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Vaccination: The Present and the Future

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Vaccines have undoubtedly saved the lives of millions, and along with improved sanitation, they remain one of the cornerstones of modern medicine. Many diseases that were once widespread are now eradicated, but vaccine programs face ongoing challenges. Safety concerns as well as limited funding have led to pockets of reduced vaccine coverage around the world — including in developed countries. Chronic and recurrent diseases such as human immunodeficiency virus (HIV†), tuberculosis, and malaria remain without effective vaccines. This review will briefly describe vaccines and the two major issues faced by modern vaccination programs: insufficient vaccine coverage and developing effective vaccines for chronic and recurrent diseases.

INTRODUCTION

Effective vaccines must induce protective immunity without pathogenesis. This is achieved by attenuating or inactivating viral or bacterial pathogens or by using subunit components of the pathogen or pathogen toxins. The success of a given vaccine depends on the stability of the antigen as well as its ability to elicit immunological memory. In modifying the pathogen or using a small part of it, some of the vaccine's immunogenicity may be lost. Therefore, some vaccines also contain adjuvants, compounds that boost the inherent immunogenicity of the altered pathogen. The most commonly used adjuvant is alum, although oil-in-water emulsions are now licensed for use in Europe and a lipid-based

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†Abbreviations: HIV, human immunodeficiency virus; DtaP, diptheria, tetanus and pertussis vaccine; MMR, measles-mumps-rubella vaccine; CDC, Centers for Disease Control and Prevention; CIA, Central Intelligence Agency; GAVI, Global Alliance for Vaccines and Immunization.

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adjuvant is licensed for use in both Europe and the United States [1]. Although alum has been used in vaccines for years, the mechanism(s) by which it improves vaccine immunogenicity are still unclear [2]. In addition to an adjuvant, multi-dose vaccines also contain a preservative to prevent contamination.

Vaccination leads to the generation of long-lived plasma cells. These B cells can survive clonally for the life of the individual and constantly secrete moderate-to-high affinity antibodies. Antibodies have two mechanisms of action. They can directly neutralize the virus, bacteria, or bacterial products, thereby preventing infection, and they can mark infected cells for destruction by other immune cells such as macrophages and granulocytes. Vaccine-induced humoral immunity can be assessed on an individual basis by measuring antibody titers to pathogen-derived antigens at various times post-immunization. Antibody half-life depends on the nature of the vaccine antigen, namely, whether it contains a repetitive epitope and innate receptor ligands, and also on the ability of the vaccine antigen to elicit "help" from T cells (which assist B cells in differentiating into plasma cells) [3]. The diptheria, tetanus, and pertussis vaccine (DTaP) contains single-epitope bacterial toxins and induces the least stable antibody responses (antibody half-life of 10 to 20 years), so protection must be maintained through booster shots every decade [4]. Conversely, the measles-mumps-rubella (MMR) vaccine contains live attenuated versions of these three viruses, and the mean antibody half-life is greater than 100 years [4].

In addition to inducing the generation of long-lived plasma cells, vaccination also leads to the production of memory B cells and memory CD8+ and CD4+ T cells. Unlike long-lived plasma cells, which are terminally differentiated B cells, memory B cells have the capacity to undergo further mutation and thereby enhance their affinity and/or to differentiate into short-lived plasma cells. The former property could be particularly important for ensuring protection against evolving viruses, and indeed, it does appear that memory B cells have undergone affinity maturation in response to repeated influenza vaccinations [5]. Generating memory T cells is not the primary outcome of vaccination because T cells can only respond to whole antigens once they are processed and presented by antigen presenting cells (nor do they undergo mutation in response to antigen, as B cells do) and CD8+ T cells require help from CD4+ T cells (also known as helper T cells) to become memory. However, unlike B cells, CD8+ T cells can directly kill infected cells. Therapeutic vaccines are a new generation of vaccines that would not protect against infection but rather induce memory T cells to clear existing viral infections or even cancerous tumors [6]. However, for infections, therapeutic vaccines may only be fully effective when viral load is low [7], and this could suggest that therapeutic vaccination campaigns will need to be repeated (and will also be more expensive) to ensure pathogen clearance.

Vaccine schedules are determined by disease risk and necessity for booster shots. Most vaccines are administered to infants and young children (age 6 and younger), who are the most vulnerable to infection complications and death. The Centers for Disease Control and Prevention (CDC) recommend that all children 6 and younger receive vaccines against the following diseases: hepatitis A, hepatitis B, rotavirus, diptheria, tetanus, pertussis, Haemophilus influenzae type B, polio, influenza, measles, mumps, rubella, varicella zoster, and pneumococcal disease [8]. All of these vaccines require at least one booster shot, and some are combined into single shots. Booster shots are necessary both because of the attenuated or inactivated nature of the antigen and because primary immune responses in infants and children may not generate sufficient memory cells [9]. The only vaccine that routinely changes is that for flu. The influenza virus can mutate and re-assort its RNA segments very rapidly, necessitating new vaccines on a yearly basis [10].

A common misconception is that vaccines can and should protect against infec-

tion on an individual basis. Not everyone who is vaccinated will be protected if exposed to the actual pathogen. However, if a sufficient percentage of the population is vaccinated, the majority will be protected from infection upon pathogen exposure. Therefore, even if one or a few individuals do get infected, the pathogen will be unable to spread. This concept, colloquially known as herd immunity, forms the basis for the success of vaccines. Herd immunity is contingent on an optimal vaccine coverage rate that depends on how quickly a given infection could spread [11]. When the percentage of immunized people drops below this threshold, the chances of a disease outbreak increase. Although herd immunity has been criticized as valuing the fitness of a community over that of an individual, it is in fact much safer for an unvaccinated individual to live in a vaccinated community than vice-versa [12,13].

OBSTACLES TO VACCINE COVERAGE: CONCERNS ABOUT MOTIVATIONS AND SAFETY

In developing countries, safety concerns often stem from distrust of Western health professionals. Some fear that vaccines are actually being used for population sterilization or even infection, fears that are not without basis [14]. Even seemingly legitimate vaccination programs have had ulterior motives. In 2011, the Central Intelligence Agency (CIA) started a hepatitis B vaccine campaign near the Pakistani compound in which Osama bin Laden was suspected to be hiding, ostensibly to collect genetic information from bin Laden family members [15]. They abandoned the vaccination program before the second round of shots, leaving the local population incompletely protected. Health officials have since expressed concerns that this sham vaccination program may undermine future vaccination efforts in Pakistan, which is one of the few countries where polio is still present, and put the lives of field workers at increased risk [16]. It is important that health officials be prepared to deal with ethical concerns about vaccine safety and vaccine programs in an honest manner by acknowledging past mistakes. It is helpful to engage the support and participation of local physicians who are familiar with the culture and language of the community. Vaccination programs can thus be adjusted to address local fears. For example, concerns about needles spreading HIV led to a precipitous decline in vaccination rates in Uganda during the 1990s, and subsequently, the Ugandan health ministry introduced auto-disable syringes (which can deliver only a single vaccine dose) into their vaccination programs, leading to a significant recovery in vaccine coverage [17].

In developed countries, some feel that vaccination programs benefit doctors and pharmaceutical companies more than the wider population. There have been lapses in ensuring vaccine safety in the past: The oral live polio vaccine, though it could actually cause the disease, was used for years in the United States despite the existence of a safer (but more expensive) inactivated polio vaccine (the oral live polio vaccine was discontinued in the late 1990s) [18]. In the United States and Europe, unfounded worries about a potential link between vaccines and autism, instigated by a paper in *The Lance*t in 1998 and propagated by a zealous network of autism advocates and celebrity attention, have contributed to significant distrust of vaccines. The study, since retracted by *The Lancet*, claimed that the MMR vaccine induced gastrointestinal problems in children on the autism spectrum [19]. Though the results were never reproduced, the MMR vaccination rate plummeted in England [20] and has yet to fully recover to an optimal rate [21]. Unfortunately, until concrete, well-publicized progress is made in understanding the genetic and potentially environmental bases for autism spectrum disorders, there will likely continue to be claims about a causal link between vaccination and autism. Health officials can allay these fears through better communication with the general public. On an individual basis, doctors should take extra time to explain to parents why their

children should receive vaccines and how vaccines work. On a broader level, health officials should partner with advertising companies to develop television and print advertising campaigns that can illustrate the importance of vaccines. Health officials should also resist capitulating to anti-vaccine movements unnecessarily. Thimerasol, a mercury derivative once used as a vaccine preservative, has been removed from many vaccine formulations because of unfounded fears that it may cause autism [22]. Only by exhibiting confidence in vaccines can health officials expect the general public to follow suit. Finally, there should be a more efficient global system for reporting adverse effects of vaccines to allow decisions about withdrawing vaccines from the market to be made more efficiently [18].

There will never be a completely risk-free vaccine, but problems can be minimized through more coordinated surveillance efforts, ensuring the accountability of vaccination programs administered by outside groups, improved dialogue about the importance and mechanism of vaccines, and programs tailored to address the concerns of the local population.

FUNDING VACCINE DESIGN AND DISTRIBUTION

Vaccines are a form of preventive care and are cost effective when used widely and when covered by insurance. However, the costs of manufacturing, distributing, and preserving vaccines can be prohibitive in impoverished countries, and this is a major impediment to achieving complete vaccine coverage. The Global Alliance for Vaccines and Immunization (now called the GAVI alliance) was founded in 2000 to alleviate the burden of vaccines on developing countries, lowering costs both through agreements made with vaccine manufacturers and through improving vaccine manufacturer competition. The alliance is financially supported by a combination of government and private donations, and the governing board includes representation from governments, global organizations (UNICEF and the WHO), and private foundations. GAVI evaluates and funds country-based vaccination programs (the vaccines are distributed by UNICEF [23]). In spite of the weakened global economy, GAVI exceeded its target donation amount at its most recent pledging conference in July 2011 [24]. GAVI has had to contend with accusations of misuse of funds; unfortunately, some of the countries with the lowest vaccination coverage rates are also those with the most corrupt governments. Nonetheless, GAVI has achieved a great deal [25], suggesting that private partnerships not only with governments but also with global health organizations are the best way forward for improving vaccine coverage.

Vaccine funding can be divided into several areas: policy, cohort development (important to ensure vaccine quality control and effectiveness), basic research, preclinical research, and clinical trials. Most funding is directed toward these last two areas despite sizable gaps in our understanding of diseases such as AIDS and malaria [26]. Increasingly, vaccine researchers are seeing the value of basic research (funding for basic research on HIV has increased over the past few years [26]) and the importance of creating communication bridges between those at the bench and those involved in clinical research [26]. Vaccine researchers themselves are starting to diversify as the complexity of pathogens, the manufacturing of vaccines, and the sheer volume of data goes beyond the scope of traditional immunologists and pathologists and necessitates the involvement of systems biologists [27]. An integrated research approach that includes basic scientists and clinicians is the best method for improving vaccine design.

MISSING VACCINES: THE CHALLENGE OF VACCINATING AGAINST CHRONIC DISEASES

Vaccine development for chronic diseases is an ongoing challenge. Combined, HIV, malaria, and tuberculosis affect more than 100 million people [28], and in some areas of the world, they are co-endemic. Un-

like diseases for which effective vaccines already exist, these three are chronic, potentially dormant in infected individuals for weeks or even months. Without visible symptoms and in areas that lack a consistent medical presence, infected individuals are unlikely to receive a diagnosis, increasing the urgency of developing effective vaccines. Additionally, a single or double-shot vaccination regimen could be insufficient for lifelong protection. Bacille Calmette-Guérin, the current vaccine against tuberculosis, prevents infection in children but is far less effective for adults [27]. Finally, while T cells may be relatively more important than antibodies for protection against these diseases [27], the immune responses to malaria, HIV, and tuberculosis remain incompletely understood. For example, while the pathogenesis of malaria (caused by one of five species of the protist *Plasmodium*) is well delineated, the relative importance of B cells and T cells remains unclear [29]. And it was only very recently that the mode of innate recognition of *Plasmodium* — the very first line of defense for the human host — was tentatively established [30]. In order to design effective or better vaccines against HIV, malaria, and tuberculosis, the immune responses to these pathogens must be better described. Research should focus on the following areas: the quality of immunological memory generated in chronic infections, the effect of co-infection on memory cells, and the role of malnutrition and/or undernourishment in shaping the quality of the immune response.

Research on immunological memory in chronic infection is still in its infancy, but many studies have suggested that B cells and T cells in chronic infection are exhausted; that is, they are functionally stunted and will soon die off. Unless they are titered to high enough numbers, functionally competent memory CD8+ T cells fail to proliferate and clear chronic infection and they also require CD4+ T cell help (in contrast to memory CD8+ T cells in acute infection) [31]. HIV infects and kills CD4+ T cells, so this could partially explain why memory CD8+ T cells are ineffectual in controlling HIV infection for progressors. Although B cells and T cells are thought to be exhausted in patients infected with malaria, it has been shown that functional memory B cells and long-lived antibodies are present in infected individuals [32]. Unfortunately, the immunological response to malaria is very poorly understood — even the *Plasmodium* epitopes and antigen-derived peptides recognized by B cells and T cells are not well characterized [29]. Insecticide-treated mosquito nets are a very cost-effective means for preventing infection [33], and it is likely that this has limited both funding for and focus on developing a malaria vaccine.

Like HIV, tuberculosis mycobacteria co-opt the immune system in order to survive. *Mycobacterium tuberculosis* can lie dormant for years inside granulomas within the lungs. Although the bacteria are unable to spread, the immunopathology induced by the granulomas can be recurrent. Unlike HIV, and to some extent malaria, the tuberculosis antigen repertoire is stable [27]. Currently, several tuberculosis vaccines that contain antigen or antigen subunits are being tested. This is promising as it may help activate a diverse enough population of T cells (and perhaps B cells) to prevent re-activation of the mycobacteria.

Co-infection is a serious concern with HIV, tuberculosis, and malaria. Disturbingly, it has been shown that HIV viral load increases occur during febrile malaria; unsurprisingly, HIV-infected individuals are more susceptible to malaria and tuberculosis infections [34]. Research on memory CD8+ T cells has suggested that there is an inverse correlation between inflammation and memory cell generation [35]. Therefore, co-infection likely adversely affects the generation of effective protective immunity, and individuals already infected may be unable to respond successfully to vaccination.

The relationship between nutrition and the immune system has yet to be sufficiently fleshed out, but it is known that vitamin A deficiency negatively affects immunity [36] and it is likely that other nutrients play similarly important roles. Chronic infections affect millions of under- or malnourished

children and adults. Ideally, food programs and vaccination campaigns could be tied together in order to enhance the generation of protective immunity in these populations, but this may not always be feasible.

CONCLUSIONS

Vaccinations are an integral part of a healthy society, but in an age where many have not seen the horrible effects of diseases that were once commonplace, they are increasingly undervalued. Health care workers can and should better communicate the importance of vaccines to skeptical patients. Additionally, doctors and researchers must acknowledge that clinical trials and vaccination programs have been undermined by medical ethics violations and improper safety standards in the past and strive to ensure that similar judgment errors do not take place in the future.

Chronic and recurrent diseases such as HIV, malaria, and tuberculosis affect millions of people, many of whom live in underdeveloped countries. Continued investments in research for vaccines against these diseases are necessary, but immunologists should not shy away from partnerships with researchers in other areas, particularly systems biology, that may help more rapidly delineate patterns in immune responses.

There is much left to understand about vaccines and how to best design and distribute them. Through cooperation between not only researchers and health officials but also political groups, investors, and public relations officials, vaccines can be better designed and distributed.

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