemm et al. 2018; Levine and Simon 2018). In response to the outbreak, and due to the limited treatment options and risk for rapid spread of this extensively drug-resistant typhoid clone, Pakistani authorities launched an emergency typhoid vaccination campaign in the most affected areas, using the WHO prequalified Vi capsular conjugate vaccine Typbar-TCV™ manufactured by Bharat Biotech (India) and approved for use in children and infants younger than 2 years (Sahastrabuddhe and Saluja 2019; Bhatti 2019) (https://www.who.int/csr/don/27-december-2018-typhoid-pakistan/en/). Another Vi-conjugate vaccine intervention effort to control a typhoid outbreak was undertaken in Zimbabwe, Africa, where *S.* Typhi isolates manifested high levels of multidrug resistance and reduced fluoroquinolone susceptibility (N'Cho et al. 2019). In February–March 2019, surveillance for febrile cases with suspected typhoid in the worst affected communities, performed three months after initiation of the vaccination effort, revealed a complete absence of typhoid cases among 24 children 6 months–15 years of age who provided blood cultures, compared with 23 of 109 (21%) positive blood cultures seen in a study directly preceding the start of the campaign. This was the first attempt to control a typhoid outbreak in Africa through vaccination and the first use of the typhoid Vi-conjugate vaccine in the continent (Olaru et al. 2019).

These examples of the purposeful use of a vaccine to control an outbreak with an AMR pathogen thus represent a new paradigm in public health that may be extended to other pathogens in the future.

Vaccines mediate herd immunity

Herd immunity is the protection conferred through broad vaccine coverage at the population level, to members of the community who are not vaccinated, cannot be vaccinated, or do not mount effective immune responses following vaccination. High vaccination rates at the population level are needed to achieve herd immunity and can both reduce transmission of AMR pathogens and limit antibiotic use by non-vaccinated individuals. Significant herd immunity has been achieved by both Hib and pneumococcal conjugate vaccines, driven in part by the reduction of nasopharyngeal colonization with pathogens expressing vaccine serotypes. Infant immunization with Hib vaccines led to a rapid fall in the rates of invasive Hib infections worldwide, in both vaccinated and unvaccinated children, an effect attributed to decreased carriage and transmission among young children (Steinhoff and Goldblatt 2003).

The introduction of PCV7 and PCV13 in pediatric vaccination programs has had significant impact on reduction of vaccine type invasive pneumococcal disease in both unvaccinated pediatric and adult populations, particularly elderly (65 years of age and older), due to the herd effect. This has been attributed to both the reduction in bacterial carriage and a substantial decrease in the incidence of invasive pneumococcal disease (Cohen et al. 2017). As described in Sect. 4.1, analyses of invasive pneumococcal disease cases identified through the U.S. Active Bacterial Core Surveillance system demonstrated significant reductions in the rates of penicillin nonsusceptible infections for the all-ages population as well as adults 65 years of age and older, which were associated with serotypes included in PCV7 (between late 1990 and middle-to-late 2000s) (Hampton et al. 2012; Kyaw et al. 2006; Pilishvili et al. 2010) and PCV13 (between middle 2000 and early 2010s) (Fig. 3b) (Tomczyk et al. 2016). In other countries, the invasive pneumococcal disease and pneumonia disease rates also declined after PCV introduction through herd immunity (Ingels et al. 2012; Lai et al. 2014; Tsaban and Ben-Shimol 2017; von Gottberg et al. 2014; von Gottberg et al. 2016). With the recent licensure of a PCV20 vaccine in adults (Pfizer 2021), the prospect of an even greater reduction in pneumococcal disease is possible.

Preventing antimicrobial resistance using viral vaccines

Although they do not directly generate antibacterial immunity, viral vaccines are an important tool for containment of AMR. First, they help prevent viral disease and thus avoid the inappropriate use of antibiotics. Additionally, bacterial infections are common secondary complications following some viral diseases and may even cause concurrent viral-bacterial superinfections that can be reduced by vaccination against a bacterial pathogen (Madhi et al. 2004). Vaccination against viral pathogens thus prevents secondary bacterial infections that may be antibiotic resistant. Influenza virus and rotavirus vaccines represent prominent examples of approved vaccines with these anti AMR benefits.

Influenza virus vaccine

An estimated 3–5 million cases of influenza occur each year worldwide, causing 290,000–650,000 respiratory deaths (Iuliano et al. 2018) (https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)). The elderly population, people with chronic pulmonary or cardiovascular conditions, and immunocompromised individuals are at greatest risk for severe influenza disease and disease complications (Mertz et al. 2013). Live-attenuated, inactivated,

and recombinant influenza vaccines, targeting influenza A and B, are produced annually to match changes in the hemagglutinin proteins contained in the strains expected to circulate in the following influenza season (https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)). Globally, the influenza season represents the period of greatest antibiotic use, in part due to the frequent inappropriate prescription of antibiotics for respiratory tract infections caused by viral pathogens. In the U.S., nearly half of all antibiotic prescriptions are written for respiratory illnesses associated with pathogens such as influenza that are not susceptible to antibiotics (Fleming-Dutra et al. 2016). Reduction in influenza infection through vaccination thus reduces antibiotic use. In Ontario, Canada, universal influenza vaccination resulted in approximately 64% reduction in influenza-associated antibiotic prescriptions (Kwong et al. 2009). In the UK, children 2–4 years of age who were vaccinated with a live-attenuated influenza vaccine had 14.5% fewer amoxicillin prescriptions during the period of influenza vaccine immunity compared with other winter seasons (Hardelid et al. 2018).

Recovery from influenza infection is accompanied by an overt risk for secondary bacterial respiratory infections (Prasso and Deng 2017), thus further amplifying the morbidity and mortality due to influenza (Kash and Taubenberger 2015). *S. pneumoniae*, *H. influenzae*, and *S. aureus* are reported as the most common causes of secondary bacterial infections associated with influenza (Joseph et al. 2013; Morris et al. 2017). Vaccination against influenza thus indirectly protects against these bacterial pneumonias that may be antibiotic resistant. Acute otitis media is another common secondary bacterial infection associated with influenza (Kash and Taubenberger 2015). Several studies worldwide provided evidence that influenza vaccination in young children decreases the incidence of this infection (approximately 50% reduction, Turkey (Ozgur et al. 2006); 54.8% reduction [$p = 0.03$], Italy (Marchisio et al. 2009); 85% [95% confidence interval, 78.3–89.8%] and 54% [95% confidence interval, 27.0–71.7%] efficacy, live-attenuated and trivalent inactivated influenza vaccines, respectively, U.S., Europe, and Asia (Block et al. 2011)), as well as reduce influenza-associated antibiotic use (13.2% [$p < 0.001$], Italy (Marchisio et al. 2009); 71, 36, and 59%, Europe, Asia Pacific, and Central America, respectively (Dbaibo et al. 2020)). Implementation of national universal influenza vaccination programs, improvement of existing vaccines towards increased breadth of efficacy to an extended repertoire of viral strains, higher efficacy in older adults and young children, and development of universal influenza vaccines would provide further impact in the fight against AMR.

Rotavirus vaccine

Diarrheal disease is a second leading cause of mortality and morbidity among children younger than 5 years, and children in low-income countries are particularly affected (https://www.who.int/en/news-room/fact-sheets/detail/diarrhoeal-disease). Rotavirus is a leading cause of severe diarrheal disease in infants and young children (https://www.who.int/immunization/diseases/rotavirus/en/). Two oral rotavirus vaccines are currently licensed for infants in the U.S.: RotaTeq® and Rotarix® (https://www.cdc.gov/rotavirus/vaccination.html), and two more are approved internationally and are WHO prequalified (https://www.who.int/immunization/diseases/rotavirus/en/). Rotavirus vaccines have had a significant public health impact through their efficacy (Giaquinto et al. 2011; Linhares et al. 2008; Vesikari et al. 2007) as well as herd protection (Patel et al. 2011; Pollard et al. 2015). As infection with rotavirus can lead to inappropriate antibiotic use if a misdiagnosis of bacterial infection is given (e.g., enterotoxigenic *E. coli* or *Vibrio cholerae*) or if treatment is sought based on symptoms, implementation of national rotavirus vaccination programs worldwide would benefit containment of AMR by reducing inappropriate antibiotic prescriptions in countries endemic for these bacterial pathogens.

Vaccines under development with potential to reduce antimicrobial resistance

Given the proven success of licensed vaccines in combating AMR, sustained efforts are being directed towards the development of new and improved vaccines targeting pathogens that exhibit increased antibiotic resistance, are associated with high antibiotic use, and are considered priority organisms by the WHO and the CDC (Centers for Disease Control and Prevention 2019; World Health Organization 2017a). In the following sections, we will discuss select examples of vaccines under development that target pathogens with demonstrated propensity to acquire antibiotic resistance, and thus hold promise in further reducing AMR (Table 2).

Bacterial vaccines in late-stage clinical development

Clostridioides difficile vaccines

C. difficile, a Gram positive anaerobic, spore forming bacillus, is the main cause of nosocomial infectious diarrhea in industrialized countries that frequently occurs consequent to antibiotic use (Guerrant et al. 1990; Kelly et al. 1994; Kyne and Kelly 1998; Magill et al. 2014; McFarland 1995). According to the CDC, there were 223,900 cases of *C. difficile* infection related to antibiotic use and antibiotic

Table 2 Examples of vaccine candidates in active clinical development with the potential to reduce antimicrobial resistance

Vaccine name	Organization	Vaccine type	Vaccine composition	Stage	NCT	Status	Study population	Reference
Clostridioides difficile								
PF-06425090	Pfizer	Toxoid	Genetically-/chemically-inactivated toxins A and B	Phase 3	NCT03090191	Ongoing	Adults at risk of developing *C. difficile* infection, ≥ 50 years	https://clinicaltrials.gov/
VLA84	Valneva	Toxoid	Recombinant fusion protein consisting of truncated toxins A and B	Phase 2	NCT02316470	Completed	Healthy adults, ≥ 50 years	https://clinicaltrials.gov/
GSK2904545A	GSK	Toxoid	Recombinant F2 antigen	Phase 1	NCT04026009	Ongoing	Healthy adults, 18–45 and 50–70 years	https://clinicaltrials.gov/
Streptococcus pneumoniae								
V114	Merck	Conjugate (15-valent)	Capsular polysaccharides of *S. pneumoniae* conjugated to CRM_{197}	Phase 3	NCT03480763	Completed	Healthy adults, ≥ 50 years	https://clinicaltrials.gov/
					NCT03480802	Completed	Healthy adults, ≥ 18 years	
					NCT03692871	Completed	Healthy infants	
20vPnC	Pfizer	Conjugate (20-valent)	Capsular polysaccharides of *S. pneumoniae* conjugated to CRM_{197}	Phase 3	NCT04382326 NCT04379713	Ongoing	Healthy infants	https://clinicaltrials.gov/
Pneumosil	Serum Institute of India	Conjugate (10-valent)	Capsular polysaccharides of *S. pneumoniae* conjugated to CRM_{197}	Phase 3	NCT03896477	Completed	Healthy infants, 42–56 days	(Moffitt and Malley 2016); https://clinicaltrials.gov/
GSK2830929A, GSK2830930A	GSK	Conjugate (11- and 12-valent)	Capsular polysaccharides of *S. pneumoniae* conjugated to non-typeable *H. influenzae* protein D (PHiD-CV)	Phase 2	NCT01616459	Completed	Healthy infants, 6–12 weeks	(Carmona Martinez et al. 2019); https://clinicaltrials.gov/
GSK2189242A	GSK	Conjugate/subunit (bivalent)	Recombinant PhtD and PlyD1 of *S. pneumoniae* plus PHiD-CV	Phase 2	NCT01204658	Completed	Healthy infants, 6–14 weeks	(Prymula et al. 2017); https://clinicaltrials.gov/
ASP3772	Affinivax	Complex (MAPS)	Capsular polysaccharides and proteins of *S. pneumoniae*	Phase 1/2	NCT03803202	Completed	Healthy adults, 18–85 years	http://affinivax.com/vaccine-pipeline/; https://clinicaltrials.gov/
Unspecified	Sanofi	Subunit (trivalent)	Recombinant PhtD, PcpA, and PlyD1 of *S. pneumoniae*	Phase 1	NCT01444352	Completed	Healthy adults, 18–50 years	(Kamtchoua et al. 2013); https://clinicaltrials.gov/
PATH-wSP	PATH/Boston Children's Hospital	Inactivated whole cell	Mutation inactivated whole cell *S. pneumoniae*	Phase 2	NCT02097472	Completed	Healthy toddlers and adults, 12 months to 45 years	(Moffitt and Malley 2016); https://clinicaltrials.gov/

Table 2 (continued)

Vaccine name	Organization	Vaccine type	Vaccine composition	Stage	NCT	Status	Study population	Reference
Group B streptococcus								
GBSIII-TT	NIAID	Conjugate (monovalent)	Capsular polysaccharide of GBS serotype III conjugated to TT	Phase 2	NCT00128219	Completed	Healthy non-pregnant women, 18–40 years	(Hillier et al. 2019); https://clinicaltrials.gov/
GBSII-TT/III-TT	Baylor College of Medicine	Conjugate (bivalent)	Capsular polysaccharide of GBS serotypes II and III conjugated to TT	Phase 2	N/A	Completed	Healthy adults, 18–45 years	(Baker et al. 2003)
GBS-NN	Minervax ApS	Subunit (bivalent)	Recombinant fusion of N-terminal domains of GBS Rib and Alpha C surface proteins	Phase 1 Phase 2	NCT02459262 NCT03807245	Completed Completed	Healthy non-pregnant women, 18–40 years	(Rose et al. 2018); https://clinicaltrials.gov/
GBS trivalent vaccine	GSK	Conjugate (trivalent)	Capsular epitopes of GBS serotypes Ia, Ib, and III conjugated to CRM_{197}	Phase 2 Phase 2	NCT02270944 NCT02690181	Completed	Healthy non-pregnant women, 18–40 years Healthy non-pregnant women, 22–46 years	(Leroux-Roels et al. 2019, 2016); https://clinicaltrials.gov/
GBS6	Pfizer	Conjugate (hexavalent)	Capsular epitopes of GBS serotypes Ia, Ib, II, III, IV, and V conjugated to CRM_{197}	Phase 2	NCT03765073	Ongoing	Healthy non-pregnant and pregnant women, 18–40 years	https://clinicaltrials.gov/
Escherichia coli								
ExPEC4V/EcoXyn-4 V or JNJ-63871860	LimmaTech (formerly GlycoVaxyn) and Janssen	Conjugate (tetravalent)	O-antigens of *E. coli* serotypes O1A, O2, O6A, and O25B individually bioconjugated to rEPA	Phase 1 Phase 2	NCT02289794 NCT02546960	Completed Completed	Healthy women with a history of recurrent UTIs, 18–70 years Healthy adults, ≥ 18 years	(Frenck et al. 2019; Huttner et al. 2017); https://clinicaltrials.gov/
Mycobacterium tuberculosis								
Multiple vaccines	Multiple	Genetically modified BCG, whole cell inactivated, subunit, recombinant vector		Phase 1–3	Multiple	Various	Various	(Andersen and Scriba 2019; Khoshnood et al. 2018; World Health Organization 2018); https://clinicaltrials.gov/
Shigella								
CVD 1208S	University of Maryland	Live attenuated	Live attenuated *S. flexneri* 2a strain	Phase 1	N/A	Completed	Healthy adults, 18–45 years	(Kotloff et al. 2007)
WRSS1	WRAIR	Live attenuated	Live attenuated *S. sonnei*	Phase 2	N/A	Completed	Healthy men, 18–22 years	(Orr et al. 2005)

Table 2 (continued)

Vaccine name	Organization	Vaccine type	Vaccine composition	Stage	NCT	Status	Study population	Reference
SsWC	WRAIR	Inactivated	Whole-cell formalin-inactivated trivalent *S. sonnei*	Phase 1	N/A	Completed	Healthy adults, 18–50 years	(McKenzie et al. 2006)
S. sonnei-rEPA	WRAIR	Conjugate	O-antigen of *S. sonnei* conjugated to rEPA	Phase 3	N/A	Completed	Healthy men, 18–22 years	(Cohen et al. 1997)
SF2a-TT15	Institut Pasteur	Conjugate	Synthetic repeats of *S. flexneri* type 2a O-antigen conjugated to TT	Phase 1	NCT02797236	Completed	Healthy adults, 18–45 years	(Barel and Mulard 2019); https://clinicaltrials.gov/
GVXNS D133	LimmaTech	Conjugate	Bioconjugate of *S. dysenteriae* type 1 O-antigen and rEPA	Phase 1	NCT01069471	Completed	Healthy adults, 18–50 years	(Hatz et al. 2015)
Flexyn2a	LimmaTech	Conjugate	Bioconjugate of *S. flexneri* type 2a O-antigen and rEPA	Phase 1 Phase 2b	NCT02388009 NCT02646371	Completed	Healthy adults, 18–50 years	(Riddle et al. 2016); https://clinicaltrials.gov/
1790GAHB	GSK	Subunit (GMMA)	OMV vaccine for *S. sonnei*	Phase 2a	NCT02676895 NCT03089879	Completed	Healthy adults, 18–45 years	(Obiero et al. 2017); https://clinicaltrials.gov/
Invaplex 50	Naval Medical Research Center/ WRAIR	Subunit	Complex of IpaB/C/D with *S. flexneri* 2a LPS	Phase 1 Phase 1	NCT00082069 N/A	Completed	Healthy adults, 18–40 years Healthy adults, 18–45 years	(Riddle et al. 2011; Tribble et al. 2010); https://clinicaltrials.gov/
Non-typhoidal Salmonella								
CVD 1000	University of Maryland	Conjugate	Conjugates of O-antigen and flagellin from *S.* Typhimurium and *S.* Enteritidis, formulated with Typbar-TCV™	Phase 1	NCT03981952	Ongoing	Healthy adults, 18–45 years	(Baliban et al. 2018); https://clinicaltrials.gov/
Paratyphoid Salmonella								
CVD 1902	University of Maryland	Live attenuated	Live attenuated *S.* Paratyphi A strain 9150	Phase 1	NCT01129453	Completed	Healthy adults, 18–45 years	(Wahid et al. 2019); https://clinicaltrials.gov/
Staphylococcus aureus								
4C-Staph	GSK	Subunit	Csa1A (Sur2), FhuD2, EsxA/EsxB, HlAH35L	Phase 1	NCT01160172	Completed	Healthy adults, 18–40 years	(Mancini et al. 2016);https://clinicaltrials.gov/
NDV-3	NovaDigm	Subunit	Recombinant N-terminal portion of Als3p of *Candida albicans*		NCT03455309	Completed	Men at increased risk for *S. aureus* colonization and disease, 17–35 years	(Schmidt et al. 2012); https://clinicaltrials.gov/

Table 2 (continued)

Vaccine name	Organization	Vaccine type	Vaccine composition	Stage	NCT	Status	Study population	Reference
Respiratory syncytial virus								
ResVax	Novavax	Nanoparticle	Recombinant RSV-F protein in nanoparticles	Phase 3	NCT02624947	Completed	Healthy third-trimester pregnant women, 18–40 years	https://clinicaltrials.gov/
RSV vaccine	Pfizer	Subunit	Engineered soluble pre-fusion site Ø–stabilized RSV F trimers	Phase 3	NCT04424316	Ongoing	Healthy third-trimester pregnant women, 18–49 years	(Schmoele-Thoma et al. 2019); https://clinicaltrials.gov/
				Phase 2	NCT03529773	Completed	Healthy adults, 18–49 and 50–85 years	
					NCT03572062	Terminated	Healthy older adults, 65–85 years	
					NCT04071158	Completed	Healthy non-pregnant women, 18–49 years	
					NCT04032093	Ongoing	Healthy third-trimester pregnant women, 18–49 years	
GSK3003891A	GSK	Subunit	Engineered soluble pre-fusion site Ø–stabilized RSV F trimers	Phase 2	NCT02360475 NCT02753413	Completed	Healthy non-pregnant women, 18–45 years	(Beran et al. 2018); https://clinicaltrials.gov/
VRC-RSVRGP084-00VP (DS-Cav1)	NIAID	Subunit	Engineered soluble pre-fusion site Ø–stabilized RSV F trimers	Phase 1	NCT03049488	Completed	Healthy adults, 18–50 years	(Crank et al. 2019); https://clinicaltrials.gov/
Multiple vaccines	Multiple	Subunit, recombinant vector, live-attenuated		Phase 1–2	Multiple	Various	Healthy children and adults	(Jares Baglivo and Polack 2019; PATH 2019)
Human immunodeficiency virus								
Multiple vaccines	Multiple	Subunit, recombinant vectors		Phase 1–3	Multiple	Various	Various	(Hsu and O'Connell 2017; Trovato et al. 2018)
Influenza virus								
M-001 (universal flu vaccine)	BiondVax	Subunit	Recombinant protein containing 9 B-cell and T-cell conserved epitopes from influenza A and B HA, NP, and M1	Phase 3	NCT03450915	Completed	Healthy adults, ≥ 50 years	https://clinicaltrials.gov/
VTP-100	Vaccitech	Recombinant vector	Recombinant influenza A NP and M1 in MVA vector	Phase 2b	NCT03880474	Terminated	Healthy adults, ≥ 18 years	https://clinicaltrials.gov/

Table 2 (continued)

Vaccine name	Organization	Vaccine type	Vaccine composition	Stage	NCT	Status	Study population	Reference
VAL-506440	Moderna	mRNA	mRNA of H10N8 HA in lipid nanoparticles	Phase 1	NCT03076385	Completed	Healthy adults, 18–64 years	(Bahl et al. 2017; Feldman et al. 2019); https://clinicaltrials.gov/
VAL-339851	Moderna	mRNA	mRNA of H7N9 HA in lipid nanoparticles	Phase 1	NCT03345043	Completed	Healthy adults, 18–49 years	

20vPnC, 20-valent pneumococcal conjugate vaccine; Als3p, agglutinin like sequence 3 protein

BCG, Bacillus Calmette Guérin; CRM_{197}, Cross reactive material 197; GBS, Group B streptococcus; GMMA, Generalized modules for membrane antigens vaccine delivery system; GSK, GlaxoSmithKline; HA, Hemagglutinin; LPS, Lipopolysaccharide; M1, Matrix protein; MAPS, Multiple antigen presenting system; mRNA, messenger ribonucleic acid; MVA, Modified vaccinia virus Ankara; N/A, Not available; NCT, ClinicalTrials.gov identifier; NIAID, National institute of allergy and infectious diseases; NP, Nucleoprotein; OMV, Outer membrane vesicle; PATH, Program for appropriate technology in health; PcpA, Pneumococcal choline binding protein A; PHiD-CV, Pneumococcal polysaccharide protein D-conjugate vaccine; PhtD, Pneumococcal histidine triad protein D; PlyD1, Pneumolysoid; rEPA, recombinant *Pseudomonas aeruginosa* exotoxin A; RSV, Respiratory syncytial virus; TT, Tetanus toxoid; UTI, Urinary tract infection; WRAIR, Walter reed army institute of research

resistance in 2017 in the U.S., along with 12,800 associated deaths (Centers for Disease Control and Prevention 2019). Older adults (65 years of age and older) are at increased risk for *C. difficile* infection, particularly when exposed to healthcare settings (Bartlett and Gerding 2008; Bauer et al. 2011; Leffler and Lamont 2015; Pepin et al. 2005; Simor 2010). Although most patients experiencing a first episode of *C. difficile* infection respond well to standard antibiotic treatment (McDonald et al. 2018), approximately 15–35% of patients suffer from at least one recurrence (Gerding et al. 2008; Leffler and Lamont 2015; Louie et al. 2011), often leading to a vicious cycle requiring additional antibiotic use. Emergence of hypervirulent pathogenic strains such as BI/NAP1/027, an increased use of antibiotics that disrupt the intestinal microflora, improved detection methods, and an increased exposure to spores in healthcare facilities all contribute to the observed *C. difficile* infection escalation in the U.S. and Europe (Donskey 2017; Gerding 2004; Lessa et al. 2015; Polage et al. 2015). The current treatment recommendations for *C. difficile* infection include vancomycin, fidaxomicin, and/or metronidazole (McDonald et al. 2018), which can cause development of AMR (Adler et al. 2015; Freeman et al. 2015; Moura et al. 2013; Saha et al. 2019). Given this burden of *C. difficile* infection and the rapid global spread of epidemic and antibiotic-resistant strains, the CDC has classified *C. difficile* as an urgent antibiotic resistance threat (Centers for Disease Control and Prevention 2019). A vaccine against *C. difficile* would both protect against disease and, importantly, limit the need for antibiotic use to treat the infection, thus also limiting antibiotic resistance.

C. difficile pathogenesis is mediated primarily by two large clostridial glucosylating toxins, toxin A (TcdA) and toxin B (TcdB) (Kuehne et al. 2010), which modify intracellular signaling pathways in intestinal epithelial cells, causing cytotoxicity, inflammation, and diarrhea (Voth and Ballard 2005). Vaccines to protect against *C. difficile* infection have focused on the development of neutralizing antibody responses against TcdA and TcdB (Giannasca et al. 1999; Kyne et al. 2001; Lowy et al. 2010; Wilcox et al. 2017). Four investigational vaccines have progressed to clinical development (Table 2). Currently, the most advanced vaccine candidate is PF-06425090, developed by Pfizer, which is in a Phase 3 trial (https://clinicaltrials.gov/ct2/show/NCT03090191; https://www.pfizer.com/science/find-a-trial/nct03090191). It is comprised of a bivalent toxoid formulation of *C. difficile* toxins A and B that are each genetically and chemically inactivated (Vidunas et al. 2016). If licensed and universally recommended, a *C. difficile* vaccine would provide an important tool for preventing AMR, as vaccinated individuals would be protected from *C. difficile* infection, thus reducing the associated antibiotic use and selection of multidrug-resistant bacterial species.

Streptococcus pneumoniae vaccines

Following introduction of PCV13, as a result of the significant effectiveness on both carriage and invasive disease, serotypes not included in the vaccine have become responsible for the majority of invasive pneumococcal disease cases in Europe and North America (Balsells et al. 2017; Kyaw et al. 2006). To help address this major unmet medical need, several pneumococcal conjugate vaccines with higher valencies are being developed for children, including 15-valent (Merck; NCT03692871) and 20-valent (Pfizer; NCT04382326, NCT04379713) polysaccharide conjugate formulations (https://clinicaltrials.gov/). If successful, these vaccines have the potential to further reduce the burden of pneumococcal diseases globally. An alternative approach to increase protection against *S. pneumoniae* is the use of conserved epitopes of pneumococcal surface proteins such as proteins A and C, adhesin A, pneumolysin, histidine triad proteins, and choline binding protein A in pneumococcal conjugate and subunit vaccines (Table 2) (Alderson 2016; Moffitt and Malley 2016). Another pneumococcal vaccine candidate comprises a macromolecular complex where pneumococcal proteins are used as the carrier for pneumococcal capsular polysaccharides (Zhang et al. 2013) (http://affinivax.com/vaccine-pipeline/). This vaccine has reached Phase 1/2 evaluation in young as well as elderly adults (NCT03803202) (https://clinicaltrials.gov/).

Group B streptococcus vaccines

Streptococcus agalactiae, also known as Group B streptococcus (GBS), is an encapsulated Gram positive bacterium common in the intestinal tract that also asymptomatically colonizes the vaginal mucosa (women) and rectum (women and men) of approximately 25% of the population. GBS can cause invasive infections, including pneumonia, meningitis, bacteremia, and sepsis across all age groups. According to the CDC's national estimate, in 2016 there were 31,000 cases of invasive GBS disease, causing 1700 deaths (Centers for Disease Control and Prevention 2019). Pregnant women and their infants are particularly vulnerable to GBS infection (https://www.cdc.gov/groupbstrep/about/fast-facts.html). Intrapartum antibiotic prophylaxis, frequently applied in the U.S. and some other high income countries, effectively prevents most early onset GBS disease in newborns (Braye et al. 2018). However, the treatment does not impact acquisition of late onset GBS disease (occurring more than 7 days after birth) and compromises the establishment of the normal microbiota in neonates. Intrapartum antibiotic prophylaxis also has the capacity to induce AMR among constituents of the vaginal microflora. Additionally, GBS resistance to antibiotics, including macrolides, is on the rise (Lu et al. 2014; Schrag et al. 2002). The CDC recognizes GBS as a concerning AMR threat. In 2016, 58% of GBS isolates tested were erythromycin resistant and 42% were clindamycin resistant, and clindamycin-resistant GBS was estimated to be associated with 13,000 illnesses and 720 deaths (Centers for Disease Control and Prevention 2019). An effective maternal GBS vaccine administered to the mother would thus not only protect against maternal and infant GBS infections, but also reduce AMR.

Investigational GBS vaccines based on the capsular polysaccharide are thus being pursued that may be used as maternal vaccines to be administered to pregnant women, inducing functional antibodies that would be transferred across the placenta during the third trimester of pregnancy and protect neonates from GBS disease. Several Phase 2 studies have been conducted with GBS capsular polysaccharide conjugate vaccines (NCT00128219, NCT02459262, NCT02270944, NCT02690181, NCT03170609; Table 2). These include mono- and bivalent vaccines (Baker et al. 2003; Hillier et al. 2019; Rose et al. 2018), a trivalent vaccine (Leroux-Roels et al. 2019, 2016), and a hexavalent vaccine (Buurman et al. 2019) (https://clinicaltrials.gov/). The hexavalent GBS vaccine being developed by Pfizer is comprised of serotypes Ia, Ib, II, III, IV, and V, representing the dominant serotypes associated with GBS disease worldwide, conjugated to cross-reactive material 197 (CRM_{197}) used as a carrier protein (Buurman et al. 2019), and is currently being evaluated in a Phase 2 trial (NCT03765073) in healthy non-pregnant and pregnant women (https://clinicaltrials.gov/). An alternative vaccine candidate, a GBS-NN bivalent subunit vaccine (Minervax ApS), comprising a fusion of recombinant N-terminal domains of the GBS Rib and Alpha C surface proteins, has been evaluated in two Phase 1 trials in healthy non-pregnant women (NCT02459262, NCT03807245) (https://clinicaltrials.gov/).

Bacterial vaccines in early stage clinical or pre-clinical development

Enterobacteriaceae vaccines

Enterobacteriaceae are a large family of Gram negative microbes that include both normal components of the gut flora and pathogens, with substantial AMR in some prominent family members. *E. coli* is the most frequent cause of urinary tract infections and bloodstream infections at all ages. *E. coli* may also be associated with intra-abdominal infections such as peritonitis as well sepsis and meningitis in neonates. Certain pathotypes of *E. coli* are also leading causative agents of foodborne infections worldwide. *Klebsiella pneumoniae* poses a similar problem; however, it tends to infect more vulnerable individuals including preterm infants and patients with impaired immune systems,

diabetes, or suffering from alcohol abuse, and those receiving advanced medical care.

E. coli and *K. pneumoniae* pose the greatest concerns because they have high levels of resistance to third generation cephalosporins and extended spectrum β-lactam antibiotics. *E. coli* infections are also associated with high levels of fluoroquinolone resistance, and *K. pneumoniae* isolates highly resistant to carbapenems have caused frequent nosocomial outbreaks. Carbapenem-resistant *Enterobacteriaceae* are given critical priority by the WHO (World Health Organization 2017a) and are considered an urgent threat by the CDC (Centers for Disease Control and Prevention 2019). Multidrug-resistant *Enterobacteriaceae* have recently achieved greater attention due to the rapid global spread of NDM-1 producing strains (Walsh et al. 2011; Yong et al. 2009), with associated spread of this gene to other Gram negative species (Nordmann et al. 2011). With the recent discovery of *E. coli* strains harboring the MCR-1 plasmid-1 conferring resistance to the last line antibacterial colistin (McGann et al. 2016), there is concern that strains containing both MCR-1 and NDM-1 may emerge, resulting in untreatable infections.

Vaccine approaches for *E. coli* have focused on lipopolysaccharides (or O-antigens) (Huttner et al. 2017; Poolman and Wacker 2016). Phase 1 clinical studies conducted in the 1990s confirmed that measurable antibody levels and rises in functional activity were induced against all 12 O-antigen types included in the vaccine developed by the Swiss Serum and Vaccine Institute and the Walter Reed Army Institute of Research (O-antigen linked to recombinant *P. aeruginosa* exoprotein A as a carrier) (Cross et al. 1994). A vaccine targeting extraintestinal pathogenic *E. coli*, containing 4 O-antigen bioconjugates (ExPEC4V/EcoXyn-4 V or JNJ-63871860), is being developed by LimmaTech (formerly GlycoVaxyn) and Janssen (van den Dobbelsteen et al. 2016) and has been evaluated in Phase 1 and 2 trials (NCT02289794, NCT02546960), including healthy women between 18 and 70 years of age with a history of recurrent urinary tract infections (Table 2) (Frenck et al. 2019; Huttner et al. 2017). Sequoia Pharmaceuticals is developing a vaccine candidate based on the *E. coli* type I fimbrial adhesin protein (FimH) (Langermann et al. 2000) that has been assessed in a Phase 1 trial (https://sequoiasciences.com/uti-vaccine-program). Phase 1 clinical evaluation of the Swiss Serum and Vaccine Institute's *Klebsiella* capsule polysaccharide vaccine found it to be safe and well tolerated, with measurable induction of anti-capsular IgG (Cryz et al. 1986; Edelman et al. 1994). While this vaccine was not pursued in efficacy studies with active immunization, it was used in combination with a *Pseudomonas* vaccine component (discussed in *Pseudomonas* vaccines later in this section) to generate a hyperimmune intravenous immunoglobulin formulation that was assessed among intensive care patients (Donta et al. 1996) where a possible trend towards efficacy against *Klebsiella* infection was noted, although this was not statistically significant. Vaccines containing inactivated strains of bacteria have also been explored. Clinical efficacy has been reported with commercially available Uromune® (a mixture of *E. coli*, *K. pneumoniae*, *Enterococcus faecalis*, and *Proteus vulgaris*) and SolcoUrovac® (6 *E. coli* strains mixed with *Proteus mirabilis*, *K. pneumoniae*, *Morganella morganii*, and *E. faecalis*) when tested against recurrent urinary tract infections (Nesta and Pizza 2018).

Other Gram negative bacterial vaccines

P. aeruginosa and *A. baumannii* infections are both associated with exposure to healthcare settings and though they do not cause high rates of infection, they are characterized by high levels of antibiotic resistance and associated morbidity. Both pathogens cause pneumonia and bloodstream infections in hospital settings, especially in critically ill patients (Centers for Disease Control and Prevention 2019; Jones 2010). Risk factors for *P. aeruginosa* infections include severe burns, cystic fibrosis, mechanical ventilation, catheterization, and immunocompromise (Gellatly and Hancock 2013). Gram negative carbapenem-resistant *A. baumannii* and *P. aeruginosa* are listed by the WHO as critical priority pathogens (World Health Organization 2017a). There were 8500 infections and 700 deaths associated with carbapenem-resistant *A. baumannii* and 32,600 infections and 2700 deaths associated with multidrug-resistant *P. aeruginosa* in 2017 in the U.S. (Centers for Disease Control and Prevention 2019). Some strains of carbapenem-resistant *A. baumannii* and multidrug-resistant *P. aeruginosa* are resistant to nearly all antibiotics (Centers for Disease Control and Prevention 2019).

Vaccines targeting *Acinetobacter* are in early pre-clinical development (Gagneux-Brunon et al. 2018). However, questions remain regarding appropriate antigen selection for an *A. baumannii* vaccine (Chen 2015) and the adequacy of animal models to predict human protection (Alving 2002). In addition, clinical studies would be challenging: though this pathogen is voracious, it occurs infrequently and affects populations for which vaccination would be a challenge. In contrast, several investigational vaccines against *P. aeruginosa* have reached clinical development. Vaccines based on *P. aeruginosa* flagellin (FlaA and FlaB) were assessed in healthy adult volunteers and patients with cystic fibrosis, demonstrating immunogenicity and tolerability and partial protection against infection, respectively (Doring et al. 1995; Doring et al. 2007); however, this vaccine was not pursued further. Another vaccine candidate, an octavalent conjugate formulation comprised of the 8 most common *P. aeruginosa* O-types linked individually to recombinant *P. aeruginosa*

exoprotein A, generated at the Swiss Serum and Vaccine Institute, induced IgG titers specific to all the administered polysaccharide antigens in Phase 1 clinical studies (Edelman et al. 1994), but did not offer significant protection against infection with *P. aeruginosa* in patients with cystic fibrosis in efficacy trials (Cryz et al. 1997). VLA43 (formerly known as IC43, Valneva) is comprised by a fusion of the surface loops of *P. aeruginosa* outer membrane proteins OprI and OprF. A Phase 2/3 evaluation of this vaccine candidate (NCT01563263) did not confirm significantly reduced mortality observed in vaccinated patients in an intensive care unit on mechanical ventilation in previous studies (Rello et al. 2017; Valneva 2016) (https://clinicaltrials.gov/ct2/show/NCT01563263?term=NCT01563263&rank=1). Several additional whole cell and subunit *P. aeruginosa* vaccine candidates have recently been evaluated in early stage preclinical studies (Hegerle et al. 2018; Meynet et al. 2018; Zhang et al. 2018).

Mycobacterium tuberculosis vaccines

M. tuberculosis is the etiologic cause of tuberculosis, a disease that is one of the top 10 causes of death worldwide and the leading cause of death by a single infectious agent. Over 90% of tuberculosis cases occur in low- and middle-income countries. The WHO estimates that 1.8 billion people—close to one quarter of the world's population—are infected with *M. tuberculosis* globally (World Health Organization 2018) (https://www.tballiance.org/why-new-tb-drugs/global-pandemic). Active, drug-susceptible tuberculosis disease is successfully treated with antibiotics, and an estimated 54 million lives were saved through tuberculosis diagnosis and treatment between 2000 and 2017. While the disease burden caused by tuberculosis is gradually falling globally and mortality rates decreased by 42% between 2000 and 2017 (World Health Organization 2018), multidrug-resistant tuberculosis remains a public health crisis and a health security threat (Koch et al. 2018). In 2017, there were an estimated 558,000 new cases of tuberculosis with resistance to rifampicin, the most effective first line drug, of which 82% had multidrug-resistant tuberculosis (defined as tuberculosis that is resistant to both rifampicin and isoniazid). In 2017, approximately 8.5% of multi-drug-resistant tuberculosis cases had extensively drug-resistant phenotypes (multidrug resistance plus resistance to at least one drug in both of the two classes of antibiotics: fluoroquinolones and second line injectable agents [amikacin, capreomycin, or kanamycin]), and extensively drug-resistant tuberculosis has been identified in more than 127 countries. AMR leads to longer treatment regimens, prolonged periods of contagiousness, and higher mortality in populations infected with tuberculosis (World Health Organization 2018) (https://www.who.int/news-room/fact-sheets/detail/tuberculosis; https://www.tballiance.org/why-new-tb-drugs/global-pandemic).

Bacillus Calmette Guérin (BCG) vaccine, composed of an attenuated strain of *Mycobacterium bovis*, is the only available tuberculosis vaccine, and vaccination of newborns in endemic countries results in a reduction of disseminated disease and mortality in young children. Re-administering BCG vaccine does not provide additional protection after a childhood dose, however, and BCG vaccine does not prevent the reactivation of latent tuberculosis to pulmonary disease in the nearly one third of the human population that is already infected and at risk. Given these shortcomings of BCG vaccine, several more modern vaccine approaches are being pursued (Khoshnood et al. 2018; Raviglione et al. 2012), that may have a profound impact on tuberculosis disease morbidity and mortality and assist in stemming AMR, through prevention of the initial infection as well as reduction of reactivation of latent infection. Whole cell vaccine candidates that have progressed to advanced clinical development include: VPM1002, double mutant BCG vaccine (https://clinicaltrials.gov/ct2/show/NCT03152903?term=NCT03152903&rank=1); MTBVAC, live attenuated tuberculosis vaccine (Aguilo et al. 2017) (https://clinicaltrials.gov/ct2/show/NCT02933281?term=NCT02933281&draw=2&rank=1; https://clinicaltrials.gov/ct2/show/NCT03536117?term=NCT03536117&draw=2&rank=1); RUTI®, detoxified vaccine based on fragmented *M. tuberculosis* cells (https://clinicaltrials.gov/ct2/show/NCT02711735?term=NCT02711735&draw=2&rank=1); and inactivated vaccines based on *Mycobacterium vaccae, Mycobacterium indicus pranii*, and non-tuberculous mycobacterium related to *M. vaccae* (https://clinicaltrials.gov/ct2/show/NCT01979900?term=NCT01979900&rank=1; https://clinicaltrials.gov/ct2/show/NCT02712424?term=NCT02712424&rank=1) (Khoshnood et al. 2018; von Reyn et al. 2010; Andersen and Scriba 2019; Sharma et al. 2017).

Live vectored tuberculosis investigational vaccines that have reached clinical evaluation include Ad5Ag85A, recombinant adenovirus vaccine expressing immunodominant recombinant antigen 85A that is shared by *M. tuberculosis* and BCG (https://clinicaltrials.gov/ct2/show/NCT02337270?term=NCT02337270&draw=2&rank=1), and MVA85A, modified vaccinia virus Ankara expressing recombinant antigen 85A (https://clinicaltrials.gov/ct2/show/NCT00953927?term=NCT00953927&draw=2&rank=1). MVA85A was subsequently abandoned due to failure to improve protection against tuberculosis infection compared to BCG vaccine alone in vaccinated infants (Tameris et al. 2013). Adjuvanted multicomponent subunit vaccine candidates for tuberculosis are also being clinically tested as booster vaccines to prevent active or recurrent tuberculosis disease (Andersen and Scriba 2019). For example, H4:IC31 (Sanofi-led consortium), has demonstrated partial efficacy

(30.5%) against sustained *M. tuberculosis* infection in high risk adolescents primed with BCG vaccine (Nemes et al. 2018) (http://www.aeras.org/candidates), and ID93 + GLA-SE (Infectious Disease Research Institute, Quratis) was found to elicit both humoral and cellular immune responses in adults with cured tuberculosis (https://clinicaltrials.gov/ct2/show/NCT02465216?term=NCT02465216&draw=2&rank=1) (Penn-Nicholson et al. 2018). The most promising of the subunit tuberculosis vaccine candidates is M72, developed by GlaxoSmithKline (Rixensart, Belgium) and containing two proteins shared by *M. tuberculosis* and BCG. In a Phase 2b study, AS01E-adjuvanted M72 demonstrated an overall 54% efficacy for prevention of pulmonary tuberculosis in HIV negative adults 18 to 50 years of age with latent *M. tuberculosis* infection (https://clinicaltrials.gov/ct2/show/NCT01755598?term=NCT01755598&draw=2&rank=2) (Van Der Meeren et al. 2018). More work is needed, however, to develop a vaccine that can have broader efficacy for a larger population demographic.

Shigella vaccines

In lower- and middle-income counties, *Shigella* is one of the top 5 causes of moderate to severe diarrhea in children less than 5 years old and contributes to excess mortality and growth impairment (Kotloff et al. 2013). *Shigella* spp. are identified as priority pathogens by the CDC due to widespread resistance to ampicillin and trimethoprim-sulfamethoxazole and rising resistance to ciprofloxacin and azithromycin (Centers for Disease Control and Prevention 2019).

Several O polysaccharide based glycoconjugate vaccine candidates for *Shigella* have progressed to clinical studies (Table 2) (Barel and Mulard 2019; Mani et al. 2016). These include monovalent vaccines developed by the U.S. National Institutes of Health (Cohen et al. 1997), the Pasteur Institute (https://clinicaltrials.gov/ct2/show/NCT02797236?term=NCT02797236&draw=2&rank=1) (Barel and Mulard 2019), and LimmaTech (Hatz et al. 2015). However, in order to provide broad coverage against shigellosis, a multivalent vaccine formulation would need to cover the four primary serotypes (*S. sonnei* and *S. flexneri* 2a, 3a, and 6). Several whole cell *Shigella* vaccines have also been tested in clinical studies, including live attenuated *S. flexneri* 2a developed at the University of Maryland Center for Vaccine Development and Global Health (Kotloff et al. 2007), live attenuated *S. sonnei* (Orr et al. 2005), and a formalin inactivated *Shigella* preparation developed by the U.S. military (McKenzie et al. 2006). The GlaxoSmithKline Vaccines Institute for Global Health has developed an outer membrane vesicle vaccine that has progressed through Phase 2 clinical studies in Kenya (Obiero et al. 2017). The U.S. Army has designed a subunit vaccine for intranasal administration, comprised of a complex of IpaB/D with *S. flexneri* 2a lipopolysaccharide (Invaplex) (Riddle et al. 2011; Tribble et al. 2010).

Non-typhoidal and paratyphoid *Salmonella* vaccines

Non-typhoidal *Salmonella* is the second most common cause of bacterial gastroenteritis in the U.S., and the most frequent cause of hospitalizations and death due to bacterial enteric disease. In the U.S., rates of non-typhoidal *Salmonella* resistance to antibiotics such as ciprofloxacin have been increasing in recent years, prompting inclusion of non-typhoidal *Salmonella* in the CDC priority list as a serious threat (Centers for Disease Control and Prevention 2019). The CDC estimated that between 2015 and 2017, 212,500 antibiotic-resistant non-typhoidal *Salmonella* infections occurred annually in the U.S., resulting in 70 deaths (Centers for Disease Control and Prevention 2019). Non-typhoidal *Salmonella* vaccine candidates that have progressed to Phase 1 clinical studies include WT05, a live attenuated *S. enterica* serovar Typhimurium (Hindle et al. 2002), and a trivalent glycoconjugate vaccine comprised of conjugates of O polysaccharides and flagellin from the two dominant circulating *S. enterica* serovars, Typhimurium and Enteritidis, formulated with Typbar-TCV (Table 2) (Baliban et al. 2018) (https://clinicaltrials.gov/ct2/show/NCT03981952?term=NCT03981952&draw=2&rank=1). Non-typhoidal *Salmonella* vaccine constructs for which clinical studies are planned include Generalized Membrane Module Antigens and O polysaccharide conjugates with CRM_{197} developed by the GlaxoSmithKline Vaccines Institute for Global Health.

Paratyphoid fever is clinically indistinguishable from typhoid enteric fever, with *S.* Paratyphi A being the most common *S. enterica* serovar (GBD 2017 Typhoid and Paratyphoid Collaborators 2019). *S.* Paratyphi A has developed increasing resistance to fluoroquinolones and ciprofloxacin (Parry et al. 2019). While efficacious typhoid vaccines are licensed and available for use, there are no *S.* Paratyphi A vaccines. Live attenuated vaccine strains and glycoconjugates are being used as platforms for *S.* Paratyphi A vaccine development (World Health Organization 2014b), and several candidates have been evaluated clinically (Table 2) or pre-clinically (Wahid et al. 2019; Micoli et al. 2012; Ali et al. 2014). An ultimate vaccine formulation would need to include coverage for serovars that are co-endemic in the same areas, bears similar risk factors and disease pathology, and is also an AMR priority.

Staphylococcus aureus vaccines

The Gram positive bacterium *S. aureus* is a common commensal component of human microflora; however, upon breaching a mucosal or epithelial barrier, it becomes an opportunistic pathogen capable of causing various skin

and soft tissue infections as well as invasive life threatening disease including bacteremia, toxic shock syndrome, infectious endocarditis, osteomyelitis, and pneumonia (Dayan et al. 2016; Tong et al. 2015). *S. aureus* treatment can be complicated by resistance to β-lactams and other classes of antibiotics. Notably, the CDC estimates that methicillin-resistant *S. aureus* contributes to over 70,000 cases of invasive disease and 9000 deaths per year in the U.S. alone (https://www.cdc.gov/mrsa/healthcare/inpatient.html). Overall, there were 323,700 estimated cases of methicillin-resistant *S. aureus* infections in hospitalized patients and 10,600 deaths in 2017 (Centers for Disease Control and Prevention 2019). Both the CDC and the WHO have placed methicillin-resistant *S. aureus* on their priority lists, highlighting the significance of AMR in this microbial species (Centers for Disease Control and Prevention 2019; World Health Organization 2017a). *S. aureus* has the propensity to develop resistance even to newer antibiotics that have been introduced, such as linezolid, a Gram positive bacterium protein synthesis inhibiting drug introduced in 2000 (Endimiani et al. 2011), and daptomycin, a Gram positive membrane disrupting drug introduced in 2003 (Marty et al. 2006). *S. aureus* glycopeptide resistance is currently a source of concern, as this class of antibiotics, including vancomycin, is one of the main resources for combating infections caused by methicillin-resistant *S. aureus*. Given the high disease burden and resistance among *S. aureus* isolates to many classes of antibiotics, a strong rationale exists to develop effective vaccines to protect individuals against this species and to reduce AMR, especially in the older adult population who are at higher risk of disease and more often undergo hospitalization.

As the mechanisms of protection for *S. aureus* are incompletely understood, this has challenged the development of vaccines, and despite extensive efforts there is currently no licensed vaccine to prevent *S. aureus* infection. Several *S. aureus* vaccine candidates developed by Nabi Biopharmaceuticals, Merck and Pfizer did not prove clinical efficacy and were discontinued due to futility (Fattom et al. 2015; McNeely et al. 2014; Pfizer 2018). A 4-component vaccine targeting *S. aureus*, 4C-Staph (Novartis, now GlaxoSmithKline), comprised of five different staphylococcal proteins, including genetically detoxified alpha-toxin hemolysin, surface proteins FhuD2 and Csa1A, and EsxAB protein, a fusion of two secreted virulence factors EsxA and EsxB, administered with a Toll like receptor 7-stimulating adjuvant (Mancini et al. 2016), has been assessed in a Phase 1 study (https://clinicaltrials.gov/ct2/show/NCT01160172?term=NCT01160172&draw=2&rank=1) (Table 2). There is no further information on 4C-Staph clinical development. An investigational vaccine NDV-3 (NovaDigm Therapeutics) contains the recombinant N-terminal portion of the *Candida albicans* agglutinin like sequence 3 protein, which has both sequence and structural homology with cell surface proteins of *S. aureus* (Table 2) (Sheppard et al. 2004). The efficacy of NDV-3 in preventing *S. aureus* nasal colonization among a population of military recruits who are at increased risk for *S. aureus* colonization and disease has been evaluated in a randomized, placebo-controlled Phase 2 trial (https://clinicaltrials.gov/ct2/show/NCT03455309?term=NCT03455309&draw=2&rank=1) and results are pending. A greater understanding of the pathophysiology of *S. aureus* disease and how a vaccine could neutralize the approaches that the bacteria uses to thwart the immune system is needed to develop a vaccine to prevent *S. aureus* infection.

Viral vaccines under development

Respiratory syncytial virus vaccines

RSV is the leading cause of bronchiolitis and viral pneumonia in infants and can lead to fatal respiratory distress, especially in neonates and young infants with underlying cardio-pulmonary disease. In the U.S., RSV is the leading cause of infant hospitalization, with approximately 50,000 admissions of children 12 months of age and younger occurring annually (American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee 2014). RSV also causes respiratory illness in older adults, with approximately 100,000 hospitalizations and 5,000 deaths annually in the U.S. among adults 65 years of age and older (Falsey et al. 2005). Like influenza, RSV infection is associated with the development of bacterial superinfections (Hament et al. 1999; Rey-Jurado and Kalergis 2017), including otitis media and pneumonia, which require the use of antibiotics. Furthermore, as described for influenza earlier in this paper, antibiotics are often prescribed inappropriately for treatment of symptoms of a viral disease before the etiological agent has been determined, contributing to AMR.

There is no RSV vaccine currently licensed. RSV vaccine development has been riddled with many failures, primarily due to an incomplete understanding of the structural and immunobiology of this important viral pathogen and technical difficulties in producing an effective vaccine. Currently, there are a variety of RSV vaccine candidates in clinical and pre-clinical development, including live attenuated, whole inactivated, particle based, subunit, nucleic acid, and recombinant vector based, incorporating different antigens (Jares Baglivo and Polack 2019; PATH 2019), with the most advanced summarized in Table 2. These vaccines are contemplated for use in maternal immunization to protect infants through maternally transferred antibodies, and young children and elderly through direct vaccination.

The trimeric RSV F surface glycoprotein, particularly its pre-fusion form (RSV pre-F), is the primary target of protective neutralizing antibodies and focus of recent vaccine development (McLellan et al. 2013; Mousa et al. 2017; Ngwuta et al. 2015). The stabilized RSV pre-F subunit vaccine candidate DS-Cav1, developed by the National Institute of Allergy and Infectious Diseases (Sastry et al. 2017), elicited serum neutralizing antibodies against both A and B subtypes of RSV, targeting pre-fusion epitopes of RSV F in a Phase 1 trial, representing clinical proof of concept for the structure-based RSV vaccine design approach (Crank et al. 2019) (https://clinicaltrials.gov/ct2/show/NCT03049488?term=NCT03049488&draw=2&rank=1). A stabilized RSV pre-F investigational subunit vaccine undergoing advanced clinical testing is also being developed by GlaxoSmithKline. Phase 2 studies in healthy, non-pregnant women 18–45 years of age demonstrated boosting of pre-existing RSV immunity by a single dose of all formulations of the vaccine (GSK3003891A) (https://clinicaltrials.gov/ct2/show/NCT02360475?term=NCT02360475&draw=2&rank=1, https://clinicaltrials.gov/ct2/show/NCT02753413?term=NCT02753413&draw=2&rank=1) (Beran et al. 2018). Pfizer is developing an engineered stabilized RSV pre-F subunit vaccine to protect infants and older adults by maternal or direct immunization, respectively (Table 2). The excellent safety profile and strong immunogenicity of this vaccine candidate (Schmoele-Thoma et al. 2019) supported its further development. This vaccine has been assessed in several Phase 2 studies in healthy young and older men and non-pregnant women (NCT03529773), older adults (NCT03572062), young non-pregnant women (NCT04071158), and pregnant women (NCT04032093) (https://clinicaltrials.gov/). Currently, Phase 3 evaluation of the vaccine efficacy and safety in infants born to women vaccinated during pregnancy is ongoing (NCT04424316).

Next generation influenza vaccines

Next generation influenza vaccines aim to provide broad protection against influenza, eliminating the need for yearly vaccine production campaigns of evolving serotypes. Approaches towards universal influenza vaccine development have been recently extensively reviewed (Elbahesh et al. 2019; Epstein 2018; Estrada and Schultz-Cherry 2019). Several universal (broadly protective) influenza vaccines are currently being evaluated in clinical studies (Table 2). Subunit M-001 vaccine (BiondVax Pharmaceuticals), comprised of several proteins conserved across influenza strains, has recently advanced to a Phase 3 study in adults 50 years of age and older (https://clinicaltrials.gov/ct2/show/NCT03450915?term=NCT03450915&draw=2&rank=1). Recombinant vector-based MVA-NP + M1 vaccine (Vaccitech) (Antrobus et al. 2014) was assessed in a Phase 2b study which was terminated (https://clinicaltrials.gov/ct2/show/NCT03880474?term=NCT03880474&draw=2&rank=1). A lipid encapsulated mRNA platform has been used by Moderna to design vaccines encoding influenza HA proteins that have progressed to Phase 1 clinical evaluation (Bahl et al. 2017; Feldman et al. 2019) (https://clinicaltrials.gov/ct2/show/NCT03076385?term=NCT03076385&draw=2&rank=1; https://clinicaltrials.gov/ct2/show/NCT03345043?term=NCT03345043&draw=2&rank=1).

Following demonstration of the utility of the mRNA vaccine technology to stop the SARS-CoV-2 pandemic (https://www.cdc.gov/media/releases/2021/p0607-mrna-reduce-risks.html), it is highly likely that this technology will be applied to influenza vaccines and may help to increase their efficacy and time to development.

Human immunodeficiency virus vaccines

HIV infection continues to be a major global public health issue. As reported by the WHO, more than 32 million people have died of HIV (https://www.who.int/en/news-room/fact-sheets/detail/hiv-aids) since the epidemic was first recognized in 1981 (Centers for Disease Control 1981). In 2018, there were approximately 37.9 million people living with HIV worldwide and 770,000 people died of HIV related causes. The African continent is most affected, with 25.7 million people living with HIV in 2018. HIV infection predisposes patients to opportunistic bacterial co-infections that require frequent use of antibiotics, stimulating development of multidrug resistance. Worldwide, 862,000 HIV positive people fell ill with tuberculosis and 251,000 people died from HIV associated tuberculosis in 2018 (https://www.who.int/tb/areas-of-work/tb-hiv/en/). Infections caused by both Gram positive (*S. pneumoniae, Haemophilus* species, *P. aeruginosa*, and *S. aureus*) (Burack et al. 1994; Hirschtick et al. 1995; HIV.gov 2020; Polsky et al. 1986) and Gram negative (*Salmonella*, *Shigella*, and *Campylobacter*), have much greater incidence in HIV infected compared with the uninfected population (Angulo and Swerdlow 1995; Haines et al. 2013; Huang et al. 2006; Nelson et al. 1992; Sanchez et al. 2005). Multiple studies have reported the isolation of antibiotic-resistant bacterial strains from HIV patients, including methicillin-resistant *S. aureus* (Hidron et al. 2010), multidrug-resistant *M. tuberculosis* (Campos et al. 2003), multidrug-resistant *E. coli* (Vignesh et al. 2008), and expanded spectrum cephalosporin-resistant non-typhoidal *Salmonella* (Miriagou et al. 2004).

While antiretroviral therapy controls the virus and reduces transmission, it does not, however, eradicate the infection and is associated with substantial cost (https://www.who.int/en/news-room/fact-sheets/detail/hiv-aids). An effective universal prophylactic HIV vaccine would be a more sustainable approach to prevent HIV, as it would not only

prevent this viral infection from occurring in the vaccinated individual but could also potentially reduce the incidence of bacterial infections and, consequently, attendant antibiotic use and spread of antibiotic-resistant strains. Developing such a vaccine is challenging, however, due to the extreme virus diversity, incomplete understanding of mechanisms of immunity, and the challenges in designing immunogens to induce broadly neutralizing antibodies (Hsu and O'Connell 2017). There are numerous investigational vaccines against HIV in pre-clinical and early clinical development, among which a few have progressed to clinical efficacy trials (Hsu and O'Connell 2017). So far, the only vaccine candidate to have demonstrated at least partial efficacy—60% one year after vaccination and 31.2% during the 3.5 years after vaccination—for preventing HIV infection is RV144, a recombinant canarypox vector vaccine (ALVAC-HIV [vCP1521]), administered in a heterologous prime-boost regimen with four priming injections followed by two booster injections of a recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E) in a Phase 3 trial in Thailand (https://clinicaltrials.gov/ct2/show/NCT00223080?term=NCT00223080&draw=2&rank=1) (Rerks-Ngarm et al. 2009). RV144 is currently undergoing pivotal Phase 2b/3 efficacy clinical evaluation in HIV-seronegative South African adults (National Institute of Allergy and Infectious Diseases (NIAID) 2016) (https://clinicaltrials.gov/ct2/show/NCT02968849?term=HVTN+702&cond=HIV&rank=1).

Global mobilization utilizing vaccines against antimicrobial resistance

The utility of vaccines as a tool to combat AMR has been broadly recognized (Centers for Disease Control and Prevention 2015; O'Neill 2016a; World Health Organization 2015). Improving the use of vaccines as an anti AMR tool requires global mobilization of diverse resources from stakeholders across the public health spectrum, including governments, regulatory bodies, academia, the biopharmaceutical industry, healthcare professionals, policymakers, and funding bodies. The Davos Declaration on Antibiotic Resistance, signed by over 80 international companies, called for collective action to create a sustainable market for antibiotics, vaccines, and diagnostics and encourage appropriate use of new and existing treatments (Review on Antimicrobial Resistance 2016). To date, incremental but measurable progress has been attained towards fulfilling the objectives of the WHO Global Action Plan on AMR (World Health Organization 2015; The Lancet 2017). In the U.S., the White House Executive Order identified antibiotic-resistant bacteria as a national security priority (The White House 2014), and the U.S. National Strategy for Combating Antibiotic Resistant Bacteria named research towards new vaccines and AMR research and development, prevention, surveillance, and control among its key strategic goals (The White House 2015). Recommendations pertaining to vaccine innovation and uptake relative to AMR were also made by the UK Review on Antimicrobial Resistance (O'Neill 2016b), the Chatham House meeting (London, UK) (Chatham House 2017; Clift and Salisbury 2017), and the Boston Consulting Group solicited by the UK Wellcome Trust (Boston Consulting Group 2019). The impact of vaccination on AMR is now also included in the Global Alliance for Vaccines and Immunization's (GAVI's) evaluation criteria for their vaccine investment strategy (Mok 2018) and is an important component of their 5 year strategic plan where the alliance committed to continue to scale up vaccines for diseases prone to AMR while incentivizing research in other vaccines that can contribute to fight AMR (GAVI. The Vaccine Alliance 2017).

Public–private partnerships and consortia that have been formed to coordinate efforts to address the threat of AMR using various strategies, including vaccines, include global non-profit partnership Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), led by Boston University and funded by the U.S. Department of Health and Human Services Biomedical Advanced Research and Development Authority (part of the Office of the Assistant Secretary for Preparedness and Response), the Bill & Melinda Gates Foundation, the National Institute of Allergy and Infectious Diseases, the UK Wellcome Trust, the UK Government's Global Antimicrobial Resistance Innovation Fund, and Germany's Federal Ministry of Education and Research. The CARB-X portfolio includes projects dedicated to important bacterial pathogens, including multivalent *S. aureus* toxoid vaccine (Integrated BioTherapeutics), *Klebsiella* vaccine (Vaxxilon), and Group A streptococcus vaccine (Vaxcyte) (CARB-X 2017–2018) (https://carb-x.org/).

Challenges and future prospects

Barriers to maximizing licensed vaccine use

The barriers to maximizing licensed vaccine use in pediatric as well as adult populations are diverse. The healthcare and regulatory barriers may include variability in national immunization laws and regulations, insufficient vaccine supply, lack of knowledge for vaccine indications and contraindications, inadequate national prioritization and budget allocation for vaccination, and a lack of population based systems to collect and consolidate individual vaccination data (Anonymous 2018; Esposito et al. 2014; Ventola 2016a, 2016b). Furthermore, vaccine hesitancy—defined by reluctance to vaccinate despite the availability of vaccines and seen increasingly in the delay or refusal of parents

to vaccinate their children—is recognized by the WHO as one of the top 10 threats to global health in 2019 (along with AMR) (https://www.who.int/emergencies/ten-threats-to-global-health-in-2019). Vaccine hesitancy has already caused a resurgence of several vaccine preventable infectious diseases, including the recent well documented outbreaks of measles in New York (https://www.cdc.gov/measles/cases-outbreaks.html) and polio in the Philippines (https://www.who.int/csr/don/24-september-2019-polio-outbreak-the-philippines/en/). Reasons for vaccine hesitancy are complex and include concerns about vaccine safety as well as moral or religious beliefs. Disproven and erroneous associations of the measles-mumps-rubella and hepatitis B pediatric vaccines with the development of autism or chronic fatigue syndrome and multiple sclerosis, respectively (https://www.cdc.gov/vaccinesafety/concerns/autism.html) (DeStefano et al. 2002; Glanz et al. 2018; Klein and Diehl 2004; Smith and Woods 2010; Taylor et al. 2014), are well-known examples of dangerous misinformation that has negatively affected the perception of vaccines and put lives at risk. Another grave common vaccine misconception is that the seasonal influenza vaccine shot can cause influenza illness (https://www.cdc.gov/flu/prevent/misconceptions.htm). The unacceptably low influenza vaccination rate among young healthy people between 18 and 49 years of age (as low as 26% in 2017–2018) (https://www.cdc.gov/flu/fluvaxview/coverage-1718estimates.htm) impacts herd immunity and bears deadly consequences for the elderly who respond sub-optimally to influenza vaccines and are at highest risk for flu related deaths that occur annually in the tens of thousands in this cohort (https://www.cdc.gov/flu/about/burden/2017-2018.htm). Additionally, negative public perception of vaccines can lead to consequent vaccine hesitancy, as in the case of Dengvaxia and polio vaccination in the Philippines (Thornton 2019). Combating the rise in dangerous misinformation through social media and other channels has also opened up as another front on the war against infectious disease (Betsch et al. 2012; Tomeny et al. 2017).

Efforts towards better utilization of vaccines to optimize their impact on antimicrobial resistance and future prospects

Much remains to be done to increase global access to already licensed vaccines. Global vaccine coverage could be improved by simultaneous licensure in developed and developing countries, faster rollout, improving vaccines delivering logistics, increasing funding, and lowering population reticence to vaccination. Adult vaccination should also be adopted as a healthcare priority at the national level. Changes in regulatory laws and policies are also required, with formal consideration given to vaccination benefits in AMR reduction. National advisory committees on immunization would need to develop the Guidance for Industry that supports including AMR data in label updates and incorporating AMR reduction benefits in health technology assessment and economic modeling. Coverage with licensed vaccines can be also improved through continuing medical education programs communicating the benefits of vaccination for AMR reduction (Jansen et al. 2018a; Esposito et al. 2014; Laurent-Ledru et al. 2011).

New vaccine candidates addressing important bacterial and viral pathogens for which vaccines currently do not exist are under development, as well as vaccines against parasitic infections such as malaria which often predispose children in endemic areas to invasive bacterial coinfections requiring antibiotic treatment (Were et al. 2011). Incentives that could be provided to enable industry to develop new vaccines that are of public interest but may not be commercially viable would include priority review vouchers, transferable regulatory data and marketing exclusivity, and research and development tax credits. In parallel, sustained investments in developing the human talent pool would provide an experienced workforce to innovate across vaccine research and development (Cawein et al. 2017).

While much has been accomplished with respect to the development of vaccines and immunization strategies, for many important human pathogens there is no available vaccine or current vaccines are suboptimal. Vaccination strategies and AMR considerations are intertwined in importance and, taken together, will drive development decisions and priorities in the decades to come.

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