

# Vaccines: Accelerating Innovation and Access

Global Challenges Report



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# Abstract

This Global Challenges Report describes the innovation process for vaccines. It explains how the restricted availability of vaccines is due to impediments at every stage of the process. Most of these obstacles are manageable, and intellectual property (IP) rights are associated with only some of them. The analysis aims to put into perspective debates around health innovation and the availability of health technologies in developing countries, especially with respect to the role of IP. In particular, it provides an overview of how IP has been used to meet global health challenges in the vaccines field, and considers whether lessons can be drawn to inform other important health technologies.

The report proceeds as follows: Section 2, following the introduction, outlines the basic principles of vaccination, while also giving an overview of the history of vaccine research. Section 3 presents the social, economic, and health benefits of vaccines. Section 4 describes the research and development (R&D) process, identifying opportunities to accelerate progress. Section 5 examines the relevant regulatory pathway. Section 6 provides information about the challenges of vaccine manufacturing. Section 7 looks at national and international health systems for vaccine delivery. Section 8 examines how IP contributes to advances in vaccines and the availability of existing and future vaccines. Section 9 offers concluding remarks.

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# 1. Introduction

Since their initial scientific development by the 18<sup>th</sup>-century English scientist Edward Jenner, vaccines have made a significant contribution to public health. They largely account for the worldwide eradication of smallpox and the restriction of polio, measles, and tetanus in many parts of the world. Each year, vaccination prevents some 2.5 million deaths (Ozawa *et al.* 2016).

Notwithstanding these impressive results, the international community needs to address three main challenges with respect to vaccination. First, sizeable gaps in vaccine coverage persist throughout the globe. Notably, 1.5 million children under the age of five die each year from vaccine-preventable diseases (WHO 2016a). Second, there are still no satisfactory vaccines for high-burden infectious diseases, such as HIV/AIDS, hepatitis C, tuberculosis, and malaria. Third, vaccines are needed to provide effective treatment and prevention of chronic non-communicable diseases (e.g., cancer, asthma, and multiple sclerosis), the major cause of morbidity and mortality worldwide (Darrow & Kesselheim 2015).

Two major policy frameworks are relevant: the United Nations (UN) Sustainable Development Goals (SDGs)<sup>1</sup> and the World Health Organization (WHO) Global Vaccine Action Plan 2011-2020 (GVAP).<sup>2</sup> Dedicated to “Health and Well-Being”, SDG 3 aims, among other things, to control AIDS, tuberculosis, malaria, and neglected tropical diseases and to reduce by one third premature mortality from non-communicable diseases by 2030, as well as to combat hepatitis, water-borne diseases, and other communicable diseases. The GVAP aims to reinforce routine immunization to meet vaccination coverage targets, accelerate control of vaccine-preventable diseases, with polio eradication as the first milestone, introduce new and improved vaccines, and stimulate research and development (R&D) for the next generation of vaccines and technologies.

Meeting these objectives requires an innovative process that ensures global availability of safe, effective, appropriate, and affordable vaccines. This process comprises the following six components, which are mutually dependent on each other (Mahoney 2011):

1. adequate support for R&D;
2. national regulatory systems to ensure safety and efficacy;
3. quality manufacturing facilities;
4. national and local distribution systems and markets;
5. international distribution systems and markets; and
6. intellectual property (IP) systems.

The public and private sectors are working towards promoting vaccine R&D and delivery on a global scale, with the emergence of many new approaches in the past two decades. However, the cost of vaccines, especially new ones, has been identified as a critical obstacle. People living in developing countries, their governments, or international donors cannot easily afford them in the quantities required. Both within the academic literature and the policy community, there is considerable debate as to what determines the cost of vaccines.

According to some, IP rights, in particular patents, are the primary cause (T’Hoen 2009). Patents confer on their owner the right, for a limited available time period defined under law, to prevent others from using, making, selling, offering for sale, or importing the invention without his or her authorization. This contributes to an environment that is supportive of a patentee’s endeavor to earn profits. Certain authors argue that IP rights allow inventors to set high prices against which the public sector has no recourse.

There are several other factors that impact price formation in the field of vaccines. These include the absence of competing products, the lack of stable demand, and a highly consolidated market. Compared to medicines, vaccines have far smaller markets, and the public sector plays a greater role in the production, pricing, and marketing of vaccines. As biological products, vaccines are more complex and costly to manufacture, and clinical trials are also more expensive (WHO 2004).

1 Adopted in September 2015, the 17 SDGs constitute the most ambitious global agenda ever developed for the social, economic, and environmental advancement of the world. In addition to the objective of ensuring healthy lives and promoting well-being for all people, they set goals to end poverty, abolish hunger, achieve gender equality, foster equitable economic growth, reduce inequality, and address climate change by 2030.

2 The GVAP was adopted by the World Health Assembly in May 2012. It is a framework to prevent millions of deaths by 2020, in particular through more equitable availability of existing vaccines for people in all communities.

## 2. What are vaccines?

### 2.1 Mechanism of vaccination

Vaccines are biological preparations that confer immunity against specific diseases, typically by provoking a response from the body's immune system. The immunogenic vector can be an attenuated or dead form of the pathogenic microorganism, parts of microbes, or microbial deoxyribonucleic acid (DNA), or compounds that mimic microbial products. Exposure to such pathogens induces the production of immune cells with pathogen specificity that the body retains for long periods of time. These immune cells provide for a rapid response upon subsequent exposure. In other words, vaccines lead to the development of immune memory, by simulating the threat of an infection and thus providing antigens derived from the specific pathogen (WHO 2016b).

Vaccines against non-communicable diseases – an emerging field of R&D – also work by modulating the human immune system. These target cells, proteins, or other molecules, rather than pathogens or pathogen-infected cells. For example, therapeutic B-cell vaccines aim at inducing neutralizing auto-reactive antibodies against important mediators of such disorders. Recent clinical trials have shown that active immunotherapy can induce disease-modifying levels of antibodies in humans (Darrow & Kesselheim 2015; Röhn & Bachmann 2010).

### 2.2 Brief history of vaccines

Vaccination has been in use for centuries. In the 16<sup>th</sup> century, Chinese physicians treated healthy people with ground smallpox scabs to reduce their chances of infection during epidemics (Alphen & Aris 1995). In 1796, the English physician Edward Jenner, who successfully inoculated an eight-year-old boy with exudate from a cowpox lesion, succeeded in proving the principle scientifically (Tognotti 2010).

About a century later, after the mechanism of microbial infection had been further understood, the French chemist Louis Pasteur pioneered vaccine technology by exposing people to dead or attenuated microorganisms. However, early vaccines were often crude preparations, which at times raised significant safety concerns. For instance, Pasteur's first rabies vaccine, for which the virus had been grown in rabbit brain tissue, induced autoimmune disease in up to one in 3,000 immunized children (Bell *et al.* 1949).

The 1940s' discovery that viruses could be grown in animal cells led to the development of several vaccines in use today, including inactivated polio, measles, and, more recently, rotavirus.

In the 1970s, researchers developed a crucial vaccine development technique known as "glyco conjugation" in which the sugary outer coat of bacteria is linked to proteins. In fact, often the bacterium by itself is not sufficiently immunogenic, whereas the addition of proteins greatly enhances the immune reaction. This technique is used in the *Haemophilus influenzae* type B (Hib) vaccine,<sup>3</sup> the Streptococcus pneumonia vaccine, and various meningococcal vaccines, which have been vital in helping to address childhood death and disease in developing countries (Trotter *et al.* 2008).

Researchers also recognized that a range of other compounds (known as adjuvants), when given concomitantly with an antigen, induced a stronger immune response. For a long time, the only adjuvant in routine use was aluminum salt. In recent years, further adjuvants have been developed, each with specific properties designed to induce a stronger (higher efficacy) and broader immune response to prevent specific diseases. These new substances (e.g., oligonucleotides) do not cause clinically significant adverse effects (Calabro *et al.* 2013; Rappuoli *et al.* 2011).

During the 1980s, sophisticated molecular biological techniques emerged that allow vaccine developers to improve the way vaccines mimic pathogens. These techniques include the use of components

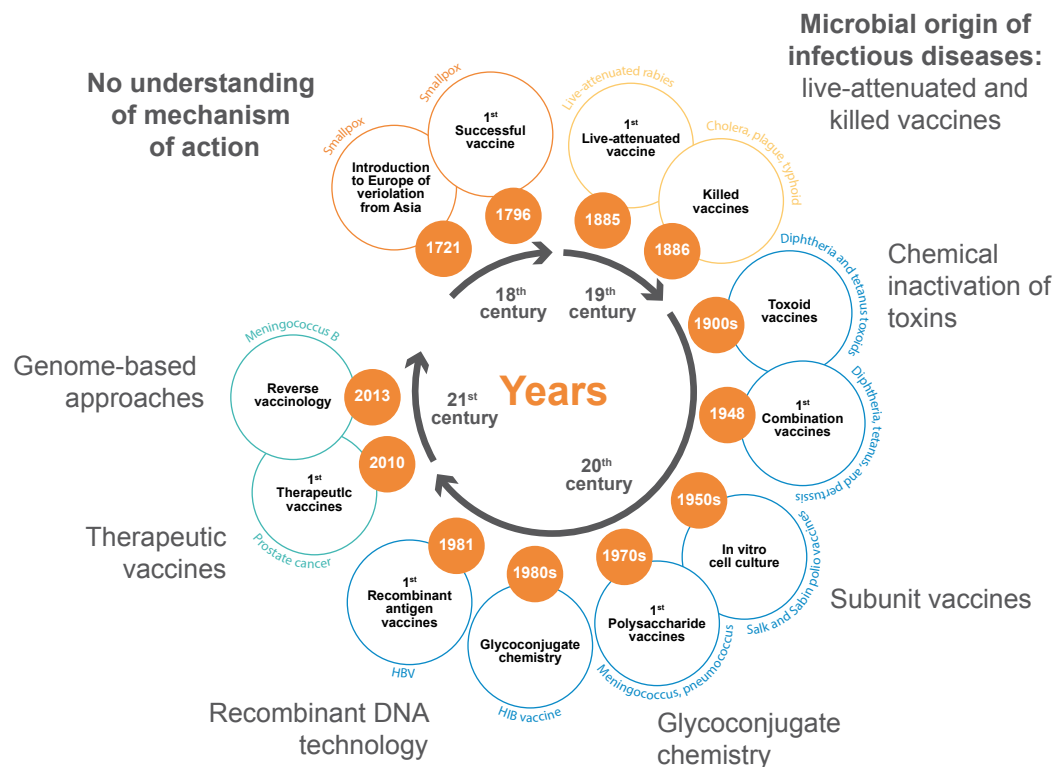
3 Mistakenly considered to be the cause of influenza until 1933 when the viral cause of influenza became apparent, the bacterium *Haemophilus influenzae* is responsible for a wide range of localized and invasive infections. In infants and young children, Hib causes bacteremia, pneumonia, epiglottitis, and acute bacterial meningitis. Due to routine use of the Hib conjugate vaccine in the United States since 1990, the incidence of invasive Hib disease has decreased to 1.7/100,000 in children. By contrast, Hib remains a major cause of lower respiratory tract infections in infants and children in developing countries where the vaccine is not widely available (CDC Chandrasekharan *et al.* 2015).

of a virus, which gives rise to so-called “subunit vaccines”, and recombinant antigens in which the genes of the virus are modified to eliminate infection but still cause immune responses (Plotkin 2014).

In the 1990s, the advent of whole genome sequencing and advances in bioinformatics opened up new avenues for vaccine development. After the biotechnologist Craig Venter had published the genome of the first free-living organism in 1995, the genomes of other microorganisms became more readily available by the end of the 20<sup>th</sup> century. The most prominent new approach to draw on the technological advances is “reverse vaccinology”. A departure from traditional methods based on growing microorganisms, this new approach consists of screening an entire pathogenic genome with the aid of bioinformatics to find genes (Rappuoli & Covacci 2003). These genes are filtered for attributes that represent convenient vaccine targets, such as outer membrane proteins. Subsequently, these targets are produced synthetically and are screened using animal models of the infection. The first vaccine to emerge from this approach was Bexsero for meningococcal group B disease, which the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) licensed in 2013 and 2015, respectively (EMA 2017; FDA 2015). Meanwhile, reverse vaccinology combined with further microbiological techniques has allowed researchers to synthesize DNA vaccines *in vitro* without the need to grow a microorganism.

These advances in technology can speed up R&D. For instance, they enabled researchers to formulate a vaccine for avian influenza A (H7N9) within only one month (Hekele *et al.* 2013). Such techniques also hold the key to rapid development of vaccines against emerging public health threats, such as the Ebola virus disease (Rajesh 2014). The major milestones in vaccine development are summarized in Figure 1.

**Figure 1: History of vaccine development**



Source: Delany *et al.* 2014

## 3. The value of vaccines

### 3.1 Introduction

Immunization has long been recognized as one of the most cost-effective public health tools. A systematic review of the literature on the cost effectiveness and economic benefits of vaccines in low- and middle-income countries identified 108 relevant articles, from 51 countries and covering 23 vaccines. Based on the 44 articles that reported costs per disability-adjusted life year (DALY) averted,<sup>4</sup> vaccines cost less than or equal to USD 100 per DALY averted (in 23 articles, or 52 percent) and less than USD 1,000 per DALY averted (in 38 articles, or 86 percent) (Ozawa *et al.* 2012). Early economic research on the benefits of vaccines focused on government savings derived from averted medical costs due to reductions in disease incidence. According to a more recent perspective, however, immunization programs produce a range of additional benefits by stimulating economic growth and poverty reduction in a number of ways (Table 1) (Bloom & Canning 2000). This broader interpretation suggests that the extension of childhood vaccination could yield considerable benefits for developing economies (Mirelman *et al.* 2014). The following subsections provide a more detailed discussion of some specific benefits of vaccination, namely productivity increases, reduced government spending, herd immunity, and reduced antimicrobial resistance.

**Table 1:**  
**The benefits of vaccination**

Benefit	Description of benefit	Macroeconomic and fiscal impact
Healthgains	Reduction in mortality	Increased labor supply and tax base
Healthcare cost savings	Savings in medical expenditures as disease incidence is reduced	Reduced public expenditure on health for vaccine treatable conditions
Care-related productivity gains	No need for parents to care for sick children, thereby saving productive work time	Increased labor supply and tax base
Outcome-related productivity gains	Increased productivity because vaccination improves cognitive functions, physical strength and school attainment	Increased productivity and consequently wage growth
Behavior-related productivity gains	Changes to household behavior due to improved child health and survival	Changes in fertility, improved education and workforce participation
Community externalities	Unvaccinated people benefit from individuals being vaccinated; less antimicrobial resistance	All of the above

Source: Barnighausen *et al.* 2011 (adapted)

### 3.2 Increased productivity

Improvements in survival, cognition, physical capacity, and educational attainment that result from vaccination can translate into strengthened workforces and greater economic productivity (Deogaonkar *et al.* 2012). Vaccines are usually given to young children, when the rate of brain development is at its peak, enabling further cognitive development through the prevention of illness and associated neurological complications (e.g., encephalitis). Results of research done in Bangladesh show that the benefits of antibodies from maternal tetanus vaccinations passing from a mother to her unborn child can lead to gains of about 0.25 years of schooling for children whose parents did not attend school (Canning *et al.* 2011). According to findings from the Philippines, vaccinations led to improvements in test scores in children, which translated into adult earning gains that represent a 21 percent return on investment on the initial vaccination (Bloom *et al.* 2012).

4 The DALY is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability, or early death. Developed in the 1990s as a way of comparing the overall health and life expectancy of different countries, the DALY is becoming increasingly common in the field of public health and, in particular, health impact assessment.

### 3.3 Reduced government spending

By saving lives and reducing the burden of disease, vaccinations can also have positive impacts on future government spending. In many cases, the initial investment in vaccination can pay for itself several times over. Studies have estimated how lives saved could influence future government expenditure, such as on social programs, health, education, and pensions, and on future government tax receipts. A study conducted in Egypt calculated that investment costs of rotavirus vaccination for infants would be entirely offset by the time they reached 22 years of age (Connolly *et al.* 2012). A study in the Netherlands examined the impact on government revenues of immunizing adults aged 50 against diphtheria, tetanus, pertussis, seasonal influenza, pneumococcal diseases, and shingles. Models showed that vaccination yielded a benefit–cost ratio of 4.09, suggesting a fourfold rate of return for government (Kotsopoulos & Connolly 2013).

### 3.4 Herd immunity

If undertaken at large scale, vaccination not only protects individuals that have been vaccinated but also those that have not. Termed “herd immunity”, the phenomenon derives from two factors (Saadatian-Elahi *et al.* 2016). When a sufficient proportion of the population is vaccinated against a disease (i) it is less likely that the bacteria or virus will spread as there are few people vulnerable to infection (Hotez *et al.* 2004) and (ii) vaccinated individuals who do acquire the disease are less infectious (Vanderweele *et al.* 2012). Herd immunity has been observed for vaccines for diseases of particular relevance to developing countries:

- A systematic literature review of articles published between 2008 and 2014 measuring the impact of rotavirus vaccine on severe gastroenteritis morbidity and mortality showed that the median herd effect across all study years was 22 percent (Pollard *et al.* 2015).
- In the United States, invasive pneumococcal disease in non-vaccinated children declined by around 70 percent following the introduction of pneumococcal vaccines (Whitney *et al.* 2003).
- Epidemiological models suggest that vaccinating susceptible populations could block future outbreaks of the Ebola virus, even for those not vaccinated (Gittings & Matson 2016).

### 3.5 Reduced antimicrobial resistance

An increasing global concern, antimicrobial drug resistance is jeopardizing the ability to treat common infectious diseases, resulting in prolonged illness, disability, and death. By reducing the need for antibiotics, vaccines can also support the fight against antimicrobial drug resistance. For instance, the introduction of a conjugate pneumococcal vaccine for infants in the United States in 2000 brought about a 57 percent decline in invasive disease caused by penicillin-resistant strains and a 59 percent decline in strains resistant to multiple antibiotics (Kyaw *et al.* 2006).



## 4. Vaccine research and development

### 4.1 Overview

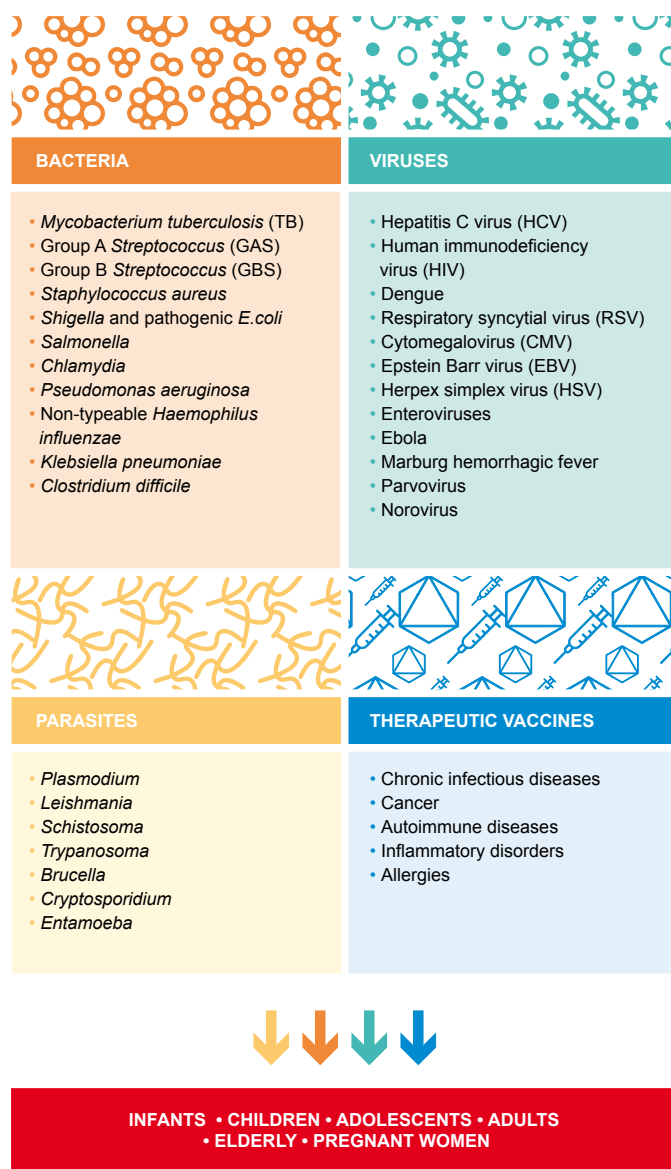
In the field of vaccines, R&D efforts focus on three major areas (Figure 2). First, they aim at the development of vaccines that prevent numerous bacterial, viral, and parasite-borne diseases. As of 2013, biopharmaceutical companies had 271 new vaccines in the pipeline at various stages of clinical development, including 137 for infectious diseases (PhRMA 2013). For example, in laboratories throughout the world, clinical trials are underway to develop a next-generation vaccine against malaria, which remains one of the deadliest infectious diseases worldwide (WHO 2017). A further example is the development of a multi-year influenza vaccine (Wei *et al.* 2012). In addition, researchers in both the public and private sectors are investigating a wide range of vaccines for neglected tropical diseases, such as dengue fever (Bethony *et al.* 2011).

Second, so-called therapeutic vaccines represent another important field of current R&D. In contrast to prophylactic vaccines, which are generally administered to healthy individuals, they aim to cure patients by strengthening their immune responses. For example, therapeutic vaccines have been demonstrated to be a viable option for active immunotherapy of late-stage cancers. Promising results from clinical trials recently led to the approval of the first therapeutic cancer vaccine by the FDA. This breakthrough not only provides a new modality for cancer management, but also lays the basis for rationally designing future vaccines with improved anticancer efficacy. Currently, scientists are evaluating numerous vaccine strategies both pre-clinically and clinically. These include, for instance, ways to counteract tumor-induced immune suppression which undermines the potency of therapeutic vaccine (Guo *et al.* 2013).

Third, drawing on improved knowledge of the immune system and on technological advances, scientists seek to design vaccines that are specifically adapted to vulnerable populations, namely elderly people, newborns, and pregnant women. A case in point is maternal immunization. Given the relative immaturity of the immune system in early life, this method allows for the effective protection of newborns through antibodies transmitted by their mothers. To the extent possible, maternal immunization should be extended to existing and upcoming vaccines. Another example is the improvement of so-called combination vaccines, which minimize the number of infant injections (Nossal 2011). Combining diphtheria, tetanus, pertussis, inactivated polio, *Haemophilus influenzae*, and hepatitis B vaccines, for instance, has significantly enhanced immunization compliance. At the same time, such combination vaccines have encountered numerous challenges, such as a reduced response to the *Haemophilus influenzae* vaccine when administered in combination, the need to consolidate the differences in the immunization schedule in the case of hepatitis B, and the necessity to improve the safety profile of the diphtheria, tetanus, and pertussis combination (Skibinski *et al.* 2011).

In recent years, several models of vaccine development have emerged which attempt to address the imbalance between public health needs, especially in developing countries, and the commercial incentives required by vaccine developers and manufacturers. Complementary to existing IP systems, these mechanisms are designed to incentivize R&D and the construction of manufacturing facilities by making commercially unattractive markets more appealing, reducing financial risk, and supporting return on investment. Broadly, they fall into two categories: “push” and “pull” mechanisms.

**Figure 2:**  
**Target diseases for future vaccine R&D**



Source: Delany *et al.* 2014

## 4.2 Push mechanisms

Push mechanisms aim to encourage the development of vaccines for specific diseases by providing upfront financial support for the R&D process. Examples include Product Development Partnerships (PDPs), grants to scientists, tax credits, and open innovation consortia.

PDPs are non-profit organizations that bring together stakeholders from the private and public sectors to promote the availability of health technologies, such as vaccines, in low- and middle-income countries. Typically, they use public or philanthropic funds to undertake R&D that might not otherwise occur due to the absence of market incentives. Because they usually lack the infrastructure to undertake research in-house, they generally leverage the capacities of private sector partners to move promising targets rapidly along the R&D pathway (Box 1).

**Box 1:**  
**PDPs – combining the respective strengths of the philanthropic, private, and public sectors**

Launched by the Program for Appropriate Technology in Health (PATH), the **Malaria Vaccine Initiative (MVI)** has been working closely with GlaxoSmithKline (GSK) Biologicals on the development of a malaria vaccine, with financial support from the Bill & Melinda Gates Foundation and scientific support from a network of African research centers engaged in clinical studies.

MVI works with GSK along the full vaccine clinical development pathway. GSK leads in its areas of strength, including applied R&D, clinical protocol development, clinical trial operations, regulatory affairs, and process development, scale-up, and large-scale manufacturing. PATH leads on African trial-site relations, contracts, and capacity building, crisis communications planning and media training for study center investigators, planning for decisions on vaccine use in African countries, and management and oversight structure for the project. Crucially, PATH also led the IP management process.

The vaccine completed phase III clinical trials in 2015, with WHO recommending in 2016 that large-scale pilot implementations be undertaken before adoption in national immunization strategies.

Based on the significant technological advances in genomics, bioinformatics and machine learning, the **Human Vaccines Project (HVP)** aims to accelerate the development of vaccines and immunotherapies against major global diseases and cancers by realizing the immune system's potential to fight disease. Accordingly, HVP's scientific plan comprises two complementary and integrated programs: (i) the Human Immunome Program, which is focused on defining the parts or components of the immune system, and (ii) the Rules Immunogenicity Program, which seeks to define the rules of immunological protection.

Funded *inter alia* by two large private foundations and several academic institutions, including the Vanderbilt University Medical Center and the J. Craig Venter Institute, HVP benefits from a network of scientific hubs, which work collaboratively to develop and execute HVP's scientific plan. They are associated through innovative legal agreements, which provide for the sharing of data and materials, the rapid public release of data, and shared IP to ensure the scientific breakthroughs reach populations on a global scale.

Created in the wake of the 2013–2016 Ebola outbreak, the **Coalition for Epidemic Preparedness Innovations (CEPI)** is a mechanism focused on the rapid development of vaccines for emerging infectious diseases (EIDs). Its initial targets are two vaccine candidates, each against three viruses with outbreak potential, namely the Middle East Respiratory Syndrome Coronavirus, Lassa Virus and Nipah Virus. Having recognized, in light of limited funding, the need to collaborate with the R&D-based vaccine industry, CEPI intends to establish a transparent and equitable system for sharing the risks and rewards of EID vaccine development. To this effect, the organization has identified several potential mechanisms, such as allowing companies to retain components or processes for commercial use, granting preferred tendering, assisting in obtaining regulatory exclusivity, and ownership of patents (Mahoney 2011). The experience of CEPI will also be useful in developing new means of risk sharing.

### 4.3 Pull mechanisms

Pull mechanisms offer rewards for the final R&D outcome and establishment of manufacturing facilities, often by ensuring a viable market that will allow for the recovery of investments in R&D. Examples include development assistance for health (DAH), advance market commitments (AMCs), milestone payments, and end prize awards.

#### *Development assistance for health*

The significant increase in DAH since 2000 may have acted as a pull mechanism for the development of new vaccines for developing countries (Dielemann *et al.* 2016). In fact, a significant proportion of DAH has been routed through vaccine-specific global health institutions, notably the Global Alliance for Vaccines and Immunization (Gavi) and the United Nations Children's Fund (UNICEF). Gavi funds

are disbursed for product procurement and the strengthening of health systems. In theory, the budget of this organization – about USD 1.8 billion per year – should signal to businesses the existence of a credible market for vaccines and therefore encourage them to commit the necessary funds for R&D. Authors have expressed skepticism, however, as to the extent to which this pull effect occurs in practice (Watson & Faron de Goër 2016).

#### *Advance market commitments*

Under an advance market commitment (AMC), a procuring entity – usually a government or other funding organization – agrees on a specific supply contract with a prospective producer. In other words, it guarantees the purchase of a certain quantity of the future vaccine at a price that has been agreed in advance (Berndt *et al.* 2007). Consequently, an AMC is expected to provide additional incentives for R&D that traditional approaches to procurement have not produced.

A prominent example is the Pneumococcal AMC, which was launched as a pilot project by Gavi in 2005. Its objective is to reduce morbidity and mortality from pneumococcal diseases, with a view to preventing an estimated seven million childhood deaths by 2030. Pneumococcal vaccines are complex preparations. In the absence of additional stimuli, they would reach low-income countries only 10-15 years after their introduction in industrialized countries. In 2009, the Governments of Canada, Italy, Norway, the Russian Federation and the United Kingdom, and the Bill & Melinda Gates Foundation, collectively committed a sum of USD 1.5 billion to finance a pilot AMC. This mechanism aims at incentivizing manufacturers to produce a pneumococcal vaccine meeting a specified product profile, including effectiveness against the serotypes most commonly found in developing countries and suitability for use in young children (Gavi 2016a). In addition, the Pneumococcal AMC seeks to accelerate vaccination manufacture and launch. Since the pilot's inception, the two currently qualified AMC manufacturers – GSK Biologicals and Pfizer – have produced more than 556 million doses of the vaccine, which has been launched in 28 countries (Gavi 2016a).

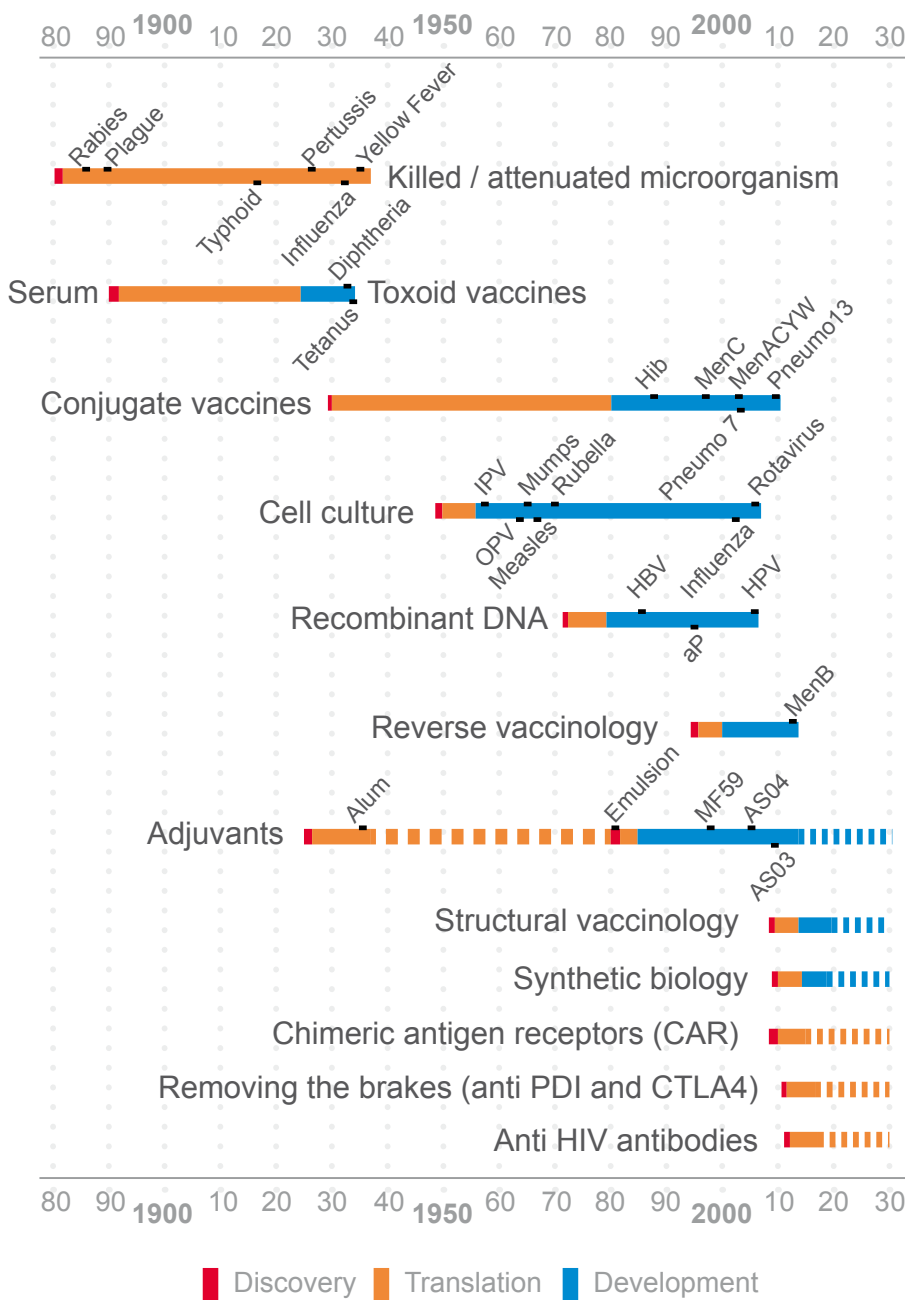
Some have criticized the AMC pilot as operating to the benefit only of established vaccine manufacturers, without creating opportunities for emerging low-cost vaccine manufacturers in developing countries (Light 2005). Another study has questioned whether the Pneumococcal AMCs could encourage investments in R&D and the establishment of manufacturing facilities (Light 2010). Evidence from the 2016 report on the AMC pilot project points to significant interest by manufacturers in the AMC market – and investments in innovation and manufacturing capacity in order to compete and serve this market. Challenges related to the AMC include financial sustainability; specifically, the difficulties faced by countries that graduate from low-income status, thereby losing the Gavi subsidies that underpin the program. Gavi has attempted to address this concern by allowing those countries to have continued access to Gavi funds and prices, provided that the countries in question fully finance the purchase themselves (Hargreaves *et al.* 2011).

Overall, evidence indicates that push and pull mechanisms are important tools both for stimulating vaccine R&D and for accelerating vaccine dissemination. Pull mechanisms, in particular, are a proven way to expand the availability of innovative vaccines. The pneumococcal AMC has resulted in the delivery of millions of doses, and the predictable market that it created attracted multiple companies to develop offerings for Gavi-eligible markets, the pneumococcal vaccine being a case in point. A recent study found that the AMC pilot had not only accelerated immunization coverage across 53 Gavi countries, but also that “manufacturers [had] made decisions to expand capacity to serve Gavi countries' requirements in response to the AMC and its supply agreements” (BCG & Gavi 2015).

# 5. The regulatory pathway

While the pace of vaccine development has increased throughout history, there is still a time lag of more than a decade between the discovery of a vaccine candidate and its translation into a safe and effective product (Figure 3). Still more time is needed to establish appropriate manufacturing facilities. To some extent, scientific advances, such as those in immunology and systems biology, can reduce the time required for certain components of vaccine development (Rappuoli & Aderem 2011). However, in spite of technological progress, the vaccine development pathway remains lengthy, largely due to two factors. First, overall regulatory requirements are steadily increasing. Second, vaccine development presents a number of challenges within the regulatory pathway that differ from other forms of drug development (Box 2).

**Figure 3:**  
**Discovery, translation, and development for various vaccines by technology**



Source: Rappuoli et al., 2014

Vaccine development comprises three main stages: preclinical development, clinical development, and post-licensure (Figure 4). Studies in the **preclinical stage** seek to collect important feasibility, iterative testing, and safety data. Their main goals are to determine the safe dose for testing in humans and to assess a product’s safety profile.

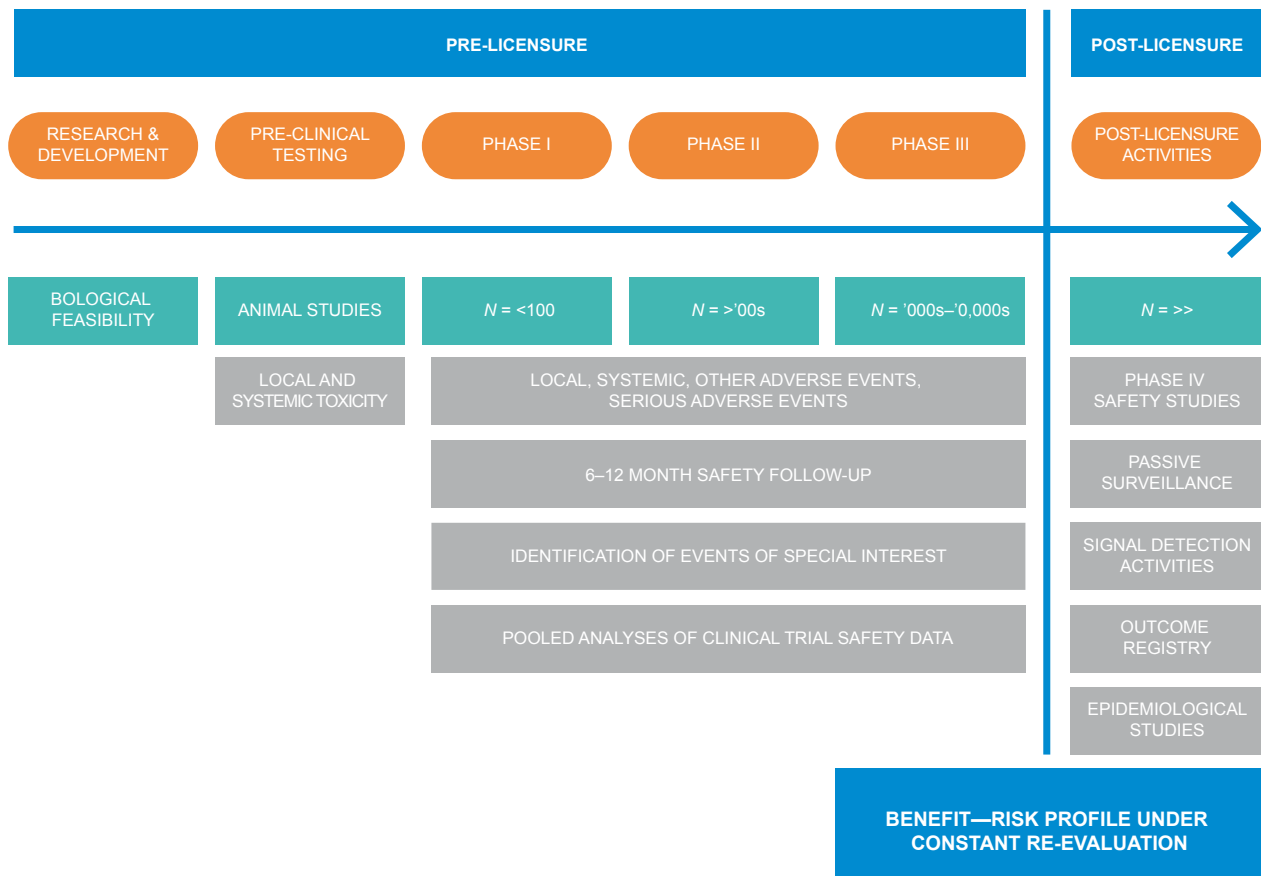
During the **clinical stage**, vaccines are tested on human subjects to identify their clinical, pharmacological, or other effects, along with adverse reactions and absorption, distribution, and metabolism in the human body in order to ascertain their safety and efficacy. The clinical stage includes three phases. In **Phase I**, a candidate vaccine is given to a small group of people, and, in **Phase II**, to a larger group of people to further evaluate its safety and efficacy. **Phase III** trials involve the largest number of subjects – up to 10,000 healthy volunteers. They seek to confirm the vaccine’s efficacy, monitor side effects, compare the results to commonly used treatments, and collect safety information. Their aim is to achieve licensure by establishing the vaccine’s safety and

efficacy. These studies also yield data on immunogenicity that are not always required for licensure. In general, they take over four years to complete. Pediatric vaccine clinical trials pose additional challenges, partly because of the ethical issues of conducting research on children.

Following the approval of a new vaccine, the **post-licensure stage** involves a range of tests, including Phase IV safety studies to gather information on the health technology’s efficacy in various populations and side effects associated with long-term use. In some cases, the public sector may sponsor the studies of this phase to evaluate the distribution, health, or financial impacts of the vaccine.

The clinical development for a successful vaccine candidate can cost in excess of USD 500 million (Leroux-Roels 2011). In addition, vaccine development is also fraught with significant uncertainty: measured from the preclinical phase, the average vaccine candidate has a market entry probability of around 6 percent (Pronker *et al.* 2011).

**Figure 4:**  
**The main stages of vaccine development: preclinical, clinical, and post-licensure**



Source: Di Pasquale *et al.*, 2015

**Box 2:**  
**Specific aspects of vaccine science related to the regulatory pathway**

- Multiple downstream processes and manufacturing runs in order to produce vaccine antigens of defined structure, antigenicity, purity, stability, and sterility.
- Increased analytical complexity of large molecule biologics compared to small molecules.
- Challenging formulation, especially due to the requirement that the antigen protein structure be characterized and conserved throughout.
- Multiple drug substance processes – as many as 20.
- Challenging antigen and adjuvant drug product processes, including production, isolation, and purification.
- Low levels of drug product dosage (some 10 milligrams).
- Need to characterize several types of components, including proteins, polysaccharides and carbohydrates.
- Involvement of proteins: multiple expression systems, diverse size range (20-2,500 kilodaltons).

Source: Alemayehu *et al.*, 2015

One promising approach to streamlining the regulatory pathway – and thus to enhancing vaccine availability – consists of using so-called correlates of immunity to define adequate clinical trial endpoints (Cragger 2014). A correlate of immunity is a blood marker, which unambiguously indicates that a person is immune to a disease (Plotkin 2008). Identifying a validated correlate of immunity could allow clinical trial evaluation of biosimilar vaccines to be completed more rapidly and at lower cost. For instance, during the clinical trials of a vaccine against human papilloma virus (HPV), MSD<sup>5</sup> carried out a bridging study involving a younger age group by comparing antibody responses to those in the older cohort in whom efficacy had been previously established (Frazer 2007). GSK has adopted a similar strategy in a noninferiority trial of its HPV vaccine following a manufacturing change, using antibody titres as the major trial endpoint (Cragger 2014).<sup>6</sup> The WHO has convened a series of expert consultations with the objective of defining antibody reference values pertaining to clinical efficacy outcomes for a pneumococcal vaccine (Ginsburg *et al.* 2012).

5 MSD (Merck & Co., Inc. in Canada and the United States).

6 Noninferiority trials test whether a new experimental treatment is not unacceptably less efficacious than an active control treatment already in use.

## 6. Vaccine manufacture

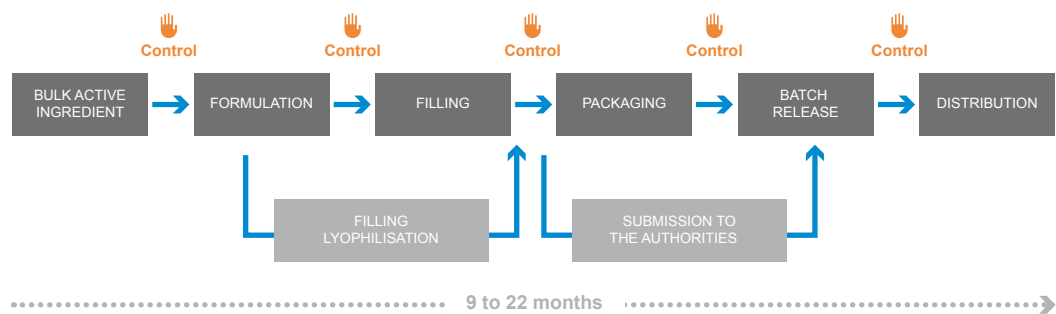
Companies wishing to bring a new vaccine to market must also invest in appropriate manufacturing facilities, the construction and validation of which are expensive and time consuming (Morrow & Felcone 2004). For example, Sanofi Pasteur's new production facility for its dengue vaccine cost some USD 300 million (Sanofi Pasteur 2016). The significant financial investment constitutes a challenge for startup companies, potentially preventing the emergence of innovative solutions. Business model innovation is one way to address this issue (Box 3).

Whereas the fabrication of conventional drugs involves relatively simple chemical syntheses, biological products vaccines require highly specific standards and procedures for all steps of production. Live attenuated vaccines (e.g., oral polio vaccine) can be prepared rapidly in large volumes, making low cost supply possible (Modlin 2010; Clendinen *et al.* 2016). By contrast, more recent biosynthetic vaccines present considerable manufacturing challenges, which add to timescales and cost. For instance, the production of complex vaccines (e.g., multivalent glycoconjugates for pneumococcus or meningococcus) involves lower yields and less consistent manufacturing processes, which are likely to lead to more write-offs.

Vaccines, especially more sophisticated products, are subject to relatively lengthy and costly quality control requirements. For instance, the FDA requires new vaccine plants in the United States to operate for at least two years prior to releasing products to the market, in order to demonstrate sterility of the process, absence of foreign particulate matter, proper freeze-drying of vaccines for reconstitution, and consistency (Kroll 2014).

Controls must exist at every stage of the manufacturing process to ensure the safety and quality of the completed batch (Figure 5). They include tests for physicochemical properties, such as pH and osmolality, component identity and stability analyses for antigens, excipients and adjuvants, microbiological testing for sterility, concentration, and potency testing and animal-based testing for toxicity (Smith *et al.* 2011). The tests imposed on vaccine manufacturers may vary according to the national legislation and requirements on the part of national regulatory agencies.

**Figure 5: Quality and safety controls during vaccine manufacturing**



Source: EFPIA, 2015



**Box 3:  
KUBio – an on-demand bio manufacturing facility**

Early-stage biotech firms struggle with the decision to invest in their own production facilities. Building in-house capability diverts resources from other critical activities. As an alternative, many startups resort to contract manufacturing, preserving their resources but subordinating themselves to another organization's priorities and engaging in time-consuming technology transfer. Both approaches have significant disadvantages that adversely impact on the potential success of emerging businesses.

General Electric has developed a solution that is based on an innovative business model. KUBio is a highly flexible biopharmaceutical factory, which comprises a configurable "design space" with a number of well-defined process-level configurations that can be rapidly adapted for manufacturing. This standardized approach not only facilitates the initial setup, but also enables firms to manufacture small quantities as needed, easily transfer processes to other facilities, and accelerate regulatory approval for products.

KUBio also allows firms to draw on expertise outside their core competencies. Frequently, the know-how of a young biotech firm is concentrated on their own technology, while their knowledge of how to transform the discoveries into a scalable process or overcome regulatory hurdles is limited. If such capabilities are co-located at the factory, translating breakthroughs to the market becomes considerably less risky. In turn, reliable access to such capabilities provides biotech firms with a clear competitive advantage.

KUBio allows the prompt establishment of biopharmaceutical manufacturing capacity by providing customers with a fully functional, ready-to-run bioprocessing facility in 14-18 months, which is significantly shorter than the time frame for constructing a traditional facility. Pre-designed to meet regulatory requirements, consistent with good manufacturing practice, KUBio helps manufacturers to respond to local healthcare needs and supports global customers in bringing solutions to market more rapidly. Moreover, its design costs are 25-50 percent lower compared with those of a traditional factory. Finally, the facility's operation is also less harmful to the environment, reducing CO<sup>2</sup> emissions and water and energy use by 75 percent and 80 percent, respectively.

Source: General Electric, 2017

## 7. Delivering vaccines

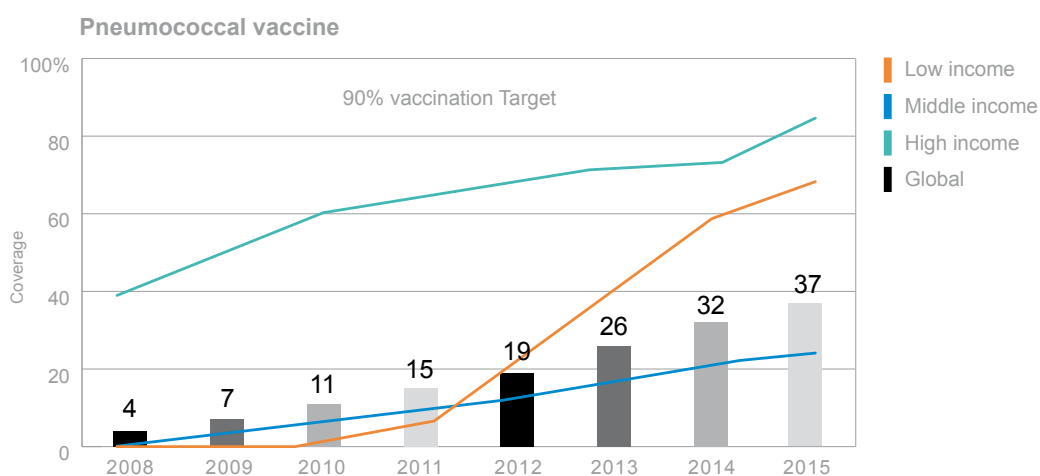
### 7.1 Challenges

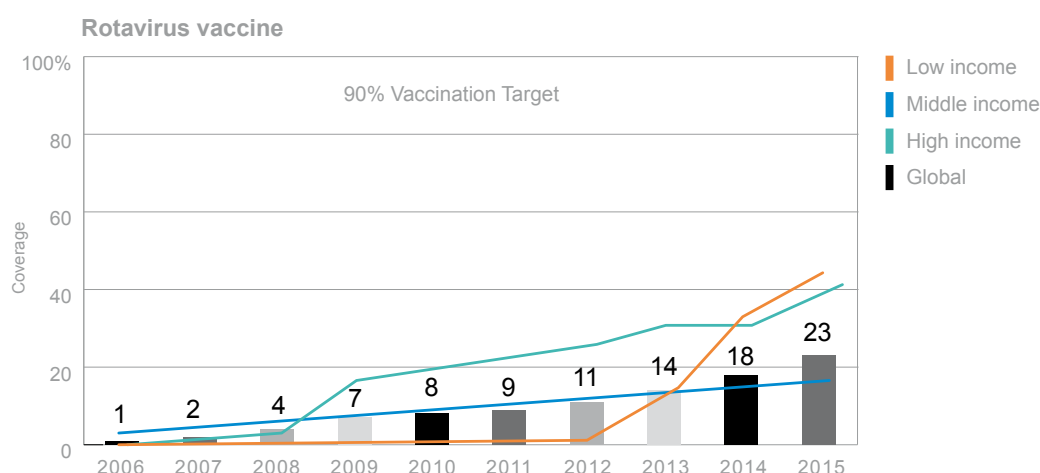
Although important progress has been made in expanding immunization coverage in developing countries, considerable challenges remain. For instance, 126 countries reached at least 90 percent coverage of the third dose of diphtheria-tetanus-pertussis (DTP3) vaccine by 2015 (WHO 2016a). However, some 19.4 million infants are still at risk. While this figure represents a noteworthy improvement on the 33.8 million children who did not receive the vaccination in 2000, coverage has plateaued since 2010. Moreover, the outcome falls short of the GVAP target of 90 percent or more DTP3 coverage at the national level in all countries (WHO/UNICEF 2016). At present, the African, Eastern Mediterranean, and Southeast Asian regions display coverage rates well below this objective. Similarly, in 2010, the average coverage achieved for measles-containing vaccine in low-income countries was 15 percent below that of high-income countries. In some countries, the coverage rate in rural areas is 33 percent lower than in urban areas, and the rate for the wealthiest fifth of the population is up to 58 percent higher than for the poorest fifth (WHO 2013).

Newer vaccines, in particular, are not evenly accessible, such as the rotavirus and pneumococcal conjugate vaccines that address the most common causes of disease and death in children - diarrhea and respiratory illness. Global coverage for these two vaccines is at 23 percent and 32 percent, respectively, with the lowest figures in middle-income countries that do not benefit from Gavi assistance (WHO/UNICEF 2016) (Figure 6). Another example is the vaccination against HPV, the predominant cause of cervical cancer. During the 2006–2014 period, HPV immunization programs targeted some 118 million girls worldwide, while covering only 1 percent from low- and lower-middle-income countries (Bruni *et al.* 2016).

In addition, overall, the cost of vaccination is on the increase. The cost of a specific vaccination package has risen by 2,700 percent over 10 years: from USD 1.37 in 2001 to USD 38 in 2011. In part, this is due to the composition of the vaccination package, which has nearly doubled from six diseases in 2001 to 11 in 2011. Two new products account for the bulk of the cost increase (Médecins Sans Frontières 2012). What is more, new vaccines are often administered to broader age groups and in far greater volumes (Lasher 2015), which is likely to increase pressure on programs and national health systems. However, it is important to consider these figures in light of the significant cost-effectiveness of vaccines (Ozawa *et al.* 2012).

**Figure 6: Coverage rates for new vaccines**





Source: WHO/UNICEF 2016

Studies have identified a range of factors that can explain the shortcomings in vaccine delivery in developing countries:

- major disconnects between the overseas supply chain and the in-country supply chain;
- inaccurate demand forecasting, leading to significant logistical problems;
- lack of coordination between procurement organizations and supply chain managers, resulting in inefficient inventory management and ineffective distribution practices;
- insufficient storage and delivery capacity when large volumes of new vaccines are added to supplies of existing regimens;
- inadequate infrastructure for transport;
- poor maintenance of shipment and storage materials, including vehicles, refrigerators, and cold boxes, posing a risk to the cold chain (Kaufmann *et al.* 2011);
- underperforming national health systems;
- insufficiently trained staff (Kaufmann *et al.* 2011; NORAD 2004);
- low staff morale among, and lack of career prospects for, health professionals, along with their international migration;
- unavailability of staff, transport, and funds for immunization activities at district level;
- few and undertrained health workers at district and service delivery level;
- failure to track available data on district immunization coverage and vaccine stock levels;
- erroneous perception of risks associated with vaccination (e.g., controversy about alleged links between the combined measles, mumps, and rubella (MMR) vaccine and autism); and
- reduced number of suppliers due to the need for significant investments in supply chains, including *inter alia* the transfer of know-how, cold chain equipment, and maintenance staff (Zaffran *et al.* 2013).

## 7.2 Possible solutions

To address these distribution problems, stakeholders have to consider a range of factors. Modern supply chains involve far more than just shipping, storing, and issuing supplies. They must also integrate with program and financial planning, forecasting, production, and procurement processes to create a seamless, continuously adjusted, end-to-end system.

In short, they require a comprehensive approach. WHO has created a framework that sets out four cumulative conditions to ensure sustainable availability of medicines:

1. rational selection
2. affordable prices
3. sustainable financing, and
4. reliable health and supply systems (WHO 2016c).

Gavi has made the strengthening of health systems a central part of its work, committing some USD 862.5 million to this area for the period 2007–2017 (Gavi 2016b). Education, including awareness programs, is an important element in promoting widespread acceptance and thus improved dissemination of vaccination (Larson & Mnookin 2016).

### *Tiered pricing*

Tiered pricing is the most widely used instrument to increase availability of new vaccines in developing countries. Under this approach, a vaccine is priced at varying levels in different countries, according to relative wealth. It is premised on the idea that the poorest countries should pay less than the marginal cost of production, with wealthier markets effectively subsidizing R&D costs. As a consequence, tiered pricing ensures the sustainability of the overall market for the product and preserves incentives to innovate. The largest multinational vaccine manufacturers in terms of sales – GlaxoSmithKline, MSD, Pfizer and Sanofi – differentiate vaccine markets according to certain criteria, including gross national income.

Parallel importation, i.e., the exploitation of price differentials between different markets, is a frequently encountered problem in tiered pricing. However, it is unlikely to occur in the case of vaccines due to the nature of the products and the way they are distributed. First, vaccines are heat-sensitive biological preparations. Second, the safety and quality requirements for vaccines are considerable, given that they are administered to healthy children, often by injection. As a consequence, their procurement and distribution are strictly controlled. Third, essential vaccines are usually provided free of charge to consumers, lessening significantly the risk of leakage, resale, and piracy (WHO 2004).

However, many of the poorest countries lack the resources to procure vaccines even at the lowest tiered price. Donor-financed pooled procurement has proven to provide a possible solution by consolidating low-income country vaccine orders. Such bulk procurement provides demand signals to manufacturers and leverage for negotiating prices to the procurement organizations (World Bank/Gavi 2012). This variant of tiered pricing has been extremely successful through UNICEF's bulk procurement of vaccines of the Expanded Program on Immunization (EPI), which allows the developing countries to buy at about 10 percent of the price applicable in developed countries (World Bank/Gavi 2012). The same approach has also been deployed successfully to increase the availability of newer, more expensive vaccines (Gavi 2016c). For instance, in 2007, it enabled a dose of the HPV vaccine, with an opening market price of over USD 100, to be offered at a Gavi price of USD 4.50 (Cutts *et al.* 2007; Berkley 2014). Another example is provided by the pneumococcal vaccines that were sold to Gavi-eligible countries at USD 3.30–3.50 per dose, i.e., less than 5 percent of the price in the United States of USD 102 (Berkley 2014).

Another challenge associated with tiered pricing is the failure to account for different socioeconomic groups within a single country. In fact, many of the world's poorest people live in middle-income countries and thus cannot benefit from the lowest prices (Moon *et al.* 2011). Finally, tiered pricing may deter additional companies from entering markets with low prices, thereby preventing further price reductions (Wilson 2010).

## 8. Intellectual property

### 8.1 IP rights and vaccines

Various IP rights are relevant for vaccines and vaccine-related technologies, including patents, trademarks, copyrights, and trade secrets.

Patents can cover the vaccine's formulation, including the combination of medicinal components.<sup>7</sup> They may also exist on the device for vaccine administration, for instance an injection delivery system or a capsule constructed to release the product in a particular area of the human body. Clinical test data protection can prevent third parties from using clinical trial data submitted to regulatory authorities to gain marketing approval for the manufacture of competing products. Trademarks, which help to establish a link between products or services and a particular organization or individual producing or providing them, may protect the brand name of the vaccine. Copyright protects the expression of ideas, and applies to the explanatory materials and designs used in relation to a vaccine. Finally, trade secrets protect knowledge which inventors and businesses choose not to publish, which is non-codifiable, or which does not meet patentability criteria (Durell 2016). In the field of vaccines, trade secrets are particularly relevant to know-how related to the manufacturing process.

In relation to vaccines, a primary function of IP rights is to encourage the significant R&D investments required for their development. Absent this incentive, vaccine innovation may not occur. In addition, IP rights such as patents can also facilitate control over vaccine production and distribution, for instance by way of licensing. This control can help to ensure vaccine quality and safety. Quality control is a critical factor influencing the public perception of the quality and effectiveness of the vaccine. Similarly, trademarks underpin quality assurance systems, allowing an innovator to benefit from the trust of patients in the protected vaccine. In this regard, it is important to note that public acceptance of a vaccine can be fundamental for the effectiveness of vaccination programs (Durell 2016).

Importantly, the exclusivity that IP rights confer on right holders is not absolute. For instance, patents are limited in scope. As a result, there may be an unpatented product outside the scope of the patent, which can be substituted for the patented product. In this case, the full price effect of the patented product may not be realized. The ability of third parties to “invent around” a protected invention is an integral part of a functioning patent system (WHO 2004). This is particularly relevant to vaccines, which can often consist of multiple technologies, only some of which are patented.

### 8.2 IP rights in vaccines research and development, regulatory pathway, and manufacture

Patents can impact the ability of new manufacturers from developing countries to participate in vaccine markets, in relation to any step of the regulatory pathway starting from preclinical R&D, to scale-up, formulation, and licensure in the markets of choice. For instance, according to a recent study, certain manufacturers based in developing countries argue that the need to navigate patents increases transaction costs and adds to their development timelines (CDC Chandrasekharan *et al.* 2015). They also express concerns about uncertainties surrounding patent claims, which they say may create difficulties in assessing the complex IP space in vaccines markets. To address these issues, the authors of the study have suggested a range of measures, including efforts to improve patent transparency and to build IP management capacity building among manufacturers.

Patents on vaccines and on essential technologies for vaccine development (e.g., adjuvants) are merely one of many factors that influence vaccines innovation and availability in developing countries. According to a recent analysis focused on Brazil, the most important challenges to expanding immunization coverage relate to inadequate regulatory structures and procedures, and low levels of investment in local capacity, human

<sup>7</sup> Combination products are patentable in only some jurisdictions, including the United States and through the European Patent Office.

resources, technology, and logistics (Possas *et al.* 2015).<sup>8</sup> The authors underscore the need to increase the number of patents submitted by residents in Brazil, a proxy for enhancing absorptive and innovative capacity domestically. To this end, they suggest *inter alia* the development of a new policy and new criteria for evaluating the scientific productivity of researchers in the country by the National Research Council.

PDPs are important instruments to enhance the availability of vaccines in developing countries. Many PDPs have overcome the potential barriers posed by patents by developing and implementing IP management frameworks that facilitate product development while ensuring affordable prices (Mahoney 2011). For example, the Medicines for Malaria Venture (MMV), a non-profit public–private partnership established in Switzerland, explicitly uses the current IP framework to pursue four key objectives:

1. to achieve freedom to operate;
2. to incentivize the contribution of private sector resources and know-how;
3. to safeguard the quality of resulting products; and
4. to promote availability of malaria vaccines.

To this effect, MMV has an active screening program to identify product leads. Patent protection is sought before putting a lead into the development pathway so as to elicit private sector interest in collaborating in further development. MMV also enforces patents to prevent the production of substandard versions of its drugs. Other organizations, such as the Meningitis Vaccine Project and the Malaria Vaccine Initiative, also strategically manage their IP in order to accelerate innovation and availability. In addition, there are several initiatives that facilitate sharing of knowledge and know-how between innovative organizations (Box 4).

**Box 4:**  
**WIPO Re:Search ([www.wipoReSearch.org](http://www.wipoReSearch.org))**

Whereas larger PDPs have relatively easy access to private-sector partners and their technology and know-how, there are numerous less well-connected research organizations which are interested in licensing IP, including access to compounds, unpublished scientific information, regulatory documentation and know-how. WIPO Re:Search offers these organizations a solution.

WIPO Re:Search is an open innovation platform or consortium that brings together a range of public and private entities from academia, industry, non-governmental organizations (NGOs) and PDPs. Members of the consortium agree to share their IP and expertise with others in the research community. They make their IP assets available on a royalty-free basis to researchers anywhere in the world. WIPO Re:Search focuses on neglected tropical diseases, malaria, and tuberculosis. Members also agree that any products arising from the research collaborations are to be sold royalty-free in all least developed countries (LDCs) and agree to negotiate in good faith access to all developing countries, taking into consideration the burden of disease and economic development of countries.

The WIPO Re:Search platform comprises a database of available IP and will soon include a comprehensive “resource platform” providing information on ongoing collaborations. It also features a Partnership Hub, administered by BIO Ventures for Global Health (BVGH), which connects members according to their research needs.

Since its launch in 2011, WIPO Re:Search has grown to include more than 120 members and over 120 collaborations have been established. This demonstrates that IP is not a barrier but can facilitate collaborations and technology transfer, including in the field of vaccines.

*Regulatory pathway*

Know-how and clinical test data are two forms of knowledge that the developers of a vaccine generally want to protect, as this helps them to recoup their investments in R&D. Know-how, such as how

8 An illustration of these constraints is the average time required for patent registrations by the Brazilian National Institute for Industrial Property: 10.8 years, compared with the United States (2.6 years); Europe (3 years), China (1.9 years) and the Republic of Korea (1.8 years). This slow pace impacts the annual number of patents granted. According to the United States Patent and Trademark Office (USPTO), in 2013, Brazil granted only 254 patents, in contrast to the United States (133,593), China (5,928), India (2,424) and Russia (417) (USPTO 2015).

to design and execute clinical trials, is protected through employee confidentiality policies. By contrast, the protection of clinical test data occurs through data protection regulations. Article 39.3 of the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) requires WTO members to protect test data submitted to regulatory authorities against unfair commercial use and disclosure, except when the public interest so requires or when the data is otherwise protected against unfair commercial use. Protection of proprietary rights to drug registration data has become a requirement for all WTO members, with the exception of LDCs, since January 1, 2000.

The TRIPS Agreement does not provide guidance as to how test data should be protected. Industry favors data exclusivity. Under this scheme, the extent to which other entities can use the data to support their own regulatory filings is limited for a defined period of time, which can range from five to 11 years, depending on the jurisdiction. Data protection provisions are enacted in recognition of the significant investment made in generating the clinical test and other data required for regulatory approval (Lybecker 2014). In most sectors, companies can protect commercially sensitive data through trade secrecy laws, but the requirement for vaccine manufacturers to disclose data to regulators puts them at a competitive disadvantage. Clinical test data protection thus ensures that competitors cannot gain regulatory approval and enter the market via reliance on an innovator's test data before the innovator has had an opportunity to recoup the costs of compiling it.

### *Manufacture*

Compared with small molecule drugs, the manufacture of vaccines involves a significantly higher level of know-how, none of which may be communicated in process or product patent applications, or through the clinical data submitted to regulatory authorities prior to marketing approval. Indeed, for most modern vaccines, know-how related to manufacture is considered to be more important than patents. Protected in the form of trade secrets, proprietary knowledge is often shared in the context of partnerships, which can considerably accelerate innovation. It may be independently discovered and, unlike the subject of a patent, used by competitors, provided it was not obtained through misappropriation or unfair commercial practices.

Moreover, it is often the case that knowledge relevant to, but not included in, patent applications may nonetheless be made available through publications or other pathways, thus advancing the work of competitors. For example, PATH worked with Bharat Biotech, the Hyderabad-headquartered biotechnology company, to develop a low-cost rotavirus vaccine that met the disease aetiology profile of India. Launched in 2001, the project led to licensure of a new vaccine in India in 2015. When the clinical trials for the Indian vaccine began, two other rotavirus vaccines by MSD and GSK had already been on the market. The fact that these manufacturers had not directly shared their know-how with Bharat Biotech did not hinder the development in India. On the contrary, Bharat Biotech must have benefited to a large extent from what had been published on effective rotavirus antigens, disease immunology, etc. because of the R&D investment undertaken by MSD and GSK (Bhandari *et al.* 2014).

A range of initiatives, such as technology transfer hubs, facilitate the sharing of production-related know-how to the benefit of vaccine manufacturers in developing countries (Box 5). These approaches are effective and illustrate that the existence of IP rights does not exclude the exchange of necessary information about the production of many vaccines.

### **Box 5: Influenza Vaccine Technology Transfer Centre**

Bilateral technology transfer deals are useful instruments provided that (i) there are clear commercial incentives for both provider and recipient, and (ii) IP issues are dealt with in a productive manner. In cases where such incentives are less obvious and where multiple recipients in different countries simultaneously need access to the technology, technology transfer hubs can be an effective model of technology transfer and knowledge sharing.

A notable example is the Influenza Vaccine Technology Transfer Centre created by WHO at the Netherlands Vaccine Institute. The Centre provides a working pilot production facility at which vaccine

manufacturers from developing countries can access standard operating procedures, documentation and training on all aspects of the production process. To facilitate the registration process, the Centre also trains national drug regulatory authorities.

This model is advantageous since it is more time and resource effective to bring manufacturers to one place to learn, rather than send experts to multiple production sites all over the world.

For a hub model to be successful, the following conditions must be met:

- there should be freedom to operate in relation to the technology to be transferred, both at the hub site and in recipient countries;
- the recipient must have manufacturing and quality control standards aligned with WHO standards;
- the hub facility must not interfere in the commercial markets of the recipients; and
- financial support must be available to support a new hub through the technology development phase, while recipients need to meet the operating costs.

Source: Friede *et al.* 2009.

The foregoing suggests that the various forms of IP rights have not posed a significant barrier to the manufacture and distribution of vaccines. Nevertheless, commentators occasionally suggest that restricting the granting and enforcement of patent rights could increase access to vaccines in developing countries (Maybarduk & Rimmington 2009). The TRIPS Agreement provides for some exceptions and limitations to patent rights, including the option for WTO members to issue compulsory licenses under certain conditions. The right of WTO members to use these so-called TRIPS flexibilities was clarified in the Doha Declaration of 2001, in the context of advancing access to medicines for all (Cohen 2005).

Under a compulsory license, a court or the responsible authority grants specific permission to an entity other than the patent owner to produce, import, sell, or use the patent-protected product, or to use the patent-protected process, provided certain conditions are met. Patent owners are entitled to receive remuneration when a compulsory license is granted. There is no obligation for patent owners to provide additional information. Therefore, manufacturing know-how is not necessarily obtained under a compulsory license. Because of this, compulsory licenses may not be as cost-effective as voluntary methods of medical technologies procurement, particularly when licenses are issued for local production in low-income countries (Beall *et al.* 2015; Milstien & Widdus 2003). In fact, manufacturers are likely to be disincentivized from sharing such information under these circumstances.

The use of compulsory licenses reached a peak between 2003 and 2005, with the tool used mainly for HIV/AIDS medicines by upper-middle-income countries. Few licenses have been issued since then (Beall & Kuhn 2012).

To date, no compulsory licenses have been issued for vaccines. There have been calls to investigate compulsory licensing of newer vaccines, particularly the HPV vaccines manufactured by MSD and GSK (Maybarduk & Rimmington 2009). According to these authors, a compulsory license for these HPV vaccines could lead to price reductions, if they incentivize enough generic manufacturers to participate. They conclude, however, that there are “perhaps insurmountable” obstacles, largely due to the scientific and regulatory challenges associated with manufacture and licensing.

Finally, the use of compulsory licenses could dissuade manufacturers from investing in and developing health technologies that address pressing global health needs (HLPAM 2016).



## 9. Conclusion

A highly cost-effective instrument, vaccination has made an enormous contribution to global health outcomes.

This Global Challenge Report has examined factors that impact the availability of innovative vaccines on a global scale, especially in developing countries. To this end, it has looked at the various components of vaccine innovation and production, namely R&D, the regulatory pathway, manufacture, and delivery. In doing so, it has noted several impediments that exist throughout this lengthy process, which the private and the public sectors address through a range of mechanisms. It has examined the contribution of policies, such as pull mechanisms and strategic IP management, in stimulating competition, innovation, and the broad diffusion of new vaccines.

To summarize, the fundamental challenge is to manage IP, together with the complex set of related issues affecting availability and access, in ways that improve human welfare, while contributing to the realization of SDG 3: *Ensure healthy lives and promote well-being for all at all ages.*

# Acronyms and abbreviations

<b>AIDS</b>	Acquired immune deficiency syndrome
<b>AMC</b>	Advance market commitment
<b>BCG</b>	Boston Consulting Group
<b>CEPI</b>	Coalition for Epidemic Preparedness Innovations
<b>DALY</b>	Disability-adjusted life year
<b>DAH</b>	Development assistance for health
<b>DNA</b>	Deoxyribonucleic acid
<b>DTP3</b>	Third dose of diphtheria-tetanus-pertussis
<b>EID</b>	Emerging infectious disease
<b>EMA</b>	European Medicines Agency
<b>EPI</b>	Expanded Program on Immunization
<b>FDA</b>	US Food and Drug Administration
<b>Gavi</b>	Global Alliance for Vaccines and Immunization
<b>GSK</b>	GlaxoSmithKline
<b>GVAP</b>	Global Vaccine Action Plan
<b>Hib</b>	<i>Haemophilus influenzae</i> type B
<b>HIV</b>	Human immunodeficiency virus
<b>HLPAM</b>	High-Level Panel on Access to Medicines
<b>HPV</b>	Human papilloma virus
<b>HVP</b>	Human Vaccines Project
<b>IP</b>	Intellectual property
<b>LDC</b>	Least developed country
<b>MMR</b>	Measles, mumps, rubella
<b>MMV</b>	Medicines for Malaria Venture
<b>MVI</b>	Malaria Vaccine Initiative
<b>NGO</b>	Non-governmental organization
<b>PATH</b>	Program for Appropriate Technology in Health
<b>PDP</b>	Product Development Partnership
<b>pH</b>	Potential of hydrogen
<b>R&amp;D</b>	Research and development
<b>SDG</b>	Sustainable Development Goal
<b>TRIPS</b>	Trade-Related Aspects of Intellectual Property Rights
<b>UN</b>	United Nations
<b>UNICEF</b>	United Nations Children's Fund
<b>USPTO</b>	United States Patent and Trademark Office
<b>WHO</b>	World Health Organization
<b>WIPO</b>	World Intellectual Property Organization
<b>WTO</b>	World Trade Organization

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