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Whither vaccines?

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Summary Currently used vaccines have had major effects on eliminating common infections, largely by duplicating the immune responses induced by natural infections. Now vaccinology faces more complex problems, such as waning antibody, immunosenescence, evasion of immunity by the pathogen, deviation of immunity by the microbiome, induction of inhibitory responses, and complexity of the antigens required for protection. Fortunately, vaccine development is now incorporating knowledge from immunology, structural biology, systems biology and synthetic chemistry to meet these challenges. In addition, international organisations are developing new funding and licensing pathways for vaccines aimed at pathogens with epidemic potential that emerge from tropical areas.

Introduction

Vaccination has been described as the single most important health intervention in human history. From the first smallpox vaccine conceived by Jenner in 1798[1] developing the idea of attenuation to the reverse vaccinology derived capsular group B meningococcal protein vaccines,[2] the requirement for protective, long-lasting host immune responses to vaccine antigens that are safe to handle and administer with broad coverage has been the aim. To deliver these requirements, the next generation of vaccine development is drawing on major scientific advances in microbiology, structural biology, immunology and most recently molecular biology. However, despite the huge success of vaccinology to date, many challenges remain involving scientific, financial, political and social domains. Here we discuss a range of these with examples impacting on child health.

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Specific vaccination challenges

Pathogen variability: Influenza vaccines

Seasonal influenza epidemic infections are commonly caused by influenza types A and B. Vaccination continues to be one of the most efficacious ways to prevent disease, reducing morbidity and mortality particularly in vulnerable groups.[3,4] Despite this, vaccine efficacy is considered only moderate and dependent on variables including vaccine type, match between circulating strains and vaccine strains and target age groups.[5] Influenza virus is considered highly variable and can evade the immune response in previously vaccinated populations.[6] Current vaccines are designed to induce the production of specific antibodies against the viral membrane surface proteins haemagglutinin (HA) of two influenza A strains and one or two influenza B strains.[3,6] Variation within the influenza virus, due to antigenic shift and drift results in the accumulation of amino acid replacements in the HA epitopes,[3,7] leading to mismatches between the vaccine strains and circulating strains, independently of all the predictions made each year by the World Health Organization (WHO).

Both live and inactivated influenza vaccines are available, but the effectiveness of these vaccines in the most vulnerable groups is suboptimal.[8] In children, inactivated vaccines also have a reduced effectiveness when compared with live attenuated vaccine in some studies but not in others.[5,9] Strategies to improve influenza vaccine efficacy include adding a second lineage of type B and a high HA dose, are currently applied to licensed vaccine.[6] Other strategies are also described and tested in different phase trials. Inactivated influenza vaccine with MF-59 as an adjuvant has been licensed in Canada in young children and the elderly,[10,11] with studies showing increased immunogenicity of the vaccine in both groups.[12,13]

Alternative options include adding TLR adjuvants like AS01 or flagellin, adding conserved epitopes from the viral nucleoprotein, the M2e or stalk of HA could yield improved vaccine efficacy.[14] Genetic vaccines, DNA and RNA based, can also contribute to produce efficacious influenza vaccines, for example, alphavirus-based H7N9 RNA vaccine have shown promising results,[6] although not yet commercially available.

Short effector memory: Pertussis vaccines

Since the introduction of pertussis vaccines in the 1940–50s, the incidence of pertussis has decreased dramatically in countries where the vaccine is given routinely. The WHO estimated 16 million pertussis cases in 2008, 95% of those occurring in developing countries.[15] Despite the availability of effective prophylactic vaccines against pertussis, there has been a rise in the incidence of disease, with epidemics throughout the world in the last decade.[16] Different reasons have been hypothesized for the outbreaks: waning immunity after vaccination, greater awareness and disease reporting, increased virulence of the bacteria and circulation of new strains.[17] The true burden of disease in industrialised countries may be underestimated with an increased incidence in previously vaccinated populations including older children and the elderly.[18]

Table 1 Estimated vaccine efficacy after administration of any brand of Tetanus, diphtheria and acellular Pertussis vaccine (TdaP) to Wisconsin residents between 1998–2000.[19]

Years after TdaP	Vaccine efficacy % (95% CI)
1	75.3 (55.2–86.5)
2	68.2 (60.9–74.1)
3	34.5 (19.9–46.4)
≥4	11.9 (−11.1 to 30.1)

Adverse reactions such as high fever, severe irritability, hypotonic hyporesponsive episodes and severe local skin reactions were described after administration of the whole cell vaccine (wP). This led to its replacement in developed countries with an acellular, less reactogenic vaccine (aP), first developed in Japan in the 1980s. Several studies have shown that immunity after immunisation with pertussis vaccines, especially after aP, can wane rapidly. A study by Koepke *et al.* in Wisconsin described the progressive reduction of aP vaccine efficacy throughout the years (Table 1).[19]

The immune mechanism induced by each vaccine may be responsible for these differences. Natural infection or immunisation with wP induces stimulation of T cell immunity, in particular IFN-γ-secreting CD4+ T cells (Th1 and Th17 cells), whereas aP vaccines induce strong antibody responses and Th2-type responses.[20] The baboon model has contributed both to our understanding and the relevance of these immune mechanisms.[21] Following natural infection or vaccination with wP or aP, their immune responses are similar to those observed in humans.[22] There is evidence that the Th17 responses induce clearance of *B. pertussis* from mucosal surfaces, thereby reducing colonisation and transmission.[23] The lack of Th17 activity following aP vaccination may account for the ongoing disease transmission and resurgence in countries widely using the aP vaccine.

In order to improve aP vaccine efficacy, possible strategies have been described including the introduction of strains that contain the *ptx*P3 promoter. These new circulating strains induce higher host production of pertussis toxin (PT), providing a possible selective advantage.[24,25] The use of new adjuvants, which may or may not be associated with aluminium, can skew the immune response and stimulate a balanced Th1/Th17 response, like CpG oligonucleotides, AS04 (combination of monophosphoryl lipid A and aluminium) and TLR-2 agonists.[20] Interventions such as using modified bacteria virulence factors like adenylate cyclase and tracheal cytotoxin,[26,27] a live nasal attenuated pertussis vaccine (BPZE1)[28] or the use of recombinant pertussis DNA vaccine[29] are also being studied.

Obtaining the right functional response: HIV vaccines

There have been various effective methods employed for HIV prevention, but many challenges remain to the development of a successful vaccine. There is uncertainty about what the protective functional response is since there is no natural recovery from infection, although long-term survival is