Delivering vaccines to the people who need them most

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Thanks to the Global Alliance for Vaccines and Immunization (GAVI), the Vaccine Fund and the Bill & Melinda Gates Foundation, the global health community has made enormous progress in providing already existing vaccines to developing countries. However, there still exists a gap to develop vaccines for which there is no market in the Western world, owing to low economic incentives for the private sector to justify the investments necessary for vaccine development. In many cases, industry has the technologies, but lacks the impetus to direct resources to develop these vaccine products. The present emergency with the Ebola vaccine provides us an excellent example where a vaccine was feasible several years ago, but the global health community waited for a humanitarian disaster to direct efforts and resources to develop this vaccine. In the beginning of 2015, the first large-scale trials of two experimental vaccines against Ebola virus disease have begun in West Africa. During the past few years, several institutions have dedicated efforts to the development of vaccines against diseases present only in low-income countries. These include the International Vaccine Institute, the Novartis Vaccines Institute for Global Health, the Hilleman Institute, the Sabin Vaccine Institute and the Infectious Disease Research Institute. Nevertheless, solving this problem requires a more significant global effort than that currently invested. These efforts include a clear policy, global coordination of funds dedicated to the development of neglected disease and an agreement on regulatory strategies and incentives for the private sector.

1. The value of vaccination and a global vaccine action plan

Society has a moral obligation to deliver vaccines to people who need them. As the Institutes of Medicine reported in a 1988 publication, the mission of public health, that is, health for all, is the fulfilment of society’s interest in ensuring the conditions in which people can be healthy. In order to execute this public health mission, a concerted global effort is needed to monitor the health status of communities, diagnose and investigate health problems, inform, educate and empower the community about health issues, develop policies and plans that support both individual and community health efforts, evaluate effectiveness, accessibility and quality of population interventions, and invest in research and development for innovative solutions to health problems such as new treatments and rapid diagnostics [1].

It is well known that vaccination is the most cost effective public health intervention. In the USA and Europe (high-income countries, HICs), vaccines have saved millions of lives, as seen with an increase in life expectancy [2]. A WHO Global Vaccine Action Plan (GVAP), endorsed by the 194 Member States of the World Health Assembly, is a framework to extend the prevention of millions of deaths by 2020 through more equitable access to existing vaccines for people in all communities [3]. WHO’s Initiative for Vaccine Research facilitates vaccine research and development (R&D) against pathogens with significant disease and economic burden, with a particular focus on low- (LICs) and middle-income countries (MICs). Two of their activities focus specifically on (i) R&D by facilitation of early-stage R&D in disease areas with no available vaccines or suboptimal vaccines, and (ii) research in order to optimize the public health impact where existing vaccines are under-utilised. The GVAP challenges the R&D community to produce new vaccines against malaria, HIV/AIDS,
tuberculosis and a universal influenza vaccine, as well as other vaccines that will address potentially vaccine-preventable diseases, such as diarrhoea and childhood pneumonia. The GVAP also challenges the scientific community to produce new platform technologies such as thermo-stable vaccines and a research-based global regulatory agenda. Further focus is placed on operational and implementation research, new manufacturing technologies and basic research [4].

2. Historical knowledge provides the drive to develop new technologies with emerging opportunities for vaccines

(a) The empirical approach

The fields of immunology and vaccinology have gone through tremendous growth and innovation over the past century (figure 1). Initial empirical observations gave rise to the origin of vaccination, as this concept was first investigated by the well-known physician Edward Jenner in the late eighteenth century. Jenner was the creator of the first successful vaccine against smallpox after showing that infectious material when inoculated into the arm of a young boy could prevent the young boy from acquiring the life-threatening virus [5]. Almost a century later, Louis Pasteur (1885), a world-renowned French chemist and biologist, also considered the ‘father of immunology’, became involved in the practice of immunization, known for his principles of ‘isolate, inactivate and inject’ [6]. Pasteur is particularly renowned for his work on the vaccine for anthrax (a bacterial infection that was decimating sheep herds at the time) and rabies (a highly contagious viral infection that attacks the central nervous system). Pasteur was able to produce an attenuated form of the virus, which he then used for immunization [7].

(b) Traditional vaccines

There are four types of traditional vaccines. (i) Vaccines containing killed microorganisms—these are previously virulent microorganisms which have been killed with chemicals or heat. Examples are vaccines against influenza, cholera, bubonic plague and hepatitis A. (ii) Vaccines containing live, attenuated microorganisms—that have been cultivated under conditions that disable their virulent properties or which use closely related but less dangerous organisms to produce a broad immune response. They typically provoke more durable immunological responses and are the preferred type for healthy adults. Examples include yellow fever, measles, mumps and rubella. (iii) Toxoid-based vaccines are derived from inactivated toxic compounds in the cases where these (rather than the microorganism itself) cause illness. Examples of toxoid-based vaccines include tetanus and diphtheria. (iv) Subunit vaccines—rather than introducing an inactivated or attenuated microorganism to the immune system, a purified fragment of the pathogens can create an immune response [8]. Characteristic examples include the subunit vaccine against hepatitis B virus that is composed of only the surface proteins of the virus and the virus-like particle vaccine against human papillomavirus that is composed of the viral major capsid protein.
(c) Nucleic acid vaccines
A new type of vaccine, created from the pathogen’s DNA, called DNA vaccine, has been developed. It works by insertion of viral or bacterial DNA (and expression, triggering immune system recognition) into human or animal cells [9]. It has been tested and applied against various pathogens and tumour antigens. In theory, this vaccine is conceptually a safe and simple method to induce not only humoral immunity but also cellular immunity. One advantage of DNA vaccines is that they are very easy to produce and store. In spite of the great promise, this technology has not yet been shown to work in humans. There are no licensed vaccines or vaccines in late phase of development.

(d) Glycoconjugation
A number of innovative bacterial vaccines are also in development and in use. Certain bacteria have polysaccharide (sugary) outer coats that are poorly immunogenic. By linking these outer coats to proteins (e.g. toxoids), the immune system can be led to recognize the polysaccharide as if it were a protein antigen. This approach of conjugating capsular polysaccharides to carrier molecules is used in the Haemophilus influenzae type B vaccine and the Streptococcus pneumoniae vaccine, and the meningococcus ACYW vaccines. They are great tools to prevent childhood morbidity and mortality [10].

(e) From genomes to reverse vaccinology
Conventional approaches to develop vaccines, as described above, are based on the cultivation of the microorganisms in vitro, and only abundant components can be isolated by using biochemical and microbiological methods [11]. Although successful in many cases, these approaches have failed to provide vaccines against pathogens that did not have obvious immunodominant protective antigens [12]. With the advent of whole-genome sequencing and advances in bioinformatics, the vaccinology field has radically changed, providing the opportunity for developing novel and improved vaccines. With this powerful technology, a new approach to identify vaccine candidates was proposed on the basis of the genomic information; this approach was termed ‘reverse vaccinology’. The novelty of reverse vaccinology was not based on growing microorganisms, but on running algorithms to mine DNA sequence information contained in the blueprint of the bacterium [13]. The reverse vaccinology approach was applied for the first time to the bacterial pathogen Neisseria meningitidis serogroup B [14,15], and has led to the development and licensure of the first vaccine for this pathogen, Bexsero (4cMenB) [16]. This is the result of more than 20 years of pioneering research in vaccine development, and should be used as a model for how investments in innovative R&D can lead to life-saving products that have a global impact.

Next Generation Technologies supports research by obtaining atomic-level information about key antigens and their epitopes, either alone or in complex with protective antibodies. This enables the use of structure-based design to modify antigens and make them ‘better’ immunogens [17]. An example of this is the surface of factor H-binding protein of meningococcus being engineered to contain non-overlapping epitopes from three meningococcal antigenic variants, which resulted in a single molecule that could induce protective antibodies against all sequence variants [18,19]. Recently, structure-based antigen design was used to stabilize the conformation of the pre-fusion form of the F protein of the respiratory syncytial virus, an excellent vaccine candidate [20]. Research on the chemical composition of immunostimulatory molecules known as adjuvants has led to the development of oil-in-water emulsions named MF59 and AS03. Both these molecules have been used to increase the immunogenicity of seasonal and pandemic influenza vaccines [21–23].

Replicating and non-replicating viral vectors such as human and chimpanzee adenoviruses, modified vaccinia Ankara and alphaviruses are used to transfer genes to cells. Many of these vectors have been extensively used in clinical trials for HIV and malaria candidate vaccines. The main candidate vaccine against Ebola is based on a chimpanzee adenovirus (ChAd3) [24].

Innovation in high-throughput computing and analysis, and the in vitro synthesis of large segments of DNA and RNA have opened a new field of synthetic biology. In this case, an RNA or DNA vaccine can be synthesized in vitro starting from the nucleotide sequence of the antigen and chemical compounds, without the need to grow any microorganism. A good example is the synthesis of the haemagglutinin (HA) and neuraminidase (NA) antigens of the influenza virus H7N9 and its use to generate synthetic vaccine seeds.

In 2013, Venter’s laboratory synthesized synthetic DNAs that encoded the HA and NA antigens of the H7N9 strain, which were used to transfect cells, together with linear plasmids encoding the other six RNA segments of the influenza virus genome [25]. During the same time frame, the synthetic HA gene from the H7N9 strain of influenza virus was used in the self-amplifying mRNA system, which is an entirely synthetic RNA vaccine that is delivered by lipid nanoparticles [25,26]. After merely one month, the vaccine was ready for immunization and analysis in animal models of infection [27]. These new technologies have made it possible for an incredibly rapid response to emerging infectious diseases and global threats such Ebola.

3. Life expectancy in low- and middle-income countries far behind high-income countries
The evolution of research from simple empirical observation to complex innovative technologies has supported the development of new vaccines that offer promise for rapid responses in decreasing morbidity and mortality due to infectious diseases. Moreover, a recent study concluded that vaccination over a period of 50 years prevented 40 million cases of diphtheria, 35 million cases of measles and a total of 103 million cases of childhood diseases [28], the final outcome being that over the past century life expectancy in the USA has risen from 43.7 to 78.7 years [29]. Through resource allocation, technological innovations and great passion from the scientific community, vaccines have contributed to improve the health of the world, although vaccines are not the sole intervention responsible for the increase in life expectancy [29].

Even with these investments and innovations, life expectancy in LICs and MICs remains lower than in HICs. This is because people still die from communicable infectious diseases [2] (figure 2a,b). Today, correct delivery of vaccines for these diseases would have an enormous impact on the
health and lives of millions of people, and an indirect benefit to society and development.

Much of the global benefit from vaccination has come through the delivery of vaccines to infants in LMICs through the WHO founded Expanded Programme on Immunization (EPI), which was introduced in 1974 to deliver basic vaccines to developing countries [31]. The EPI, along with UNICEF’s Universal Childhood immunization campaign, has been key for the delivery of vaccines against diphtheria, tetanus, pertussis, measles, poliomyelitis and tuberculosis to more than 80% of the world’s children [32], and is being used to roll out vaccines against Haemophilus influenzae B (Hib), rotavirus and pneumococcus. The success of the EPI in LMICs has been underpinned by support from the Global Alliance for Vaccines and Immunization (GAVI), which was established in 2000 as a public–private partnership with a mission to improve global health through increased access to vaccines in LICs [33].

Thanks to the GAVI, the Vaccine Fund and the Bill & Melinda Gates Foundation, we have made enormous progress in providing already existing vaccines to developing countries. However, we are still struggling to develop those vaccines for which there is no market in the Western world, because there is no incentive for the private sector to justify the investments necessary for vaccine development. In many cases, we have the technologies, but not the resources to develop these vaccines. The present emergency with the Ebola vaccine provides an excellent example where a vaccine was feasible several years ago, but we waited for a humanitarian disaster to rush a vaccine into development.

During the past few decades, several institutions have dedicated their efforts to develop vaccines against diseases present only in LICs. These include the International Vaccine Institute, Korea, the Novartis Vaccines Institute for Global Health, Italy, the Hilleman Laboratories, India, the Sabin Vaccine Institute and the Infectious Disease Research Institute, USA (table 1). Nevertheless, solving this problem requires a more significant global effort than what we have now. There is a need for clear policy, and a global coordination of funds dedicated to the development of neglected vaccines for diseases such as dengue, leishmaniasis, cholera and typhoid fever, as well as an agreement on regulatory strategies and incentives required for the private sector [34].

4. New initiatives for developing vaccines for neglected diseases: research institutes for global health

Several health institutes and industries have come together to create a task force dedicate to creating solutions to the global burden of neglected infectious diseases. The Novartis Vaccines for Global Health Institute (NVGH) is one of these institutes, created in 2007 with the not-for-profit mission to develop effective and affordable vaccines for neglected infectious diseases in developing countries. It is a unique concept: an institute created by a large vaccine manufacturer to enable the knowledge and resources within the company to be used to make vaccines that are desperately needed in the developing world, but would not be profitable enough to attract the substantial investment required from commercial sources. To achieve its mission, NVGH works closely with researchers in developed and developing countries, with public and private funding organizations, and with vaccine manufacturers, especially vaccine manufacturers in developing countries [35].

One of the lead projects of NVGH is to develop an affordable and effective vaccine for typhoid fever, an enteric febrile illness caused by Salmonella enterica serovar Typhi (S. Typhi). This disease has been a plague of humanity, and is still today the only enteric disease for which morbidity and mortality rates have not declined since the 1990s. The estimated number of typhoid fever episodes in 2010, adjusted to account for the low sensitivity of blood cultures for isolation of the bacteria, was 26.9 million [36]. South Asia records the highest number of episodes (47%), followed by sub-Saharan Africa (46%) [37].

Control and management of typhoid fever has become increasingly difficult, because of an increase in drug-resistant strains, poor diagnostic tests and insufficient data on effectiveness of existing vaccines. The use of the available Vi polysaccharide (Vi-PS) vaccine in endemic countries has been limited owing to (i) insufficient data on its effectiveness and (ii) the Vi-PS vaccine cannot be delivered to children under 2 years of age as part of the EPI.

To solve this problem, a Vi-conjugate vaccine has been developed by the NVGH with the support of non-profit Italian organizations. The new conjugate typhoid vaccine (Vi-CRM197) was developed by chemically linking Vi polysaccharide with the CRM197 protein [38,39]. This vaccine was used for immunization of infants in developing countries during EPI visits, and was reported to be safe and effective [40]. The Vi conjugate vaccine technology developed at NVGH has been transferred to Biological E, preparation for clinical manufacturing in India is ongoing, and further clinical studies are planned to substantiate the potential for inclusion of the vaccine into the EPI schedule.
Table 1. Several Institutions dedicated to the development of vaccines for diseases with a greater burden in low- and middle-income countries (LMICs).

<table>
<thead>
<tr>
<th>Institute</th>
<th>country</th>
<th>disease focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Vaccine Institute</td>
<td>Korea</td>
<td>cholera, shigellosis, enteric fever, (typhoid and paratyphoid)</td>
</tr>
<tr>
<td>Novartis Vaccines Institute for Global Health (NVGH)</td>
<td>Italy</td>
<td>shigellosis, enteric fever, meningitis, rotavirus</td>
</tr>
<tr>
<td>Hilleman Laboratories</td>
<td>India</td>
<td>rotavirus, cholera, polysaccharide conjugate vaccines, MenA, C, W, Y, X</td>
</tr>
<tr>
<td>Sabin Vaccine Institute</td>
<td>USA</td>
<td>human hookworm, schistosomiasis, Chagas disease, leishmaniasis, SARS</td>
</tr>
<tr>
<td>Infectious Disease Research Institute</td>
<td>USA</td>
<td>tuberculosis, leishmaniasis, leprosy, malaria, pandemic influenza, Chagas disease</td>
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Another fundamental objective of NVGH is to ensure that the vaccines that are developed are actually used. This involves a complex set of issues that focus on the initial choice and design of vaccines; a combination of controlling the cost of manufacture coupled with funding mechanisms to make the vaccine affordable; and, above all, informed health professionals and government officials in target countries who can realistically evaluate the benefits and limits of the vaccine, so that they can make appropriate recommendations for inclusion in national health programmes. NVGH aims to maximize the utility of vaccines it helps develop by (i) choosing vaccines that have a high potential health benefit and a reasonable feasibility of manufacture; (ii) ensuring intimate involvement in the development programme of researchers and health professionals from counties where a vaccine is likely to be used; and (iii) supporting in-country manufacturers, where appropriate, in order to increase the likelihood that the country will use the vaccine. This will provide a local market to enhance sustainability of manufacture, but also the incentive to undertake the investment in manufacturing infrastructure and the effort to obtain licensure.

Industry has now made an effort to invest in research aimed at developing country health issues. GlaxoSmithKline (GSK) is one of the main players in the global health arena and has opened several research institutes to target developing country diseases. GSK has invested in the malaria vaccine candidate RTS,S—which is currently in late-stage clinical trials in several African countries. The malaria vaccine would have no market in developed countries to offset its R&D costs. GSK has therefore committed to achieving only a small return on this product. In their economic model, this money will be fully reinvested in the development of next-generation malaria vaccines or other treatments for diseases of the developing world.

GSK has also been in the forefront of the Ebola health crisis, working closely with WHO and other stakeholders as part of an international initiative to dramatically accelerate development and production of the GSK/NIH Ebola vaccine candidate. GSK is investing considerable resources, manufacturing capacity and expertise, and relies on significant support from the WHO, regulators, governments and others involved in the global response to help overcome a number of challenges in the clinical development and manufacturing scale-up processes. Furthermore, this accelerated development programme is a true collaboration made possible by the support of academic partners in the UK, US, Switzerland and Mali, and the generous financial support provided by partners including the Wellcome Trust, the European Commission and the Bill & Melinda Gates Foundation. To date, partners have committed approximately £18 million to support development of the candidate vaccine. Earlier this year, the first batch of Ebola vaccine arrived in West Africa [41,42].

Another global health advocate is Sanofi Pasteur, which has been working on a dengue vaccine for more than 20 years. The company’s goal is to make dengue the next vaccine-preventable disease, with a safe and effective dengue vaccine accessible in all regions of the world where dengue is a public health issue. The company is committed to supporting the WHO’s ambition to reduce dengue mortality by 50% and morbidity by 25% by 2020 [43].

Each year, an estimated 500,000 people, including children, have severe dengue requiring hospitalization, putting a huge strain on healthcare systems during outbreaks. Dengue has dramatically increased over the past 30 years with an acceleration over the past decade. Reported dengue cases in the Americas increased fivefold from 517,617 cases in 2003 to the unprecedented level of 2.3 million cases in 2013. The French company Sanofi Pasteur is the primary dengue vaccine candidate contender, with ongoing phase III clinical trials. The 20-year, $1.7 billion investment in a live-attenuated tetravalent (addresses the four strains) vaccine (CYD-TDV) has been shown to be highly effective against severe dengue [44].

5. Evaluating the greatest health impact through the global burden of disease and SMART vaccines: criteria to analyse the true value of vaccination

A general lack of leadership in most decision-making bodies has pressured decision-makers to use health economics analysis to decide on vaccine implementation. Unfortunately, there are no appropriate tools to calculate vaccine values, and tools imported from other disciplines are not adequate to calculate the cost effectiveness of vaccines [45]. These primitive analyses restrict the calculation, and as a consequence the calculated value of vaccines is probably one or more orders of magnitude lower than the effective benefits that vaccines provide to society.

Consequently, these tools lead to incorrect decisions, because vaccines are prioritized purely on the basis of economic considerations without calculating the price we would assign to a human life [46]. To overcome this dilemma, the Institute of Medicine has developed a new platform termed ‘strategic multi-attribute ranking tool for vaccines’ (SMART vaccines) that tries to capture many of the tangible and intangible attributes of vaccination and improve decision-making [45–47]. A potential mechanism to enhance adoption and use of SMART vaccines would be to integrate this tool into public health, health policy, health systems management, decision science and biomedical engineering educational courses. As a multi-criteria decision support tool, SMART
6. New economic initiatives for neglected vaccines and rapid access to existing vaccines: the Global Alliance for Vaccines and Immunization, Advance Market Commitment and Health Impact Fund

An important shift in the business model for vaccines started in 2000 with the creation of GAVI, whose mission is to improve access to new and underused vaccines for children living in the world’s poorest countries. A unique public–private partnership, GAVI was created to bring together the best of what key UN agencies, governments, the vaccine industry, the private sector and civil society had to offer in order to improve childhood immunization coverage in poor countries and to accelerate access to new vaccines—GAVI’s model leverages both the financial resources as well as scientific expertise in order to make vaccines more affordable, more available and sustainable [33].

In order to test this new model, GAVI launched the Advance Market Commitment (AMC) for vaccines, an innovative way to incentivize companies in creating and manufacturing vaccines primarily needed in LICs. AMC tackles the longstanding development problem—persistent market failures to develop and produce vaccines needed in poor countries owing to perceptions of insufficient demand or market uncertainty. Donor countries commit money to subsidize the price of vaccines required by developing countries. The approach offers the necessary financial incentives by way of donor commitments for suppliers to develop the vaccines, including research and training staff. By forging long-term contracts with suppliers, the programme ensures lasting supply of vaccines for countries that need them. A pilot AMC for pneumococcal vaccines was started in 2009 to demonstrate the feasibility of the programme in creating affordable vaccines to meet the growing demands and also offer donor countries a mechanism to assess the effectiveness of the programme and expand it to include other diseases [33].

New funding mechanisms such as the AMC and recently the Health Impact Fund (HIF) are an important shift in financing research and development of medicines that have the greatest health impact. As reported in the Lancet, Pogge and co-workers state that present market forces and intellectual property rights provide little incentive for innovation in the diseases of LIC, such as diarrhoeal disease, lower respiratory tract infections, perinatal infections and other cancers prevalent in poor countries [58,59].

In brief, the HIF proposes a new way of paying for pharmaceutical innovation by incentivizing the development and delivery of new medicines through pay-for-performance mechanisms. All pharmaceutical firms worldwide would have the option of registering new medicines with the HIF. By registering, a firm would agree to provide its drug at cost anywhere it is needed, and in exchange for foregoing the normal profits from drug sales, the firm would be rewarded based on the HIF’s assessment of the actual global health impact of the drug. Governments and other donors would finance the HIF. At present, the development of new medicines is driven by the reward of temporary market exclusivity. When a new medicine is protected from generic competition, its profit-maximizing price inevitably prevents a large proportion of the world’s population—including many in affluent countries—from purchasing it. As a result of this system of incentives, (i) people suffer and die needlessly and (ii) research is focused on those medicines from which investors can make the most money, rather than on those that would lead to the greatest improvements in human health [60].

The HIF proposes a minimum level of $6 billion to be distributed annually. This money would be divided up in proportion to the assessed health impact of each product each year. Thus, firms would compete to earn a share of the money by developing and distributing new medicines to obtain the largest possible global health impact. Health impact assessment would be conducted annually by the HIF for each registered medicine. The HIF has the potential to be an institution that benefits everyone: patients, rich and poor alike, along with their carers; pharmaceutical companies and their shareholders; and taxpayers [60].
In conclusion, it is crucial that there is a global consensus on priority for emerging and neglected vaccine-preventable diseases; and a commitment to providing funds for research, development and delivery of these vaccines worldwide. The scientific community must make health prevention issues an important thematic discussion in the global health political agenda. This was elicited by the publication in the Lancet by Jameson et al. [61]. In that issue, the Lancet revisited the case for investment in health and developed a new framework, with clear measurable objectives, in order to achieve dramatic health gains by 2035. The world approaches the 2015 deadline for achieving the Millennium Developmental Goals, in which we unite public and private forces specifically targeting those related to health in order to: (i) reduce child mortality; (ii) improve maternal health; and (iii) combat HIV/AIDS, malaria and other diseases. The Global Health 2035 is an ambitious new investment framework to begin closing this health gap within a generation. As the report states—‘A unique characteristic of our generation is that collectively we have the financial and the ever-improving technical capacity to reduce infectious, child and maternal mortality rates to low levels universally by 2035, to achieve a ‘grand convergence’ in health. As scientists and members of the global society, our responsibility is to accept the global challenge, invest in research and create solutions for the future [61].

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