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Anti-infective vaccination in the 21st century — new horizons for personal and public health

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The 21st century has seen the licensure of new anti-infective vaccines that have demonstrated their benefit for both individual and population (herd) protection. Despite this there are still many human pathogens for which no vaccine is available. As we learn more about these pathogens, and as technologies advance, more opportunities for vaccine development have become available. This review will address these advances and highlight the paradigm shift from vaccines that are used on a population basis, to others which will have an individual benefit, if successfully licensed, but are not expected to have widespread population based use. The development of the latter vaccines has resulted in a paradigm shift toward vaccinating individuals at specific risk for infection from bacteria such as *Staphylococcus aureus* or *Clostridium difficile*, which are members of normal human flora but can cause severe disease under certain circumstances. Increasing levels of antibiotic resistance in such bacteria such as *S. aureus* have also driven the urgency for the identification of alternative methods of protection that do not rely on treatment or prophylaxis with antibiotics.

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Introduction

Mass vaccination campaigns deployed in the twentieth century had the potential to eradicate, or significantly curtail, major childhood infectious diseases including measles, mumps, rubella, varicella, smallpox, diphtheria, hepatitis, polio, influenza, pertussis and tetanus. Provided that these vaccines are widely employed, both the individual and the population can be protected from disease, through induction of herd immunity. Herd immunity requires vaccination rates to be high; when numbers decline, diseases can re-emerge, as has been observed with recent measles outbreaks in the US. In eight US states, the measles/mumps/rubella (MMR) vaccination rate for children entering kindergarten had fallen to <90% for the 2013–2014 school year [1], placing the broader population at risk. Measles cases in the US went from a median of 60 cases a year (2000–2010) to over 600 cases in 2014 [2]. The majority of these cases were in unimmunized individuals; 16% of cases were reported in children under one year of age, too young to be routinely immunized with MMR [2,3]. This current example illustrates that high immunization coverage is important not only for the protection of the broader immunized population but also for the protection of vulnerable populations who are either too young to be effectively vaccinated or have medical conditions that contraindicate vaccination. Though this is a critical concept for vaccines that protect from most infectious diseases, there are also vaccines in development that will have individual impact, but will not be used in mass vaccination campaigns. For healthcare associated pathogens, such as *Clostridium difficile* and *Staphylococcus aureus*, patients who are at risk of infection can be vaccinated, circumventing the need for mass vaccination.

This review will trace the history of anti-infective vaccines in the 21st century, from recently licensed vaccines, to vaccines in late state development and then to vaccines that are either early in development or for which no technical path forward has been established.

Vaccine breakthroughs this century

The end of the twentieth and dawn of the 21st century saw the introduction of polysaccharide conjugate vaccines for the prevention of childhood meningitis and invasive diseases caused by *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* and *Neisseria meningitidis*. All of these pathogens evade the human innate immune system by cloaking themselves in polysaccharide capsules. Polysaccharides alone are poorly immunogenic in the very young [4]. With the discovery that conjugation of polysaccharides to proteins, usually detoxified bacterial toxins, could induce a long lasting immune response in infants and toddlers, immunogenic and protective vaccines to these pathogens could be developed [4]. Prior to the introduction of prophylactic Hib vaccines, disease rates in US children under 5 years of age were over 37 cases per 100 000 population (100k/p) in 1989; however, within only 2 years after Hib vaccine implementation the disease burden had

dropped significantly to <10 cases per 100k/p [5]. Similar success was observed after the introduction of pneumococcal conjugate vaccines, where the overall pneumococcal disease rates of 98.7 per 100k/p in children under 5 years of age were reduced to <23.6 per 100k/p 7 years after implementation of the vaccine into the US infant vaccination schedule [6]. Significantly, coverage of pneumococcal serotypes contained in the vaccine approached 100% [7]. In addition to this enormous positive impact on public health, an additional and unanticipated major benefit of vaccine introduction in infants and toddlers was observed in unvaccinated adults where invasive pneumococcal disease cases dropped by >28% within 4 years of licensing the pneumococcal conjugate vaccine by the induction of herd immunity [8,9].

While the majority of Hib disease is caused by a single capsule type there are over 30 disease-causing serotypes of pneumococci. The first pneumococcal conjugate vaccine covered 82% of disease-causing serotypes in children <5 years [6]. After introduction, there was an increase in disease caused by some serotypes not included in the heptavalent vaccine (PCV-7, Pfizer) [6,10], therefore 10-valent and 13-valent vaccines were developed that covered 65–85% and 80–90% of the remaining disease, respectively [11]. Pneumococcal conjugate vaccines have also recently been demonstrated to be highly effective at inducing long lasting immunity [12–14] and efficacy against invasive disease and community acquired pneumonia in adults [15]. Vaccines with expanded serotype coverage are now in development to protect against additional serotypes [16,17].

Like pneumococci, *N. meningitidis* bacteria are classified by their polysaccharide capsules. Of the 12 described capsules, 5 (A, B, C, Y and W) cause the majority of disease [18]. The first polysaccharide conjugate vaccines were developed to prevent serogroup C disease in children [19]. Mass vaccination campaigns in the UK saw disease rates decline from 0.55 per 100k/p to 0.02 per 100k/p [20] and as with pneumococcal conjugate vaccines herd immunity was observed. Through prevention of disease and asymptomatic carriage in adolescents and young adults, who are the primary reservoir for this pathogen, protection was afforded to babies and toddlers [21]. With the success of monovalent serogroup C vaccines, tetravalent-polysaccharide vaccines were developed to protect against serogroups A, C, Y and W. A polysaccharide conjugate approach was not feasible for serogroup B (MnB) due to the fact that the serogroup B capsular polysaccharide is composed of polysaccharide sialic acid structures that are similar to those observed on human neuronal cells, and thus such vaccine candidates were poorly immunogenic [22]. Antigenic plasticity and differential expression of many meningococcal surface proteins further complicated the development of an effective MnB vaccine [23,24]. In the last two years the significant medical need of protecting against MnB has now been addressed, with the recent licensure of two vaccines. Both vaccines share a component, a factor H binding protein (fHBP) which is an important meningococcal virulence factor. fHBP is a lipoprotein that is expressed by over 97% of MnB strains [25] and can be classified into two antigenically and immunologically distinct subfamilies [26,27]. The first vaccine licensed in the US (Trumenba®) [28] contains one lipidated fHBP from each subfamily and was demonstrated in prospectively designed licensure studies to provide broad coverage against MnB disease. The second vaccine (Bexsero®) [29] contains a single and non lipidated fHBP variant from subfamily B [30] and contains a Neisserial adhesin A (NadA) and a porin A (PorA) that are restricted to a more limited number of strains but may contribute to additional coverage [31,32]. It will only be after these vaccines are implemented into immunization schedules that their true effectiveness can be assessed.

Another achievement in the 21st century is the development and deployment of MenAfriVac™. This is a meningococcal serogroup A glycoconjugate vaccine, with the goal to eradicate serogroup A meningococcal disease from sub-Saharan Africa. Disease rates in this region, described as the 'meningitis belt', were as high as 120 cases per 100k/p [33]. The development of MenAfriVac was based on a successful collaboration between public and private groups including CBER, and since 2010, more than 217 million doses have been delivered [34,35]. Since introduction, disease rates have plummeted, with some vaccinated areas reporting incidence as low as 2.5 per 100k/p [34] and thus MenAfriVac is another example of the public health value of vaccines.

Advances have also been made in reducing the burden of viral diseases, by introduction of vaccines against human papilloma virus (HPV) and rotavirus. In 2006 Merck licensed the first vaccine (Gardasil®) against HPV to prevent genital warts, precancerous lesions and cervical and other cancers caused by the HPV types covered by the vaccine [36]. The vaccine is composed of four non-infectious virus-like particles that are formed after expression of the major viral capsid protein in yeast [37]. The efficacy studies conducted with Gardasil® in women, 15–26 years of age demonstrated exceptional efficacy of 98% against persistent infection, external genital lesions and cervical intraepithelial neoplasia by the targeted serotypes. Recent post-licensure studies have demonstrated a significant decrease in disease rates in the US despite the relatively modest vaccine uptake rates of 57.3% and 34.6% in adolescent girls and boys respectively [38]. A second vaccine, Cervarix®, a bivalent vaccine that targets the cancer causing serotypes included in Gardasil® (GSK), received US licensure in 2010 [39] In 2014 a second generation vaccine from Merck, Gardasil-9® was approved in the US. This adds additional protection

against five more cancer causing HPV types, thus affording broad and more global coverage. In principle, with optimal immunization rates, Gardasil-9 has the potential to prevent approximately 90% of cancers caused by HPV and, similar to Gardasil, >90% of genital warts [40].

While HPV can cause cervical cancer, rotavirus causes severe, dehydrating diarrhea in children under five years of age. Rotavirus gastroenteritis (RVGE) is a leading cause of infant hospitalizations and deaths in both industrialized and resource deprived nations. In 2008 the WHO estimated 86 deaths per 100k/p in children under 5 years accounting for 5% of all child deaths [41]. Two vaccines are currently available internationally (Rotateq®, Merck/Sanofi-Pasteur; Rotarix®, GSK) [42–44] and have demonstrated a remarkable efficacy reducing RVGE cases by 90% in nations where these vaccines have been implemented in child immunization programs [45]. The further development and implementation of these life-saving vaccines was almost stalled when in 1999, Rotashield® manufactured by Wyeth was withdrawn nine months post-licensure due to potential safety concerns of a rare intestinal disorder called intussusception in very young infants (<3 months) [46]. To be able to document the safety of the vaccines and obtain licensure of rotavirus vaccines, manufacturers were required to conduct unprecedentedly large safety studies (>60 000) prior to market authorization, and good safety profiles were demonstrated, allowing global implementation of these important vaccines [45]. The impact of these vaccines is enormous; in Mexico, for example, implementation of rotavirus vaccination has reduced the incidence of diarrheal deaths in children <5 by 40–50% [47].

Vaccines currently in development

Many devastating childhood diseases are now preventable through vaccination, which is considered the most important public health measure second only to the provision of safe drinking water [48]. This achievement has led to a change in focus from providing immunity against infectious diseases for the larger population, to targeting protective immunity for specific at-risk populations. Here, we describe two vaccines currently in development focused on protection of high risk populations threatened by Dengue virus and Ebola virus (EBOV) infections, as well as vaccines directed toward individuals with high risk of *S. aureus* and *C. difficile* disease.

Dengue virus causes an estimated 50 million infections each year globally, resulting in 500 000 hospitalizations due to Dengue hemorrhagic fever [49,50]. Dengue, a mosquito-borne disease, is caused by one of four viral serotypes and is prevalent in tropical and subtropical climates and in some temperate areas within the US, Europe, Africa and the Middle East [51]. Control of epidemics has largely relied on vector control, however, for most efficient control, a prophylactic vaccine is clearly needed [49]. A recent Phase 3 trial of a recombinant live, attenuated tetravalent dengue vaccine (CYD-TDV, Sanofi-Pasteur) conducted in healthy Latin American and Mexican children demonstrated good efficacy (60.8%) by per-protocol analysis. Furthermore, serotype specific efficacy was high, reducing dengue-related hospitalization by 80.3% [51]. The success of this trial, coupled with the development of several other dengue vaccines, suggests a solution to this devastating disease will be available in the very near future.

The EBOV epidemic in West Africa was declared a public health emergency of international concern in August 2014 [52]. Cases of EBOV are usually sporadic and localized; however, in the recent West African epidemic, the virus spread rapidly to large population centers and the number of cases and deaths has surpassed all previous outbreaks combined [53]. With almost 24 000 suspected cases reported and with an average case fatality rate of 50%, the WHO has granted permission to expedite the development of a prophylactic vaccine [54]. Three vaccines are currently in development; two use an adenovirus vector to deliver the Ebola glycoprotein (cAd3-EBO, GSK and Ad26.ZEBOV/Mva-BN-Filo, J&J) while the other utilizes an attenuated vesicular stomatitis virus platform (VSV) platform (rVSV-ZEBOV, Merck) [55]. A Phase 1 trial of the bivalent cAd3-EBO demonstrated protective titer of glycoprotein Zaire-specific antibodies [56]. These promising results provide a solid background to produce a protective vaccine against EBOV.

While Dengue virus and EBOV vaccines have focused on protection of large populations, the development of *S. aureus* vaccines is focused on protection of the individual. *S. aureus* is a major public health concern causing significant morbidity and mortality in hospital-associated and community settings. *S. aureus* surgical site infections carry a particularly high mortality rate with survivors typically requiring additional 13–17 days in the hospital, significantly increasing costs and draining valuable healthcare resources [57]. The diverse range of disease and rapid accumulation of antibiotic resistance has led to a focus on the development of an efficacious vaccine. Two vaccines, with reported clinical data, have used a multiantigen approach containing *S. aureus* capsular polysaccharide conjugated to carrier proteins and various surface expressed proteins (SA4Ag, Pfizer) [58] or detoxified toxins (GSK) [59]. While vaccine induced responses cannot be compared between the two candidate vaccines, both vaccines were safe and immunogenic during Phase 1 trials and development of the Pfizer vaccine is proceeding into a pivotal efficacy study [58,59]. A third vaccine focusing on a protein and toxin-based approach has been in development (Novartis/GSK) but no human safety or immunogenicity data have been reported [60]. The introduction of an efficacious vaccine against *S. aureus* will dramatically reduce the burden placed on healthcare institutions by

S. aureus and may constitute a first example of a vaccine designed for the protection of individuals at risk.

In the early 2000s, hospitals began reporting dramatic increases in severe *C. difficile* infection. These infections were linked to high levels of antibiotic use disrupting the intestinal flora, which provides the opportunity for the spore-forming *C. difficile* organism to flourish and cause toxin-mediated diarrhea and colitis. Two vaccines, both composed of detoxified forms of the two major *C. difficile* toxins (A and B) are currently in clinical trials [61–63]. Proof of concept studies with anti-toxin monoclonal antibodies have demonstrated that a vaccine has the potential for preventing this disease [64]. These developments demonstrate the recent paradigm shift in vaccinology, from designing vaccines to provide community and population protection to a more personalized medicine approach, offering vaccination to specific at risk individuals.

Vaccines with new paths forward

Advances in vaccine design, driven by a deeper understanding of disease pathogenesis and what constitutes a protective immune response, and coupled with an evolution in regulatory thinking and approaches, has enabled the development of vaccines to protect the world's most vulnerable citizen: newborn babies. Neonates have immature immune systems and thus are at increased risk of infection, disease and death. Although some vaccines, such as those for hepatitis B virus, are administered at or close to birth, for most vaccines there is a gap of up to one year before protective immunity can be elicited through direct immunization of an infant. One means of bridging this gap in neonatal immunity is by immunizing the pregnant mother, which enables transfer of protective antibody to the fetus *in utero* and to the newborn through maternal antibody. Immunization of pregnant women has traditionally been perceived to be risky from a safety standpoint and to this day, no vaccine has been formally licensed for use in pregnant women. However, based on the exquisite safety profile of existing vaccines such as Tdap and influenza vaccines that have been used safely in millions of individuals and the need to protect neonates from these life-threatening infections, the US Advisory Committee on Immunization Practices (ACIP) issued 'Guidance on vaccination practices in pregnant and breastfeeding women,' clarifying the regulatory process for maternal immunization [65]. The CDC subsequently recommended these vaccines for use in pregnant mothers for each pregnancy, as well as other vaccines such as hepatitis B for use in pregnant women at risk of infection [65]. Currently, pregnant women in the US are recommended to receive both their seasonal influenza immunization and Tdap (tetanus, diphtheria and acellular pertussis). Importantly, the Tdap vaccine is recommended not for the prevention of disease in the pregnant woman herself, but instead is for the prevention of pertussis in her newborn infant. Recent studies conducted to assess the effectiveness of maternal immunization against influenza have shown the important public health impact of such an approach [66,67].

In utero, during and after birth, developing fetuses and neonates are vulnerable to many more life-threatening/altering infections in addition to influenza and pertussis. Infections with group B streptococcus (*Streptococcus agalactiae*) for example, cause neonatal sepsis and are acquired during birth from a colonized mother. While screening and intrapartum antibiotic prophylaxis have somewhat reduced the infection rates, these measures are not as practical in low resource countries where most of these infections occur. Therefore, safe and effective vaccines are the best measures to prevent these devastating diseases. Another example of an important pathogen to cause devastating illnesses and death in neonates and very young infants is respiratory syncytial virus (RSV), which causes life-threatening pulmonary infections in newborns and especially in premature infants. It has become clear over the last few years that RSV infection and disease in the very young infants may be best addressed through maternal immunization. With the advent of appropriate recommendations and newly forged regulatory pathways to anticipate development and licensure of vaccines for maternal immunization, development of vaccines against each of these pathogens appears now feasible and is being actively pursued [68]. This represents a new strategy of immunizing not just to protect the immunized individual, but also to protect specific at-risk populations (babies *in utero* and neonates).

In addition to a changing regulatory environment, recent technological advances have provided new hope in the quest for a RSV vaccine. RSV vaccine development has been hindered by the failure of RSV vaccine trials in the 1960s, where immunized children experienced more severe disease, including two deaths, than unvaccinated controls and multiple attempts of producing vaccines to protect young infants have failed [69]. Antibodies directed against the fusion (F) protein have been shown to be neutralizing. Indeed, the only therapy currently on the market for infants at high risk of RSV disease consists of a humanized neutralizing anti-F protein monoclonal antibody (palivizumab, Synagis®) [70]. The F viral glycoprotein, which facilitates fusion of the virion and host cell membrane via a dramatic transition from a metastable prefusion conformation to a postfusion state, is a target of several potent neutralizing antibodies [71]. Significant advances in structure-guided protein engineering has led to the identification of an F protein variant with a more stable prefusion conformation that is able to induce neutralizing antibodies significantly more potent than Synagis® [72,73]. Prior F protein vaccines were based on the postfusion form which was less immunogenic and mainly elicited neutralizing antibodies that were not protective [72]. These recent developments and findings have sparked new interest in the development of an efficacious RSV

vaccine, and may enable immunization of pregnant women with a RSV vaccine to protect newborns.

Vaccines with medical need but unclear paths forward

There are still many infectious diseases that could be potentially targeted by vaccines but for which a clear scientific path is not apparent. Vaccines against sexually transmitted infections (STIs) are clear examples of where some successes have been achieved but where challenges still remain. The development and introduction of HPV vaccines were fueled by the understanding of how to elicit an appropriate immune response in the genital tract to prevent infection and disease with this important pathogen and the introduction of these vaccines opened the door to the societal dialogue about and acceptance of a STI vaccine. Despite these successes, most STIs remain a major unmet medical need and continue to pose a significant developmental challenge. Two important examples of these are human immunodeficiency virus type 1 (HIV-1) and *Chlamydia trachomatis* infections, which remain the leading viral and bacterial causes of vaccine-preventable STIs worldwide.

An estimated 35 million people currently live with an HIV infection and approximately 2 million new infections are reported globally each year [74]. Current therapeutic regimens have provided a substantial decrease in HIV-related morbidity and mortality [75,76], though a prophylactic vaccine would offer the greatest impact on HIV spread [77]. Several challenges have impeded this effort such as HIV's ability to rapidly establish a latent reservoir of infection via integration of its genetic material into the host chromosome and its genetic plasticity and complexity of major vaccine target antigens [78]. Because of the genetic diversity of HIV, vaccine efforts have focused on developing a vaccine that elicits broadly neutralizing antibodies [79] and effective cytotoxic T cell responses [80]. Thus far only limited efficacy (31%) has been achieved with a canarypox vector/protein prime-boost vaccine in a clinical trial [81] while 121 vaccines (prophylactic and therapeutic) have been or are currently in development [82]. It remains to be seen if this large effort coupled with continued technological advances will provide the understanding and means to develop a HIV vaccine.

The WHO has estimated that approximately 100 million *C. trachomatis* (CT) infections occur globally [83], more than 1.4 million of these infections are reported in the United States alone [84]. In contrast to *Neisseria gonorrhoeae* (GC), CT infections are largely asymptomatic in nature and therefore go often unnoticed. Infection can lead to pelvic inflammatory disease (PID) and chronic disease sequelae such as chronic pelvic pain and infertility. Because of the polymicrobial etiology of PID (CT and GC being major reportable causes [85]), it is unclear what impact a CT vaccine, if it could be successfully developed, might have on the disease. Vaccine trials in the 1960s against the ocular form of chlamydial infection using formalin-fixed whole organism demonstrated the ability to induce short-term immunity and a reduced incidence of scarring in vaccinated children. Despite these successes, immunity was serovar-specific and enhanced disease was observed in some individuals. Therefore, a subunit vaccine approach has since been a major focus [86]. Thus far no *C. trachomatis* STI vaccine has been in clinical trials, partially because of a lack of a complete understanding of human immune correlates of protection (T cell and/or antibody) and partially because of the difficulties in producing native antigens expressed by Chlamydia [87,88]. Significant advances in the identification of *C. trachomatis* genes associated with immunopathology and the ability to genetically inactivate their function have provided more promise to an attenuated whole organism vaccine approach [89].

Conclusion

In summary, the positive public health impact of prophylactic vaccines remains medically undisputed. For vaccines that have been used for a while, the most pressing issues that remain are their implementation and continued use in the poorest countries globally, particularly in those that are ravaged by war and other political turmoil. To achieve even better global coverage however, will require the continued collaboration and strong commitment of the public and private sector. It is also encouraging that over the last few years, increases in scientific knowledge, changes in recommendations and policy and new regulatory pathways are now providing the foundation to develop vaccines for use in pregnant women to address important neonatal infections and diseases for which other approaches have either failed or were previously not feasible. Finally, after more than 100 years in developing and implementing vaccines to protect populations, a new class of vaccines is being developed that have the potential to protect individuals or groups of individuals at risk for certain infectious diseases.

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