

VACCINES

Contemporary Vaccine Challenges: Improving Global Health One Shot at a Time

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Vaccines have proved to be one of the most powerful and effective ways of reducing disease. However, if we are to maximize their impact on global health, then we need to develop new vaccines for additional diseases as well as to improve their supply and delivery, particularly in developing countries.

Vaccines are incontrovertibly one of the most successful and cost-effective disease prevention strategies ever implemented. Annual use of recommended vaccines for children has been estimated to avert up to 3 million deaths per year globally, with even greater numbers of prevented cases of illness and substantial disability (1). Immunization has eradicated smallpox and nearly eradicated polio from the world, substantially decreased the number of cases of measles and rubella worldwide, and reduced disease incidence, disability, and death from other vaccine-preventable diseases that are too numerous to mention here. In the United States alone, vaccines have induced a 98% reduction (compared with 20th century annual morbidity) in combined cases of nine vaccine-preventable diseases, including smallpox, diphtheria, pertussis, tetanus, poliomyelitis, measles, mumps, rubella, and *Haemophilus influenzae* type b (2, 3). Indeed, for the 2009 birth cohort, routine childhood immunization in the United States will prevent an estimated 42,000 early deaths and 20 million cases of disease, with savings of US\$13.5 billion in direct costs and US\$68.8 billion in societal costs (4). Substantial gains have also been achieved in Europe. For example, in the European Union there has been a 90% reduction of measles between 1993 and 2007 and a 99% reduction of rubella in the whole World Health Organization (WHO) European region between 2001 and 2010 (5, 6). For the period 2011 to 2020, just three vaccines—*Haemophilus influenzae* type b (Hib), pneumococcal, and rotavirus—are expected to prevent 102 million illnesses and 3.7 million deaths worldwide with cost savings estimated at US\$63 billion, which takes into account treatment costs and lost

wages and productivity due to death and disability (7). Universal adoption of currently available vaccines could extend these health and cost benefits on a global scale.

Vaccines by their very nature have many advantages over therapeutic interventions. By stimulating immune memory responses, a few doses (through injections, oral drops, or intranasal spray) of a vaccine early in life can usually provide long-term and frequently life-long immunity against many vaccine-preventable diseases. Moreover, vaccines provide not only individual immunity but most also provide community protection when vaccine coverage is high enough (8). This herd immunity protects children too young for vaccination, those with immunocompromising conditions that prevent an adequate immune response to vaccines, and those with legitimate contraindications to vaccines.

In addition to fighting acute infectious diseases, vaccines can also prevent chronic diseases, including cancer. The use of hepatitis B vaccine has dramatically reduced the burden of chronic hepatitis and hepatocellular carcinoma in Taiwan, a country with a high burden of hepatitis B, decreasing the prevalence of the virus in vaccinated populations by a factor of 10 and decreasing the incidence of liver cancer by half (9). Routine use of the human papillomavirus (HPV) vaccine has already notably reduced the prevalence of infections by vaccine-specific strains in countries where the vaccine has been used (10). For instance, in Australia, which has achieved high coverage of HPV vaccine (71% of girls turning 15 years old in 2011) there has already been a 75% reduction in vaccine strains of HPV among women aged 18 to 24 years and a 92% decrease in genital warts among women under 21 years old compared with the pre-HPV vaccine era (10). Increasing uptake is expected to drastically reduce the incidence of cervical cancer as well as other throat and anogenital can-

cers in the United States, and the potential for worldwide prevention of cervical and other cancers is in the realm of hundreds of thousands of cases annually (10).

Nevertheless, there are still challenges and inequities to be overcome in the arena of vaccines and vaccination. Though today probably less than 5% of children receive no vaccines, there are still 22 million children who are not fully immunized with the basic six vaccines of the Expanded Programme on Immunization (EPI), a program of WHO with the goal to make all relevant vaccines universally available to all at risk. A third of these underimmunized children (6.8 million) are in India alone. However, and more importantly, only 5% of children today receive all 11 vaccines globally recommended by the WHO (BCG, Tetanus, Pertussis, diphtheria, polio, measles, rubella, pneumococcal, rotavirus, Hib, and hepatitis B). These disparities occur primarily in developing countries and among poorer and marginalized subpopulations in developed countries. The full suite of existing childhood vaccines has yet to be fully implemented globally. New and improved vaccines are needed for remaining major causes of death and illness, including HIV, malaria, dengue, tuberculosis, and influenza.

IMPROVING USE OF EXISTING VACCINES

Vaccines that remain in the vial are 0% effective. Historically, one of the biggest challenges for vaccines in global health has been getting existing vaccines out to the people who need them. The first big push toward overcoming this obstacle came in 1974 with the EPI, with another push in 2000 with the creation of the Global Alliance for Vaccines and Immunisations (GAVI)—today called Gavi, the Vaccine Alliance—whose role is to scale up the use of new and underused vaccines in the poorest countries. Indeed, immunization coverage with three doses of Diphtheria-Tetanus-Pertussis (DTP) in targeted countries rose dramatically as a result of these efforts—from less than 10% in 1980 to more than 60% in 1990, rising to 83% by 2012 (11, 12). However, although this is positive progress, it only represents one snapshot of the total vaccine picture, with <5% of the world's children fully immunized. Projections suggest that even with all globally recommended vaccines, barely more than half the world's children will be immunized by 2030. Just counting the 73 poorest countries, those supported by Gavi,

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this figure is still only forecast to be ~70%, which is too low given the current reach of DTP-containing vaccines (13).

ENGAGEMENT

Clearly, one key priority moving forward has to be increasing coverage of currently available vaccines. It is critical to engage communities to prioritize receipt of vaccines and advocate for them through active social mobilization for vaccination. Advantages of vaccination to public health should be addressed in target populations, as should concerns regarding safety—both legitimate and those not supported by scientific studies.

DATA

On the supply side, it is important to collect and properly evaluate both local and global data to optimize vaccine delivery. With measles, for example, an increase in the proportion of cases in older age groups can bring an increased risk of complications, such as encephalitis (14). Recent rises in cholera cases and resurgences of yellow fever, as a result of changes in vector transmission, may result from climate change, urbanization, and deforestation (15, 16). Countries with changes in epidemiology should be prepared to make changes in immunization delivery, such as targeting specific new age groups for a recommended vaccine.

INSECURITY AND INSTABILITY

Areas of political or social instability often experience severely disrupted delivery of health services, including and sometimes especially vaccines, as has been the case recently with the targeting of polio workers in Pakistan (17). Immunization programs affected in this way should adapt as quickly as possible and take advantage of opportunities for access such as delivery of vaccines bordering areas of instability—for instance, targeting refugee camps, as happened recently on the edges of North Waziristan in order to vaccinate Pakistani refugees escaping northwest Pakistan (18).

LOGISTICS

Supply chains that have made it possible to deliver low-cost vaccines to the remotest regions of the world are straining to keep up with increased volumes of vaccines as more vaccines are added to the routine immunization schedule. There have been some promising recent developments with more thermally stable vaccines, such as the MenAfriVac meningitis A vaccine, which is now approved

for up to 4 days outside of the cold chain, allowing for simpler distribution. But for the final mile, refrigeration is still required for the vast majority of vaccines throughout the supply chain (19). New computer modeling tools are emerging, optimizing the design and efficiency of supply chains and reducing waste. Additionally, third-party service providers increasingly support immunization programs in managing customs clearance, warehousing, distribution, fleet and cold chain equipment management, and maintaining the data-monitoring required to keep a good supply chain. To manage these diverse efforts, the modern EPI manager must also become an expert logistician. In fact, there is a new movement to try and professionalize the cadre of logisticians associated with vaccine delivery. By investing in better transport and community health workers, countries such as Ethiopia have extended their reach and improved immunization coverage. Similarly, Pakistan has invested in 100,000 trained Lady Health Workers (20).

COST

However, even with vaccine education and optimized delivery, vaccine cost remains a crucial concern, especially in middle-income countries, which house more than 70% of the world's poorest people but are not helped by tiered pricing structures, such as those offered by Gavi. Gavi provides support for low-income countries and lower-middle-income countries with a gross national income (GNI) per capita \leq US\$1570. Countries not eligible for Gavi support are a heterogeneous group; some have substantial investments in health systems and social sectors with adequate human health capital, whereas others have expanding incomes due to the availability of natural resources, such as oil or minerals,

but have not invested in their social sectors and thus have capabilities similar to countries with much lower GNI indices. It is this latter group of countries that are most likely to struggle with immunization.

DEVELOPING NEW AND IMPROVED VACCINES FOR HIGH-BURDEN DISEASES

Even with improved coverage for existing vaccines, there is an urgent need to develop vaccines for diseases with high burden for which no good vaccine exists—such as for HIV, malaria, and dengue—as well as to improve vaccines for tuberculosis control and influenza. These five diseases cause more than 300 million severe cases of illness and ~3.9 million deaths annually, which could potentially be reduced through new or improved vaccine development (Table 1).

Vector-borne diseases such as malaria and dengue are still a major problem in the developing world. Every year there are ~207 million cases of malaria and 627,000 deaths due to malaria, mostly among children under 5 years old. (21) Dengue is the second-most prevalent vector-borne disease, with ~50 million to 100 million cases of dengue fever, 500,000 cases of dengue hemorrhagic fever, and 20,000 deaths caused by dengue annually (22).

Although mortality from HIV/AIDS has been declining since 2006, HIV/AIDS is still ranked among the top five causes of disease burden in 26 countries and remains a problem throughout the world. In 2012, there were 35.3 million people living with HIV/AIDS and 1.6 million deaths from HIV/AIDS globally (23). Antiretroviral therapy (ART) helps those infected with HIV manage the disease and slows or prevents progression to death; however, for every person put on

Table 1. Global burden of selected diseases for which new and improved vaccines are needed

Disease	Annual global cases (in millions)	Annual global deaths (in millions)
Malaria	207.0	0.627
Dengue	96.0	0.02
Tuberculosis	8.6	1.300
Influenza	4.0	0.375
HIV	2.3	1.600
Total estimated burden	317.9	3.9

Malaria cases and deaths are estimates from the 2013 World Malaria Report (21). Dengue global cases are estimates from 2010 (22). Tuberculosis cases and deaths are estimates from 2013, WHO Global TB report (25). Influenza cases and deaths estimates are from WHO Fact Sheet 2014 (26).

antiretroviral treatment there are 1.5 new infections. (24) Furthermore, 95% of new infections occur in poorer countries, where many people do not have access to prevention, care, or treatment (23).

Even for high-burden diseases for which current vaccines are available, such as tuberculosis and influenza, there is a need for development of improved vaccines. WHO estimates that one third of the world's population is infected with *Mycobacterium tuberculosis*, and ~2 million people die every year from these infections. The burden of tuberculosis falls mainly on 22 countries, most of which are low to middle income, emphasizing the need for an improved vaccine, in particular in HIV-infected populations. (25) Moreover, despite the availability of seasonal influenza vaccines, influenza globally affects ~5 to 10% of adults and 20 to 30% of children per year, causing substantial illness: ~3 million to 5 million cases of severe illness and ~250,000 to 500,000 deaths per year—more in pandemic years (26).

OPTIMIZING DEVELOPMENT OF NEW VACCINES

The ability to develop vaccines for these and other diseases is limited by difficulties in identifying and inducing a protective immune response. When the human immune response to natural infection is poor or poorly understood, such as in the cases of these five diseases, the natural immune response does not provide a good model for vaccine development to emulate. Organisms such as HIV, influenza viruses, and the malaria parasite are constantly mutating, making it difficult to identify immune responses that will provide universal or near universal immunity against these pathogens. Immune correlates of protection, such as levels of antibody produced against the pathogen, can play a major role in aiding the development of vaccines that also induce those correlates without inducing illness (27). But for these pathogens, correlates of protection do not exist to date, or in the case of influenza viruses, there are no correlates for universal protection. Tuberculosis bacteria do not induce a measurable serologic response for an expected duration of time, making it very difficult to study. An incomplete understanding of both cellular and cytokine responses to BCG impedes progress. The difficulty with dengue viruses lies in the variability of cross-protectiveness of serotypes and the failure so far to develop a vaccine that successfully prevents dengue type 2 (8). These examples give a clue as to

the depth and complexity of the challenges in solving these immunogenic puzzles.

HIV

An HIV vaccine has been pursued for decades and is seen as the best weapon against HIV because there is no cure. After early predictions of quick success with AIDS vaccines, the difficulty of the scientific task has become clear. Many approaches are being explored to develop an HIV vaccine, including whole inactivated virus, subunit vaccines, DNA live recombinant vaccines (made of a live viral or bacterial vector), prime-boost immunization regimens, and synthetic peptide vaccines as well as vaccines that target mucosal immunity (8). More than 40 HIV vaccine candidates have been evaluated over the past 27 years. Early efficacy trials with GP120 vaccines to develop an antibody response demonstrated 100% seroconversion to laboratory-adapted HIV strains but did not demonstrate protection against wild-type virus (28). Scientists then shifted their focus to cellular immunity and attempted to develop a protective CD8⁺ lymphocyte response to control viral replication. An efficacy trial of an Ad-5 vector failed to show efficacy—and in fact suggested an increased infection rate in those vaccinated (29). Two other efficacy trials of similar vaccines also failed. In 2012, a combination regimen of the first neutralizing antibody vaccine tested and shown to not be efficacious was combined with a relatively weak canary-pox vector and led to an unexpected positive but modest efficacy trial result of 31% protection (30). The source of protection was not clear but might be due to nonneutralizing or weakly neutralizing antibodies. Subsequent hypothesis-generating post hoc studies suggested V1/V2 antibodies may have contributed to protection against HIV-1 infection, but these studies remain inconclusive. Recent identification of a range of broadly neutralizing antibodies against HIV and identification of the targets of these antibodies has transformed the science behind HIV vaccine development. Although structure-based rational drug design is the norm for new drug development, this is entirely new for vaccines, and so although promising, it is difficult to accurately predict timelines for any new breakthroughs (31). It has also been observed that the broadly neutralizing antibody development process in humans takes time and includes important postsomatic changes. As a result, new ways of generating these changes and evolving the immune responses are also under investigation.

MALARIA AND DENGUE

Although there are multiple approaches to try and control vector-borne diseases and the vectors that carry them, including netting and insecticides, vaccination may be one of the most important strategies for successful control. Although there are several malaria vaccines in early stages of development, a promising vaccine candidate for malaria may be on the horizon. RTS,S has a reported vaccine efficacy against clinical malaria in children aged 5 to 17 months of 46% (95% confidence interval 42 to 50%), although protection weakens over time (32). Efficacy in young infants was much lower. The safety profiles for RTS,S are acceptable, and the vaccine could be licensed by 2015. This vaccine has the potential to make a public health impact, especially in areas of high endemicity such as sub-Saharan Africa, although work remains on how to best deploy such a vaccine. Other malaria vaccine concepts have explored the use of live attenuated recombinant bacterial and viral vectors, prime-boost regimens, attenuated sporozoites from mosquitoes, and combination strategies.

A tetravalent vaccine is needed to protect against all four types of dengue virus; several potential vaccines are undergoing preclinical and early clinical development using multiple approaches, including live attenuated (including chimera technology), purified inactivated, recombinant subunit, DNA, and virus-vectored candidates (8). Recently, phase III results were reported from the CYD Sanofi Dengue vaccine. This vaccine met its primary end point of protection against symptomatic, virologically confirmed dengue with an efficacy of 56.5% overall. Protection against serotype 2 was somewhat lower at 35% efficacy (not statistically significant), with the other three strains above 50%. These recent results from partially efficacious vaccines for important conditions such as dengue and malaria are encouraging but raise issues as to effective use and deployment (33).

TUBERCULOSIS

Although there is a current vaccine for tuberculosis—the related bacteria *Bacille Calmette-Guérin* (BCG)—it does not have optimal efficacy. BCG provides limited duration of protection as well as variable protection depending on the growth medium used for the vaccine and the sensitivity of the population to whom the vaccine is administered. For example, it is more effective in infants than in adult populations, who are already sensitized to mycobacterial antigens (34,

35). Moreover, the emergence of multidrug-resistant and extensively drug-resistant tuberculosis have made control activities more challenging and more urgent (21). The interaction between tuberculosis and HIV also presents challenges in developing vaccines because of suboptimal vaccine efficacy and higher rates of adverse events (primarily disseminated infection) in immunosuppressed populations, the very population for which the vaccine would be most needed (36).

INFLUENZA

Although vaccines do exist to prevent influenza, the efficacy and duration of protection are suboptimal because of insufficient immune responses among certain vulnerable populations, especially the very young and the very old; waning of immunity; and antigenic shift and drift, which result in “new” influenza strains that the immune system may not recognize. A universal influenza vaccine is needed to reduce the frequency of vaccination and improve immunogenicity and duration of protection in order to further reduce illness and deaths. The major problem with current influenza vaccines is that the immunodominant but variable globular head of the hemagglutinin changes. As a result, antigenic drift allows the virus to evade vaccine-induced protection. Vaccines that provide more universal protection are urgently needed. There is some hope that this can be accomplished through enhancing the immune response to the more conserved stem region of the hemagglutinin or to targeting conserved determinants, such as m2e (37). Thus, a universal influenza vaccine could potentially eliminate the need for annual/seasonal vaccination and the accompanying guesswork that goes into predicting the appropriate strains to target.

VACCINES: LOOKING TO THE FUTURE

Recent advances in vaccine technologies have the potential to make vaccine delivery more efficient and safer and overcome logistical problems faced in developing countries related to fragile supply chains and health systems and limited human resource capacity. Needle-free delivery such as jet injectors, microneedles, and dry, aerosolized vaccines have the potential to reduce the risk of unsafe injection practices, wastage, biohazards, and the need for training of health care personnel while improving mass vaccination capacity and in some cases vaccine acceptance (20). These technologies have been developed to some extent but have yet to be implemented on a massive scale.

Adjuvants are used with vaccine antigens so as to induce a better immune response. Many inactivated vaccines are delivered with adjuvants, primarily derived from aluminum salts. However, other types of adjuvants, such as oil-in-water, have been successfully used with some vaccines and offer promise. Understanding of innate immunity has allowed precise targeting of different Toll-like receptors, and this has led to a range of new and potent adjuvants. Adjuvants targeted to enhance specific components of the immune response are under development. The use of novel adjuvants could allow immunocompromised persons to mount better responses and allow the use of less antigen in the general population, thus maximizing vaccine supply to meet global demand. Adjuvants may also have a role in inducing cell-mediated immunity, mucosal immunity, or a broader immune response, enhancing cross-protection.

Many opportunities for development of future vaccines—HIV, dengue, and others—lie in new scientific approaches, such as systems biology. Systems biology approaches have been used to identify molecular signatures of gene expression induced within a few days of vaccination, which predict the magnitude of the later T cell and antibody responses, and are beginning to yield new biological insights about the immune response (38). These studies highlight the utility of systems approaches in identifying predictors of vaccine efficacy in clinical trials, and in delineating new mechanisms of vaccine immunity. Thus, systems biology could help in predicting which vaccines are likely to be effective in determining which candidates to advance in clinical trials. In addition, by identifying genes that need to be turned on or off in order to optimize immune responses, systems biology could pave the way for the addition of adjuvants that could affect those genes.

The traditional vaccine model, of low volumes and high costs, is changing. With Gavi's engagement, purchasing vaccines for 60% of the world's children and providing reliable demand forecast data, we have seen the vaccine marketplace change substantially, allowing manufacturers to produce greater quantities more efficiently. This has helped drive down the cost of production and the cost of fill-and-finishing, the final steps of production that are often seen as an expensive bottleneck in the manufacturing of vaccines. The resulting price drops are good news for developing countries because it makes vaccines more affordable and more available. By driving production costs down, the cost of goods

sold in their primary profitable markets has also dropped because of efficiency gains and volumes of scale, increasing profitability in those markets as well. In the United States, the public market price for Pfizer's pneumococcal conjugate vaccines, for example, is more than US\$100, whereas Gavi-eligible countries pay US\$3.30 a dose.

However, lowering the cost is not the only priority. Vaccines are difficult to make, and even in the best of circumstances, there will occasionally be problems with production. Therefore, it is essential to keep a critical mass of manufacturers in the market so as to avoid a lack of vaccine availability when manufacturing problems do arise. With the Vaccine Alliance's expansion of the marketplace and long-term demand forecasts, developing country vaccine manufacturers (DCVMs) have expanded their engagement, thus reducing price and increasing supply security. However, to date, DCVMs have only limited investments in research and development. Hopefully, with a larger role and more profitability, they will also increase investment in research and development and new vaccine development. If not, we risk driving down vaccine prices so severely that the large multinational vaccine research and development companies may withdraw from the market, making new vaccine development an even bigger challenge. A functional prototype of a software tool for prioritizing vaccine development (SMART Vaccines, an abbreviation for Strategic Multi-Attribute Ranking Tool for Vaccines) has recently been developed by the Institute of Medicine to support decision-making and guide vaccine development and may be useful to public health authorities, researchers, manufacturers, and others deciding which vaccines to prioritize (39).

Vaccines and vaccination have been one of the world's great success stories in reducing disease, disability, and death. The progress expected in the next decade will lead to the prevention of ever greater health burdens. However, to maintain this impact and to achieve the full potential vaccines have to offer, current efforts, using existing vaccines, must be sustained and even bolstered. And new vaccines, now under development or to be developed in the future, must be made available to all countries with populations that could benefit from those vaccines. This includes removing financial barriers to vaccine access while assuring that financial incentives remain in place to develop new vaccines. In addition, delivery systems must be supported in order to make sure that vac-

cines can be transported to all populations, can be stored at recommended temperatures, and can be administered to all in need. Optimal control of disease through vaccination can be facilitated by the development of vaccines that do not require a cold chain and do not require delivery through needle and syringe. Vaccines are the one medical intervention recommended repeatedly for all children, and efforts should be made to link vaccination efforts to the delivery of other critical health care services. There is also a need to support a research base to develop new vaccines so as to increase the numbers of diseases preventable by vaccination. In addition, it is critical to have substantial interaction between vaccine developers and regulatory authorities in order to assure that development plans, if successful, will yield a licensed vaccine. Thus, the vaccine enterprise will require collaboration of basic scientists, vaccine developers, manufacturers, vaccine and vaccination financiers, governments, regulators, and public and private sector vaccine deliverers, among others, to create successful, complex systems and products for the future.

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