International Federation of Pharmaceutical Manufacturers & Associations

Delivering the Promise of the Decade of Vaccines



Perspectives and Contributions of the Research-based Vaccine Manufacturers

Addressing the <u>Availability</u>, <u>Affordability</u>, <u>Adoption</u> and <u>Alliances</u> Needed to Achieve 90% Coverage of Vaccines by 2020



Vaccination is one of the world's most important and cost-effective public health measures.

Investment in R&D, largely by the pharmaceutical and biotechnology industry, has resulted in a broad range of vaccines targeting over 25 infectious disease categories.

Still three million children die each year from vaccine preventable diseases; informed policymaking can bring full benefits of vaccines to individuals' health and to societies by 2020 or sooner.

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Abbreviations

- AIDS Acquired Immune Deficiency Syndrome
- AMC Advance Market Commitment
- BMGF Bill and Melinda Gates Foundation
- CSO Civil Society Organization
- DoV Decade of Vaccines
- DoVC Decade of Vaccines Collaboration
- FDA Food and Drug Administration
- GAVI Global Alliance for Vaccines and Immunization
- GVAP Global Vaccine Action Plan
- HBV Hepatitis B Virus
- HIV Human Immunodeficiency Virus
- HPV Human Papilloma Virus
- IFFIm International Financing Facility for Immunization
- IFPMA International Federation of Pharmaceutical Manufacturers and Associations
- IP Intellectual Property
- MDG Millennium Development Goal
- NGO Non-Governmental Organization
- OECD Organization for Economic Co-operation and Development
- PAHO Pan American Health Organization
- PPP Public Private Partnership
- R&D Research and Development
- TB Tuberculosis
- UNICEF United Nations Children's Fund
- WHO World Health Organization

Executive Summary

Immunization Agenda: Vaccines for All

Recognizing the ongoing challenge of global vaccine access for a range of preventable diseases, the Bill and Melinda Gates Foundation (BMGF) pledged to extend, by 2020 and beyond, the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live [1].

In May 2011, BMGF launched the Decade of Vaccines (DoV) initiative with a USD 10 billion pledge and a vision of achieving immunization goals and meeting key milestones in the discovery, development, and delivery of life-saving vaccines to people around the world. Despite this significant pledge and call for action, significant gaps remain. BMGF called for others' help to fill these critical gaps to make DoV a reality.

The DoV will succeed if the World Health Assembly-endorsed goals of global eradication and elimination of many vaccine-preventable diseases are achieved by 2020. This means polio will have been eradicated, progress made towards elimination of measles, rubella and neonatal tetanus will have been accelerated, and most vaccine-preventable diseases will no longer be major public health problems around the world. Initially, this will require countries to prioritize diseases that can be addressed through routine immunizations (e.g. tuberculosis, diphtheria, tetanus, pertussis, Haemophilus influenzae type b, hepatitis B, rubella, polio, and measles); by new and/or underutilized vaccines (e.g. pneumococcal, human papillomavirus and rotavirus); and vaccines intended for regional or high risk populations (e.g. meningitis A, Japanese encephalitis, yellow fever, cholera, and seasonal influenza).

This challenge of achieving DoV's objectives cannot be achieved by countries acting alone. A country-led, broad-based, collective approach involving players from public, nongovernmental, and private sectors is critical. Beyond the stakeholders, sustained access to and use of high quality and innovative vaccines are required for making DoV a reality.



DoV Action Plan and the Research-based Vaccine Manufacturers

In preparation of the 2012 World Health Assembly, the Decade of Vaccines Collaboration (DoVC) launched a series of consultations with stakeholders to solicit input and strengthen the Global Vaccine Action Plan (GVAP). The consultation seeks input from governments, policymakers, civil society, healthcare professionals, global development organizations, academics, private sector players, including vaccine manufacturers, and other key stakeholders involved in immunization, health and human development.

Although there is likely to be general agreement on the purpose of the DoV initiative, each stakeholder is expected to provide insights on the operational challenges and research and development (R&D) contributions during 2011-2020 – the Decade of Vaccines.

With a long-standing and a proven track record of researching and developing high quality vaccines, research-based vaccine manufacturers, who are members of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), have a significant role to play and contributions to make to achieving the DoV vision. With active research and development (R&D) in more than 25 infectious disease categories, vaccine manufacturers individually and collectively contribute to improved global health through increased access, availability, affordability, and adoption of vaccines in developing and developed countries.

Recognizing the unique expertise and contributions of the research-based vaccine manufacturers, the DoV action plan envisions a key role for these companies: continue to innovate, develop, produce and supply high quality vaccines. Specifically, the manufacturers are well-positioned to:

- participate in open dialogue with countries and the public sector to ensure sustained access to current and future high quality vaccines
- advance innovation in R&D and manufacturing
- support rapid vaccine adoption as new or improved vaccines become available
- develop partnerships that support increasing manufacturing capabilities, supply and innovation
- work in coordination with other partners on vaccine and immunization advocacy.

The IFPMA and its members strongly support the vision of the DoV and based on decades of vaccine experience believe that to significantly improve health all around the world, the GVAP should fully address availability, affordability, adoption, and alliance building.

This paper highlights insights from the experience of the IFPMA and its membership of research-based vaccine manufacturers and proposes proven solutions for availability, affordability, adoption, and alliance building.

1 Global Health and the Value of Vaccination

Vaccination saves more lives than any other public health innovation with the possible exception of improvements in sanitation and water safety. The health benefits of vaccination are wide-spread for individuals and societies at large. They improve health, save healthcare costs and lost income as well as contribute to economic activity. While vaccination has eradicated or eliminated diseases like smallpox and poliomyelitis, millions of children still die each year from vaccine-preventable diseases. The scope of diseases that can be prevented by vaccination is expanding. Hepatitis B Virus (HBV) and human papilloma virus (HPV) vaccines are already used to prevent liver and cervical cancers, and progress is being made on the therapeutic use of vaccines for other cancers and the management of non-communicable diseases. Malaria, dengue and improved tuberculosis (TB) vaccines are on the horizon and vaccination against human immunodeficiency virus (HIV) may ultimately become a reality.

Given the social and economic importance of health and the unique role that vaccines play, vaccination should be valued for its ability to prevent disease and to support good health worldwide. Vaccination not only benefits individuals but also has positive spill-over effects on society, because of diminished disease transmission, or blocking of and even eradicating pathogens. Despite these positive results, the short- and long-term benefits of vaccination remain underappreciated by many policymakers. The IFPMA encourages policymakers to support sustained vaccine development, access, and usage, and generating supportive evidence so their societies can realize the full benefits of vaccination.

2 'Availability': Sustainable Innovation, Manufacturing and Supply

The scientific expertise and manufacturing capacity of individual research-based vaccine manufacturers underlie their leadership in developing and delivering vaccines. While both private and public partners, including academia and research institutes, play an important role in basic vaccine research, manufacturers generally lead most research, development and registrations that result in new vaccine approvals. Vaccine development remains a complex, arduous, expensive, and high-risk venture. It requires mastery of multiple technologies, funds for laboratory research, clinical trials and manufacturing facilities, sophisticated scale-up processes, expertise in navigating demanding regulatory environments in multiple regions simultaneously, and managing rigorous safety monitoring.

Vaccine development process: Working with the public and academic sectors research-based vaccine manufacturers play a critical role in every step of the vaccine development process from research to delivery. This includes:

- taking calculated risks in determining whether to pursue a vaccine candidate
- translating basic science to applied research
- passing stringent regulatory requirements and consistently manufacturing millions of doses per year, with rigorous parameters of quality and potency.

Quality and harmonization: The IFPMA and its members strongly support upholding international quality standards in order to guarantee equal quality care to vaccinated people in all countries. Failure in high quality vaccine development would be detrimental to the success of the GVAP. Steps to support these standards include disseminating best practices in manufacturing and quality control, investing in R&D capabilities, and strengthening regulatory systems. The IFPMA also advocates harmonization of regulatory requirements to reduce unnecessary administrative hurdles and to speed up access to needed medicines and vaccines.

Capacity building – partnering with local vaccine manufacturers: Several companies engage in joint ventures and other forms of partnership that strengthen and support emerging-country vaccine manufacturers. These relationships sometimes involve sharing of vaccine technology. IFPMA vaccine manufacturers generally are open to considering technology transfer, in particular where the necessary enabling conditions are in place. These include committed partners, a viable and accessible local market, political stability and good governance, clear local development priorities, effective regulation, availability of skilled workers, adequate capital markets, intellectual property (IP) rights and enforcement, and a good relationship between government and vaccine manufacturers.

Dialogue to ensure vaccine supply: The IFPMA members support better aligning demand and supply. To achieve greater alignment, global and regional organizations (e.g. United Nations Children's Fund (UNICEF) Supply Division and Global Alliance for Vaccines and Immunization (GAVI)) should continue to support improved communication among countries, vaccine manufacturers and public-sector organizations. Through these fora, countries could more clearly communicate expected demand for vaccines and provide guidance on desired product profiles. Consequently, increased dialogue enhances supply security by reducing uncertainty around volume demands and product features.



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3 'Affordability': Universal Access, Equity and Pricing

Preventive measures such as clean water, vaccination, and sanitation are important to preserve health in communities and should be funded through national public health budgets. This is not always the case for immunization programs, as budgets are often limited in developing countries. The current budgeting 'silo' approach between prevention and other health services and technologies could be overcome by a wider recognition of the positive spillover effects of vaccination on social and economic development. To accommodate for this financing gap, individual vaccine manufacturers have pledged at several high-level meetings to continue making efforts to improve affordability, for example by differentiating prices, providing those countries with the least ability to pay with access to the lowest prices. This makes vaccines accessible to some countries that would not otherwise have access.

Reconciling access and innovation: Access to vaccines at affordable prices does not conflict with IP rights and vice versa. Public policies and incentive mechanisms can play a crucial role in this regard. Preserving IP rights is the linchpin of achieving not only short-term but also long-term efficiencies and structurally paving the way for sustainable access to vaccines.

Maximizing the benefits of differential pricing: While the IFPMA believes that differential pricing has contributed significantly to increasing access in poor countries already and could go a long way towards making vaccines affordable on a large scale in developing countries, and at the same time preserving incentives for R&D, the ability of individual vaccine manufacturers to continue using differential pricing is being challenged by higher income country governments and their procurement agents who seek to extend the prices afforded to poor countries to their home markets. If the benefits of differential pricing to public health, including a high level of access to vaccines in the poor countries, are to be preserved, it is up to governments and legislators to address these challenges.

Stimulating R&D through subsidies: For diseases that are endemic only in the developing world, there are not sufficient revenues from vaccines to offset the cost of R&D and investment in capacity. In these cases, 'push and pull' mechanisms can create the necessary incentives to invest in vaccines for developing country diseases. However, it is important that a 'push' mechanism partnership does not create a monopolistic situation, eventually putting at risk the security of supply.

4 'Adoption' – Financing Systems and Public Awareness

This decade will bring new and improved vaccines and presents new opportunities and challenges particularly for developing countries where vaccine preventable diseases are still a major cause of morbidity and mortality. However, these are also the countries where the cost of achieving and sustaining high immunization coverage is the greatest. This is due to the weak healthcare infrastructure, the limited availability of trained staff and poor public education about the value of vaccines and immunizations. In addition, national budget funding immunization in most countries remains sub-optimal.

Innovative and sustainable financing for vaccines: To address the funding gap, increased national government resources must be mobilized, complemented by funding from international donors. The IFPMA and its members support innovative financing mechanisms that are designed to accelerate innovation and access to vaccines in the developing world. Novel mechanisms such as the International Finance Facility for Immunization (IFFIm) and Advanced Market Commitments (AMCs) could make significant strides toward addressing these challenges. Such innovative mechanisms are needed to sustain current immunization programs, introduce new vaccines, and strengthen healthcare infrastructure.

Communicate for successful vaccine uptake: Evidence-based policies need to be systematically developed and the public at large better educated/informed, which in turn influences the support and demand for immunization. In the case of vaccines, effective communication entails reaching out to healthy people, a task that is complicated by the fact that several anti-vaccination lobbies are vocal in dissuading people from becoming vaccinated. Social mobilization and promotion of the benefits of immunization through mass awareness raising campaigns are key elements of successful introduction and adoption of vaccination into national preventive medicine programs. The IFPMA vaccine manufacturers share the view of the DoV that considerable efforts must be made to provide concise and balanced information to the general public. Adapting this information to local conditions and perceptions is critical for national acceptance.

5 'Alliances' – Building Durable Public Private Partnerships

Public private partnerships (PPPs) generally complement the value of the legitimacy, credibility and expertise of the public sector with a strong private sector voice able to mobilize significant expertise and resources as well as take calculated risks. The process inherently recognizes the importance of achieving equity and accountability in the relationship by involving equitable representation of a number of stakeholder groups and their views. As DoV considers future strategies for collaboration between the public and private sectors, governance structure will be of key importance to ensure all stakeholders are adequately represented.

Governance for and advantages of manufacturer involvement in PPPs: The IFPMA welcomes the inclusion of non-governmental organizations (NGOs) and companies driven by both commitment to sustainable and viable business models for global health, and corporate social responsibility in the formation of new global governance structures that have a more balanced stakeholder membership than in the past.

Some may argue that the participation of private sector companies in the governance of public-private partnerships introduces a challenge to the decision-making process. However, any potential conflict of interest can be resolved by upholding rules of engagement. Through the IFPMA, research-based vaccine manufacturers have ten years of experience as member of the GAVI Board. The 27-seat board has one seat for the elected representative of the industrialized country vaccine manufacturers, and one seat for the representative of the developing country manufacturers. Despite manufacturers being a minority partner, this distribution has proven to work well in the past and continues to be supported by the majority of stakeholders. This diversity offers great potential for increased quality of group performance and decision-making.

1 The Quest for Global Health – Vaccines for the World

1.1 Global Health and the Value of Vaccination

Vaccination saves more lives than any other public health innovation with the possible exception of improvements in sanitation and water safety [2]. The health benefits of vaccination extend to individuals as well large groups. In addition, vaccination provides societal benefits in the form of decreased healthcare costs and avoidance of income loss due to illness. Healthy workforces contribute to increased economic activities, which can attract foreign direct investment to developing countries.

Eradication of smallpox and the elimination of poliomyelitis and measles from large parts of the world saved millions of lives. Despite these successes, three million children still die each year from vaccine preventable diseases [3]. Pneumonia, meningitis and diarrhea account for a quarter of childhood deaths, many of which could be prevented with currently available vaccines.

The scope of diseases that can be prevented by vaccination is expanding. HBV and HPV vaccines are already used to prevent liver and cervical cancers, and progress is being made on the therapeutic use of vaccines for some cancers and the management of non-communicable diseases such as hypertension, diabetes and drug and alcohol addiction. Malaria, dengue and improved TB vaccines are on the horizon and vaccination against HIV may ultimately become possible.

Given the social and economic importance of health and the unique role that vaccines play, vaccination should be valued for their ability to prevent disease and to support good health worldwide. Vaccination not only benefits individuals but also has a positive spill-over effect on society, because of diminished disease transmission and blocking and even eradicating of pathogens. Despite these positive results, the short- and long-term benefits of vaccination remain underappreciated by many policymakers. The IFPMA encourages policymakers to support sustained vaccine development, access, and usage, and generating supportive evidence so their societies can realize the full benefits of effective vaccine programs.

Vaccination is one of the world's most important and cost-effective public health measures, and has wide socio-economic effects on society [4]. Despite these positive external effects there are several problems with the analysis of benefits of vaccination used in the past. The IFPMA and its members encourage policymakers to consider the real value of vaccination and to sustain an international environment that encourages progress in the prevention and treatment of infectious diseases.

First, the experience of development over the past half century shows that good health fuels economic growth. Second, typically the cost of averted infections that may occur several years later is not taken into account. Healthy children perform better at school, and healthy adults are both more productive at work and better able to tend to the health and education of their children. Third, healthier societies make stronger economies and may be stronger magnets for foreign direct investment and tourism than those where disease poses a constant threat. **Societies** benefit from 'herd immunity'. When a high percent of vaccination is achieved, communities benefit as the spread of disease declines. One generation benefits subsequent generations when eradication or elimination is achieved.

Governments benefit as vaccination complement preventive health measures, such as screening, counseling and behavior change interventions (i.e. diet modification for lower risk of heart disease, and screening for breast, cervical and colorectal cancer).

Employers benefit from a healthy, more productive workforce.

Families benefit when the main income earners stay healthy and family members do not need to make up for lost income, parents do not miss work caring for sick children, and vaccination is a 'point of contact' with the health system for the entire family for other interventions, health education and routine childhood examinations.

Individuals benefit because vaccines reduce the pain, suffering, disability and death from disease, thereby lowering individuals' costs for medical care, minimizing days of work lost due to illness or the need to care for an ill family member. Furthermore, 'herd immunity' protects vulnerable individuals, who are not or cannot be vaccinated.

Table 1: Contributions of Vaccination to Health and Well-being

1.2 Investing in New and Improved Vaccines

Investment in R&D, largely by the pharmaceutical and biotechnology industry, has resulted in a broad range of vaccines targeting over 25 infectious diseases.

During the last 30 years, vaccine development has accelerated due to scientific breakthroughs in biotechnology, genetic decoding and information technology. This resulted in new vaccines such as those against cervical cancer (human papillomavirus), meningococcal infection, pandemic-potential influenza, pneumococcal diseases, rotavirus, diarrhea, and varicella zoster [5]. Table 2 reviews recently introduced vaccines. Biopharmaceutical manufacturers continue to make significant investments to extend the range of available vaccines. This includes work on preventing infectious diseases, including those that disproportionately affect the developing world, such as HIV/AIDS, malaria and TB, while a number of vaccines now in development are designed to treat non-infectious diseases such as cancer. Table 3 provides an overview of vaccines in development by research-based vaccine companies.

Vaccine Target	Disease Impact	Vaccines	
Cervical cancer caused by human papillomavirus (HPV)	HPV is the major cause of cervical cancer, which is responsible for 240,000 deaths worldwide and affects 500,000 women each year, 80% of whom are in the developing world.	Two vaccines are available that protect against the 16 and 18 sub-types of the virus, which are responsible for 70% of HPV cervical cancers. One of the vaccines also protects against the 6 and 11 sub-types, which are responsible for genital warts.	
Meningococcal disease	Meningococcal infection can lead to meningitis. Several meningococcal sub-types exist, with subtype A prevalent in the African 'meningitis belt' causing frequent epidemics. Of those infected, between 10% and 20% die, and of the survivors 20% are likely to suffer permanent disability, such as hearing loss, mental retardation or paralysis. Subtype B is prevalent in industrialized countries. Generally, severe cases can also be caused by type C.	Polysaccharide vaccines are used during outbreaks, but are not highly effective in young children and do not result in long-lasting immunity. A number of conjugate vaccines against type C are now available whereas others targeting different subtypes are in development. A conjugate vaccine covering subtypes A, C, W and Y, which account for many cases of the disease, is also available in a number of countries. Monovalent MenA conjugate vaccine has recently been launched in the countries of the African 'meningitis belt'.	
Pandemic and pre-pandemic influenza virus	Previous influenza pandemics have resulted in large numbers of deaths. The largest pandemic of the last century, in 1918-19, caused 40-50 million deaths. Scientists predict that a future pandemic could result in millions of fatalities and cause great disruption to society.	Several vaccines have received preliminary approval for use during a pandemic, once the exact virus strain is available for production. Others based on potential pandemic strains (such as H5N1) have been developed for stockpiling or use prior to the occurrence of a pandemic.	
Pneumococcal diseases	Pneumococcal diseases are responsible for approximately 1.6 million deaths worldwide each year. Many of these deaths occur in young children, particularly in the developing world. WHO recommends routine vaccination, particularly where child mortality is high.	The first pneumococcal vaccines were based on polysaccharides and given to older children and the elderly. They we are not as effective children under 2 years old. However, new conjugate vaccines offer protection to this important at-risk group. There are now two PCVs on the market – a 10-valent and a13- valent presentation.	
Rotavirus diarrhea	Rotavirus is an important cause of acute diarrhea, and in 2004 was responsible for the deaths of over 500,000 children under the age of five, the majority of whom were in the developing world.	Two vaccines are now available and used in a number of countries. The vaccines have undergone extensive clinical testing to establish their safety, following the occurrence of rare but serious complications called intussusception with an earlier unrelated rotavirus vaccine.	
Chickenpox caused by vari- cella zoster virus	Varicella zoster virus is responsible for chickenpox, a highly contagious disease prevalent in children. Chickenpox is usually mild, but can be severe in adults and those with compromised immune systems, such as those with HIV.	Vaccines against the disease are available and are used in many industrialized countries.	
Shingles caused by varicella zoster virus	After chickenpox recovery, the varicella zoster virus remains in the body and can cause a painful skin rash commonly called shingles years later. The disease is quite prevalent, with an estimated 1 million cases annually in the US alone, most commonly in those over 50 years old.	A vaccine specifically designed to protect against shingles is available. Testing in thousands of adults showed that the vaccine can reduce the incidence of shingles by approximately half, and neuralgia was reduced by two-thirds.	

Bacterial diseases	Viral diseases	Parasitic diseases	Therapeutic treatments
Clostridium difficile Chlamydia Escherichia coli Helicobacter pylori Meningococcus B Plague Pseudomonas Aeruginosa Shigella Staphylococcus Streptococcus group A & B Tuberculosis	Cytomegalovirus Dengue fever Ebola Epstein-Barr Genital herpes Hepatitis C Hepatitis E Herpes simplex HIV Influenza (universal) Parainfluenza Respiratory syncytial virus SARS West Nile	Hookworm Leishmaniasis Malaria Schistosomiasis	Allergic rhinitis (hay fever) Alzheimer's Breast cancer Cervical cancer Cocaine addiction Colorectal cancer Lung cancer Melanoma Multiple sclerosis Nicotine addiction Pediatric tumors

Table 3: Overview of Vaccines in Development

Source: WHO/IFPMA

1.3 Global Public Private Partnerships

Vaccine manufacturers individually and through associations such as the IFPMA have a long history of working with governments, academia and nonprofit organizations to research and develop new and essential vaccines. Research-based vaccine manufacturers are a committed partner of the global immunization community, working to ensure that people in all countries have access to high-quality, safe, and effective vaccines through sustainable programs [6]. As an expression of their commitment to ensure access to healthcare in the poorest countries, research-based vaccine manufacturers, members of the IFPMA, became a founding partner of the GAVI Alliance – a global partnership launched in 2000. The many achievements notwithstanding, much work remains to be done. At the World Economic Forum in Davos, Switzerland, in January 2010, the BMGF launched the Decade of Vaccines by pledging USD 10 billion to support worldwide efforts to develop and deliver vaccines to the world's poorest children in the next decade [1]. Although this pledge could save the lives of more than eight (8) million children, this sum still does not enable vaccines to reach their full potential towards contributing to the achievement of Millennium Development Goal (MDG) # 4: to reduce the mortality rate in children under five (5) years of age by two-thirds between 1990 and 2015. Partners in the DoV know that there are crucial gaps in policy, resources, advocacy, and funding that need to be addressed. Table 4 explains why this is the right time for partners to start planning for this decade.



✓ Great progress made over the last 10 years

- An estimated 3 million deaths per year are averted by current immunizations
- Eight (8) new vaccines introduced; coverage of existing vaccines significantly expanded
- Gap significantly reduced between high and low income countries

Continued unmet need

- Vaccine-preventable diseases still account for significant mortality and morbidity
- Coverage deficits and delivery challenges, especially in rural and poorer areas

Present is promising and opportune

- Increased country ownership (and therefore greater likelihood of long-term commitment and sustainability, especially in less developed countries)
- More diseases are becoming vaccine preventable
- Information technologies combined with higher levels of education, especially among women and poor, leading to better information dissemination about vaccine benefits and more informed patient population, leading to higher rates of adoption

✓ ...But also challenges

- Difficult macro-environment
- Shifting geopolitical forces
- Turbulent economic environment

Table 4: Past Achievements and Future Opportunities for Vaccination

Source: BMGF

2 'Availability' – Sustainable Innovation, Manufacturing and Supply

2.1 Value Chain of Vaccine Development and Delivery

The value chain of vaccine development and delivery is complex and requires significant resources. Multistakeholder support and expertise are needed to advance innovative products through five stages of development as illustrated in Figure 1: (1) discovery and research; (2) development of discoveries into usable products; (3) regulatory processes to ensure product safety and licensure; (4) introduction of new vaccines into health systems; and (5) scale-up and effective use of products by populations, including post-marketing monitoring of adverse reactions. Achieving sustainable impact on public health requires successful and timely progression through the entire value chain from research to usage [7].

Vaccines are highly regulated not only because of their social importance but also because they are biological products by nature. Governments are concerned about regulating all aspects of development, including product safety, clinical testing, pricing and reimbursement, coverage under national and international health care plans and systems, patent protection, and R&D incentives. In light of the fact that societies are becoming increasingly risk averse, the regulation with the greatest impact on biopharmaceutical product development, including vaccines, is that of extensive

pre-clinical and clinical testing. This, combined with the associated soaring R&D costs and the downward pressure on market prices, make it increasingly difficult for many pharmaceutical and vaccine companies to recoup their R&D expenditures before the patent expires. The investment risks become even greater when companies develop vaccines or drugs for diseases mainly prevalent in the developing world.

2.2 Vaccine Research, Development and Manufacture

Development of the earliest generation of vaccines was to some extent empirical and involved the use of completely killed organisms, attenuated organisms or inactivated toxins. Development often took place in the absence of the specific molecular understanding of how vaccines work. The new vaccines can now take advantage of a much greater knowledge of the complexities of the immune system and of the development of powerful molecular techniques that allow targeted changes to be made in pathogenic organisms and in experimental hosts. Vaccine development has become much more sophisticated, with immunologists working closely with molecular biologists and chemical engineers to design and produce highly purified vaccines that are safe, consistently manufactured and effective.

Research

Development

Regulatory Processes

Introduction Strategies

Scaled-up Effective Use

Figure 1: Value Chain of New Vaccine Development

Product

Vaccine manufacturers must demonstrate to regulatory authorities that a vaccine is safe, efficacious and can be produced with consistent quality [8]. This involves extensive characterization of the product, provision of a suitable antigen dose and administration schedule, and the application of good manufacturing practices to show it can be manufactured in a reproducible way. Antigen dose is based on relevant immune responses in preliminary (Phases I and II) clinical studies, which also monitor the safety of the candidate vaccine. This stage of development may require the use of the vaccine in hundreds of volunteers of various ages (starting with healthy young volunteers) to determine an acceptable dose and administration schedule for the chosen vaccine formulation. In order to establish the safety, efficacy and consistency of the 'final' product studies in greater numbers of subjects using at least three vaccine lots are carried out in Phase III. Up to 100 000 study participants may be needed to demonstrate that the vaccine is safe and efficacious. Finally, the vaccine developer and manufacturer will have to collate a voluminous dossier to submit to competent national and/or supranational regulatory authorities, which will describe, in great detail, the work that has been done to substantiate the claim that the candidate vaccine is safe and efficacious for the vaccination of humans. Postmarketing monitoring is needed to detect and report any adverse events in practice.

The vaccine manufacturing process is equally complicated and capital intensive. A significant proportion is spent on quality testing and manufacturing controls to make sure the vaccines are of the highest standard. Vaccines are often based on living organisms with inherent variability. The exact molecular elements that provide protection are not always wholly understood so there are significant challenges in completely characterizing the final product. Even tiny variations in the production process may result in products with significantly different biological properties. The result is that vaccine manufacturing must follow highly defined and validated processes and quality control steps to ensure consistent production. Regulatory authorities require strict adherence to these processes, and as a result of this regime, the manufacturer's product license is intrinsically linked to the manufacturing process and its precise location. Even transferring part of the process within the same production facility requires significant testing, validation and regulatory approval.

2.3 Managing Risk: Supply, Demand and Forecasting

For vaccines, the costs and risks of technical development and clinical testing have increased over the past few decades because vaccines are, unlike traditional drugs, administered to healthy people to prevent infection and disease either immediately or at some future date. The U.S. Food and Drug Administration (FDA) estimates that it takes on average between eight and nine years to study and test a new pharmaceutical before its approval for use by the public [9]. The development of new vaccines is often more complex and takes even longer than pharmaceuticals. The Biomedical Industry Advisory Group estimated in 2006 that developing a new vaccine takes on average 18.5 years and costs over USD 500 million [10].

Reasons for rising costs of vaccines:

• R&D costs have risen significantly and tens of thousands of persons must now be tested in clinical studies in order to obtain regulatory approval instead of hundreds or thousands in the past. Authorities have become extremely prudent in granting approval because of liability issues and public pressure.

• The overall time for inventing and developing innovative medical products has increased despite all modern scientific tools and equipment being mobilized by highly-educated experts; the 'easy' diseases have been tackled but huge challenges remain for more 'difficult' diseases like TB, malaria, dengue, and HIV, which are of particular interest to developing countries.

• Because of the long lead times, the cost-of-capital must be factored in from an investment and capitalbudgeting viewpoint. It should be noted that stricto sensu the 'opportunity cost' should also be incorporated (i.e. the opportunity foregone by not developing more profitable products targeted at the more affluent markets in the world).

• Commercial returns on successful medicines have diminished (although this is more the case for drugs than vaccines). Nonetheless, the majority of products on the market fail to cover their R&D cost, leaving researchbased companies dependent on the emergence and subsequent marketing of a small number of blockbuster drugs to fund future R&D.

• From company and investor perspectives and in order to generate the necessary return-on-investment, the cost of developing and testing vaccines that never reach the market for a variety of reasons must be factored into the price of all products that do.

Given the unique complexities of vaccine development, manufacturing, and regulatory oversight, supplying current and future products takes significant time and investment to come on stream. Simultaneously, up-front investment to meet future demand requires a long-term commitment to vaccination, combined with careful planning and detailed forecasting from governments and supranational agencies. Vaccine manufacturers benefit greatly from predictable demand scenarios and mitigating demand risk through adequate forecasting.

GAVI's marshaling of significant and long-term financing for vaccines for low-income countries coupled with improved demand forecasting has provided an important signal to vaccine manufacturers that there is a substantial and viable market for vaccines in low-income countries. These producers have made significant investments and strengthened their industrial capability to become credible players in the global vaccine market [11]. Since production units carry a high fixed cost, and cannot be switched on and off easily, long-term planning and forecasting are essential to getting vaccines on the market. However, long term commitments and obligations for manufacturers, whether on price, supply, etc. need to be both reasonable in their scope and reciprocated by those procuring the vaccines. Currently, neither UNICEF nor the Pan American Health Organization (PAHO) or the novel Advance Market Commitment (AMC) financing system in support of vaccine procurement have any obligation to purchase the quantities they award

although these same quantities are binding obligations on the individual manufacturers at prices laid down in the contract.

2.4 Technology Transfer – A Collaborative Approach

IFPMA vaccine manufacturers generally are open to considering technology transfer, in particular where the necessary enabling conditions are in place. These include committed partners, a viable and accessible local market, political stability and good governance, clear local development priorities, effective regulation, availability of skilled workers, adequate capital markets, IP rights and enforcement, and a good relationship between government and industry. Because of the high degree of technology involved, such transfers ideally happen in collaboration with the original manufacturer [11].

Producing safe, high quality vaccines is complex and requires many stages of processing and purifying. The manufacturing process takes many months, sometimes even more than a year. A significant proportion of this time is spent on quality testing and manufacturing controls to make sure the vaccines are of the highest standard. Quality testing against strict pharmacopeia standards and biological product regulations is undertaken on every batch produced, at various points in the manufacturing process to avoid contamination or even minimal alterations to the product. Production under these stringent processes and strict regulatory oversight requires capital intensive manufacturing facilities, highly skilled and trained staff, and time. Experience has shown that using a stepwise process of first transferring downstream manufacturing processes prior to developing vaccine bulk production capacity has the highest probability of success. This is illustrated in Figure 2.

The quality control and testing process for a vaccine can be further complicated by different regulatory agencies that use different release criteria and require different testing methods in their specific jurisdictions. Therefore, the quality control test profile is specific to each vaccine and to each country of release. The administrative burden is enormous and harmonization of requirements is overdue [12]. While WHO's pre-qualification process generally assumes this responsibility for countries benefiting from UN and global procurement agencies, simplifying these procedures through mutual recognition of regulatory requirements will certainly need to be done over time. Under no circumstances can quality be compromised.

A stepwise approach securing downstream processes prior to developing bulk production capacity

Each manufacturer must present extensive information on the product submitted to allow qualified assessment teams to evaluate its quality, safety and efficacy. Any doubt about standards of product quality, safety and efficacy would rightfully create suspicion and massive protests by patient groups, governments and antivaccination lobbies.

Despite local industrial policy aspirations – in addition to public health motives – investment in local production must make economic sense. The decision to make or

buy a vaccine is never easy. However, both options may serve nations well in an era of global trade. Just as it would not make sense to build car factories in every country of the world, the world would not be served by going back to the times when every industrialized country had its own vaccine supplier. The result would be an inability to achieve economies of scale and an overcapacity of production. The latter may initially be beneficial to the population but ultimately pushes many firms out of business; a situation that jeopardizes supply security.

3 '<u>Affordability</u>' – Universal Access, Equity and Pricing

3.1 Reconciling Access and Innovation

In order for the general population in developing nations to have appropriate access to vaccines, existing vaccines must be affordable. At the same time, funding to reward innovation is needed to develop new and improved vaccines [13]. This presents a potential dilemma: prices that are high enough to pay for R&D can make vaccines unaffordable in developing markets. Differential pricing (also called tiered pricing or economic price discrimination) can offer a solution, at least for vaccines supplied to both the developing and developed world. Prices in affluent countries – and to a lesser extent in middle-income countries – could potentially generate sufficient revenue to pay for R&D, whereas prices in developing countries need only to cover their marginal costs.

Affordable prices do not conflict with IP rights nor vice versa. Preserving IP rights is the linchpin of achieving not only short-term (static) but also long-term (dynamic) efficiency, and structurally paving the way for sustainable access to vaccines. Patents on vaccines do not limit access to vaccines in poor countries, and thus absence of IP rights will not improve access. Nonetheless, for diseases that are endemic only in the developing world, there are not sufficient revenues from vaccines to offset the cost of R&D and investment in capacity. Hence, additional subsidies are indispensable to attract R&D for these diseases. 'Push and pull' mechanisms can create the necessary incentives to invest in vaccines for developing country diseases.

3.2 The Impact of Differential Pricing

Providing different prices to various markets is a common business practice in many industries, including airlines, retail, electric utilities and pharmaceuticals. Achieving the benefits of differentiated pricing for medicines (i.e. drugs, vaccines and diagnostics) is dependent on the global distribution. If a disease is widespread, a large proportion of the fixed R&D costs can be shared with affluent countries, provided the disease is prevalent in more affluent countries as well. This is the case for many of the newer vaccines including those for HBV, streptococcus pneumonia, rotavirus, HPV, and pandemic influenza. Another benefit of price differentiation is that it creates supply economies of scale by offering lower prices to customers who purchase larger volumes.

Differential pricing leads to a 'win-win' situation for both public and private sector stakeholders (government, business, and society). It implies that users with a higher ability-to-pay will be charged higher prices relative to users with a lower ability and willingness-to-pay. If differences in ability-to-pay or willingness-to-pay are primarily determined by differences in income level, individual companies independently applying differentiated prices would be expected to charge users with higher incomes more than those with lower incomes. It has been proven that this not only optimizes social welfare but total business revenue as well. The concept turns out to be very powerful in the health sector. Here, differential pricing aims to reduce the potential financial barriers to access to vaccines in low-income countries while simultaneously providing manufacturers with a profitable market in affluent countries. This gives companies an incentive to invest in building sufficient production capacity as well as in new product R&D.

3.3 Barriers to Differential Pricing

Individual vaccine manufacturers determine their own pricing and pricing policies independently. Differential pricing is an approach to setting prices that individual manufacturers can independently choose to employ, and many have historically done so. However, in light of the competition laws of many jurisdictions, prudence dictates that companies refrain from agreements regarding their pricing structures, even when those structures may have the effect of ensuring low pricing to the poorest countries.

Historically, a number of research-based vaccine manufacturers have opted to make their products available to the poor countries at very low prices – comparable with those of local generic firms in lowincome countries. Access to those very low prices has, the IFPMA believes, been one of several critical elements in achieving the high level of vaccination seen in the poor countries today.

Offering those very low prices has, however, been possible only because individual manufacturers have been able to recoup the significant costs invested in R&D through higher-priced sales in other more affluent markets. High income countries typically have paid the most, while middle income countries have had access to the vaccines at lower, preferential prices, be it prices above the level afforded by the poor countries and contributing to part of the R&D expense.

Looking forward, if the public health benefits of differential pricing are to be preserved, including as regards newly developed vaccines, it is up to governments and legislators to address key challenges to this approach which are emerging today. Most important, in IFPMA's view, is so-called 'external price referencing' between market segments or countries with different social and economic profiles.

External price referencing occurs when governments or procurement agencies use low foreign vaccine prices as benchmarks for regulating their domestic prices. Price referencing may, seen in isolation, help the individual purchaser push down the price it ultimately is able to procure a vaccine at, in particular where that purchaser enjoys significant buying power. However, applied in the context of vaccine procurement in developing countries the practice risks undermining individual manufacturers' ability to recoup their R&D costs, in turn creating a risk of eroding those manufacturers' ability and incentive to continue applying lower prices in less affluent markets. Faced with 'price leakage' a firm's rational response could be to instead set a single price or narrow the price band which could lead to unaffordable prices for the lowest income countries. The incentive for individual vaccine manufacturers to continue investing in vaccine supply to these regions would, with time, also risk being undermined.

These are important challenges in the context of ensuring continued supply of quality vaccines from a viable base of suppliers and the IFPMA encourages the global immunization community to promote and maintain a policy environment that leaves to individual manufacturers the possibility to differentiate prices according to the social and economic status of countries. Ultimately this will require political support especially in higher-income countries that are not offered the same lower prices.

3.4 Stimulating R&D through Subsidies

For diseases that are predominantly or exclusively prevalent in low-income countries, revenue from vaccine sales is not sufficient to offset the cost of R&D and investment in capacity. In those cases, both 'push' and 'pull' subsidies are necessary. While early-stage projects may benefit from 'push' incentives, market-based 'pull' incentive schemes often work better once proof-ofconcept has been delivered.

'Push' subsidies fund R&D directly, usually through specialized public-private partnerships aiming to develop new vaccines, or antigens, adjuvants, product formulations and presentations adapted to the needs of developing countries (e.g. easy mode of administration, thermo stability, etc.). The challenge here is to select and subsidize 'winners' early. It is important that a 'push' mechanism partnership does not discourage another manufacturer (outside the partnership) to work in the same therapeutic area. This could create a monopolistic situation, eventually putting at risk the security of supply.

Whereas 'push' funding aims to support products in the early stages of R&D, market-based 'pull' mechanisms are purchase commitments that in principle work best when the concept of a new vaccine is proven. Proof of concept usually occurs in an intermediate stage of development, somewhere along the transition between basic research and product development.

An example of a successful 'pull' mechanism is the GAVI Alliance, which through its long-term purchase commitments which signals developing countries are a viable and long-term market. However, GAVI's pull effect has not been powerful enough to stimulate the development of new, breakthrough vaccines. This is largely due to markets with limited or no buying power. To remedy this limitation, supplementary incentive mechanisms need to be mobilized. The Advance Market Commitment (AMC) model is a 'pull' mechanism designed to stimulate R&D on vaccines that would primarily benefit the developing world.

Under AMC arrangements, donors/governments make a legally binding commitment to pay a specified price for up to a specified number of doses of the vaccine, provided that developing countries commit to using the product and paying their share of the price for a number of years. If the disease is predominantly or exclusively prevalent in the developing world, e.g. malaria, TB, dengue and neglected tropical diseases, the subsidy should aim to cover the entire risk-adjusted cost of the project; for illnesses afflicting developing countries as well as affluent countries, these costs can to some extent be recovered by means of differential pricing. Thus the size of the subsidy varies depending on the disease prevalence.

The G8 leading industrialized nations expressed their support for AMC for vaccines at the inaugural conference in Rome in 2005. The appeal of AMCs to donors is that they pay only if firms successfully develop the appropriate new vaccines, whereas with push subsidies, donors pay in advance and bear the full risk of R&D failure. The IFPMA as well as individual manufacturers have expressed their support on various occasions. Meanwhile, the pneumococcal vaccine has been selected by an independent committee of experts to become the pilot project for testing this new incentive mechanism. While well-designed AMCs could play a role in mid-stage development, they are unlikely to be a practical way to drive R&D for challenging earlystage vaccines that face substantial scientific obstacles. In those cases, a combination of 'push-pull' will be necessary.

In conclusion, differential pricing alone will not stimulate R&D for vaccines that prevent diseases that are mainly prevalent in developing countries. The optimal strategy would include the use of both supply-side and demand-side subsidies, as 'push and pull' incentives reinforce each other.

4 'Adoption' – Financing Systems and Public Awareness

4.1 Achieve Sustainable Long-term Financing

Several actions are required to sustain sufficient levels of funding and supply of vaccines of assured quality. In many developing countries where vaccine preventable diseases are still a major cause of morbidity and mortality, the cost of achieving and sustaining high immunization coverage in every district and every segment of the population that needs to be vaccinated is the greatest, given the weak health care systems. There is a need for strengthening the infrastructure, and building capacity in management and policy making through training and education. Most importantly, more funds are needed to bridge the widening gap in financing. Government resources need to be mobilized, complemented by external funding from donors in industrialized and emerging economies. New financing systems need to be explored.

The IFPMA supports innovative financing mechanisms that are designed to accelerate access to vaccines in the developing world. Novel mechanisms such as the International Finance Facility for Immunization (IFFIm) and Advanced Market Commitments (AMCs) could significantly address these challenges. IFFIm issues government-backed bonds in international capital markets to fund immunization programs and to support health system improvements in low- and middleincome countries. By borrowing on capital markets, IFFIm generates immediate revenue to accelerate access to vaccinations in low-income countries, and donors make payments over a longer period of time. However, front-loading resources has created difficulties for IFFIm to secure legally binding commitments from donors, in part due to concerns about creating debt for future generations. While IFFIm supports the implementation of vaccination programs, AMC supports specific R&D programs.

These financing mechanisms will not suffice to maintain coverage at current levels for existing vaccines and at the same time support the accelerated adoption of new vaccines. Governments will have to step up their efforts. The daunting reality is that donor funding may remain flat in the next few years, if not be reduced, and the need for long-term financing of new vaccine development and utilization will increase. It is estimated that by 2030 there may be as many as 20 vaccines in routine use [13] whose application across the world might cost as much as USD 20 billion a year, a sum far in excess of the USD 1-2 billion a year currently available [15]. It is not realistic to expect from donors to contribute all the additional funds required; increased contributions from recipient countries will be essential.

4.2 Enhanced Adoption through Empowerment

In this decade, country ownership should be further strengthened. This can be facilitated by gradually switching from a 'global lead-country support' system to a 'country lead-global support' model. IFPMA members believe that increasing country ownership of immunization programs based on local priorities will improve coverage and impact. A centrally-defined fixed menu of supported vaccines should be replaced by a country's ability to prioritize among marketed vaccines based on local needs. A well-managed transition would lead to greater responsibility and accountability at the country-level. For this to happen, authorities in developed and developing countries must be persuaded that vaccinations are justified as they will need the continuous support of the electorate to spend taxpayers' money on any globally or nationally-financed vaccination program.

Stronger country ownership will result in an increase in the proportion of immunization costs met by governments, an increase in investments in health sector as a whole, and legislation assuring government financing enacted in each country. To reinforce country ownership, specific actions can be taken to support robust country planning and enhance local decision making and accountability, reduce dependencies, and facilitate sharing of best practices and tools. To improve country planning, mechanisms are needed to coordinate national immunization program inputs, ensure they are reflected in national health plans and incorporate country-specific targets. Local decision making can be bolstered through a series of institutional innovations. These include creating or strengthening of independent bodies that guide country decision making. They also include developing more effective ways for national agencies, including ministries of health and finance, to collaborate.

Ultimately these actions rely on strong political will at the highest levels. To generate political will, immunization managers and other champions of immunization programs should ensure that budgetary and policy decision makers regularly receive compelling and relevant data on immunization program performance.

4.3 Stakeholder Engagement and Advocacy

Increased public information on immunization will be required to raise the public's awareness that immunization is a vital good delivered by governments and supported by civil society organizations (CSOs). To make these institutional changes happen, CSOs, the media, academia and the private sector can act as catalysts. The Royal Society of the United Kingdom convened a meeting to review the ways in which vaccines are deployed, including an examination of adequate communication strategies [16]. A proposal was made to set up independent vaccine information institutes, committed to the improvement of public knowledge about vaccines, as information dissemination centers. However, no matter how strong the science may be and how uniform the expert consensus, the general public will remain sensitive to alarms raised by anti-vaccination movements, and will be swayed by

the opinions of friends, actions of their peers and the media. This needs to be recognized and responded to by pairing up independent and informed advisors with parents' groups, opinion leaders and media experts. They can, in turn, address any real or unfounded fears and explain the risks of vaccine apathy as well as vaccine use, adopting the spectrum of modern communication channels to which the younger generation (of parents) is most amenable.

Regrettably the prejudice against vaccines and immunization has fostered the perception that they offer great benefits but can also cause harm. Disbelievers regularly attribute all those diseases of unknown cause to vaccines and vaccination (particularly if widely used). How does one increase public trust so that vaccines are again perceived as the best insurance across different generations and geographies? It has been argued that public questioning of vaccines and decision making related to vaccine acceptance is not only driven by scientific and economic evidence, but also by a mix of psychological, socio-cultural, and political factors, all of which need to be understood and taken into account by policy and other decision makers [17].

A growing body of academic work suggests that ordinary citizens react to scientific evidence on societal risks in much the same way [18][19]. People endorse whichever position reinforces their connection to others with whom they share important commitments. As a result, public debate about science is strikingly polarized. Unless efforts are made to improve public confidence and trust in vaccination, there is a risk that gains made in combating the morbidity and mortality of infectious diseases will be lost. Improving communication programs means that we need to learn more about how to present information in forms that are acceptable to culturally diverse groups, and how to structure debate so that it avoids polarization. More research is needed to gain better insight into not just the determinants of public trust, but the mix of factors that are most likely to sustain public trust. This will be instrumental in helping define effective strategies that increasingly consider social contexts when planning health interventions.

5 '<u>Alliances</u>' – Building Strong and Durable Public Private Partnerships (PPPs)

5.1 Nature and Purpose of Public Private Partnerships

A public private partnership is generally defined as an agreement between government(s) and one or more private partners (which may include the technical operators and the funders), where the private partners deliver the service or good in such a manner that the public service delivery objectives of the governments are aligned with the profit objectives of the private partners. The effectiveness of the alignment depends on a sufficient transfer of what is called 'risk' to the private partners [20]. For an overview of definitions, see Table 5: Definitions of Public Private Partnership.

The distinguishing feature is the focus on what is understood by 'partnership'. Some critics object to the use of the term partnership in 'public-private partnerships'. They argue that partners share the same objectives whereas in a PPP, the public and private partners, given their different natures, do not: 'the objective of the private sector is to make a profit, whereas governments deliver services to their citizens'. Undoubtedly, this is too narrow of an interpretation of partnership. It denies the reality of corporations acting as good corporate citizens [21]. The argument also brushes aside the fact that public sector work comes at the expense of taxpayers' money. Moreover, while it is relatively easy for governments to measure their input in setting-up and running a variety of social and economic programs, governments often have great difficulty in measuring efficiency output.

The true advantage of PPPs can be found in their ability to increase efficiency and to manage risk through cooperation between public and private stakeholders. PPPs can be situated on a spectrum that represents all possible combinations of public/private involvement in its various forms of service or goods delivery, classified according to the risk allocation between these parties. In the case of products (e.g. vaccines), the government typically sets the quality and quantity required, and allows the private partner to design and manufacture the asset (e.g. R&D facilities and production plants). Leaving the design to the private partner creates room for the public sector to improve the level of efficiency and cost-effectiveness of the ultimate service that must be provided (e.g. immunization). If the government prescribes the design or builds the asset, and assumes the role of innovator, it would have to carry the risk resulting from faulty design.

Governments nowadays prefer to leave that risk, as well as the possible efficiency gains or failures, to the private partners. Firms will try to manage risk factors in such a way that actual outcomes diverge from the expected (or most likely) outcome. Managing risks in a competitive environment drives companies to be technically efficient (obtaining maximum outputs with minimum inputs), while at the same time being X-efficient (preventing the wasteful use of inputs).

5.2 Creating Effective Partnerships

To understand global issues regarding health, the environment, and climate change, observers usually divide the associated organizations into three sectors: government, business, and civil society organizations. No one sector has the capacity or legitimacy to solely address these challenges and find sustainable solutions because these challenges generally cross sectors. Consequently, the pressure on entrepreneurs and leaders in each sector forces them to work together in multi-sector collaborations; sometimes called crosssector collaborative partnerships [22][23][24].

Traditionally, private actors such as firms or NGOs were not acknowledged as subjects in international bodies and their governance. More recently, however, alternative schools of thought have contributed to the formation of global governance structures that have a more balanced stakeholder membership. Increased recognition for the importance of corporate social responsibility, companies able to contribute to improved global health should be part of the global governance structure of PPPs. • OECD (2008): defines a public-private partnership (PPP) as an agreement between the government and one or more private partners (which may include the operators and the financers) according to which the private partners deliver the service in such a manner that the service delivery objectives of the government are aligned with the profit objectives of the private partners. The effectiveness of the alignment depends on a sufficient transfer of risk to the private partners.

• International Monetary Fund (IMF, 2006:1 and 2004:4): 'public-private partnerships' refer to arrangements where the private sector supplies infrastructure assets and services that traditionally have been provided by the government. In addition to private execution and financing of public investment, PPPs have two other important characteristics: 1) there is an emphasis on service provision, as well as investment, by the private sector; and 2) significant risk is transferred from the government to the private sector. PPPs are involved in a wide range of social and economic infrastructure projects, but they are mainly used to build and operate hospitals, schools, prisons, roads, bridges and tunnels, light rail networks, air traffic control systems, and water and sanitation plants.

• European Commission (EC, 2004): 'public-private partnership' is not defined at the community level. In general, the term refers to forms of co-operation between public authorities and the world of business which aim to ensure the funding, construction, renovation, management and maintenance of an infrastructure of the provision of a service.

• **Standard and Poors:** 'public-private partnership' is any medium- to long-term relationship between the public and private sectors, involving the sharing of risks and rewards of multi-sector skills, expertise and finance to deliver desired policy outcomes (Standard and Poor's, 2005).

• European Investment Bank (EIB, 2004:2): 'public-private partnership' is a generic term for the relationships formed between the private sector and public bodies often with the aim of introducing private sector resources and/or expertise in order to help provide and deliver public sector assets and services. The term PPP is thus used to describe a wide variety of working arrangements from loose, informal and strategic partnerships, to design-build-finance-and-operate (DBFO) type service contracts and formal joint venture companies.

Table 5: Definitions of Public Private Partnership

Cross-sector collaborative relationships (CSCR) represent a revolution in governance. Part of what is revolutionary is that the governance of CSCR is not 'housed' in any one of the collaborating organizations or sectors. The governance occurs 'above' the existing organizations and individual sectors. Another revolutionary aspect is that no one sector controls the governance. In different aspects of the project, one sector may provide more capacity or legitimacy than others. Overall no one sector dominates. Each sector needs the other, and each can stop the project by withdrawing. Executive decision-making is customarily done by consensus, rather than casting votes where the majority then wins.

Unsurprisingly, these sectors are defined by conflicting ideologies, different logic, and conceivably distrust of one another [25]. However, there has been much cross-learning over the past decade. Cross-sector communities will work only if organizations of each sector recognize the others' values. In that regard, business has come a long way in terms of corporate social responsibility (i.e. ecological standards, environmental protection, health and security, etc.). Many civil society organizations (CSOs) understand the importance of value creation – through efficiency and profit – in the business sector. Government sees its role as a convener and enabler of sound principles promoting sustainability.

In sum, the richness of PPPs lies in the active participation of the main stakeholders. Board members engage in its governance through a process of balanced strategic decision-making, innovation and partner collaboration. Given its collaborative structure, however, conflicts of interest are an unavoidable reality in PPP operations. Potential conflicts of interest among members of the Board, Executive Committee, and Advisory Bodies involved in decision-making can be resolved by a conflict of interest policy, which the Governance Committee should draft and defend. As a result, PPPs are able to properly manage any perceived conflict and thus mitigate the operational and reputational risks inherent in such conflicts.

6 Conclusion

The IFPMA vaccine manufacturers can play a significant role as a partner in global health with its know-how, expertise and proven track record of inventing and producing high-quality vaccines for the populations of developed and developing countries. For many years IFPMA members have supplied high-quality vaccines for use in the developing world at preferential prices negotiated through international agencies such as UNICEF and are committed to further increasing access to vaccines through equitable pricing. Experience shows that applying differential pricing as a model carries significant potential for making vaccines affordable on a large scale in developing countries, while preserving incentives for R&D. The result is a win-win for consumers and suppliers. In this decade, there will be opportunities to transform the dynamics of the immunization environment such that population and government demands become stronger and national capacity and self-reliance in decision making are enhanced. Achieving this transformation will require renewed and increased communication efforts that are supported by social science and communications research to identify the barriers and drivers of vaccination with the objective to define the most effective strategies in each context. Most importantly, it is recommended

that a comprehensive qualitative and quantitative assessment is made on how to address the future finance gap. Despite its considerable resources, the Gates Foundation will not be able to fund the proposed expansion in vaccine coverage on its own, but its financial commitment should act as an incentive for donor governments to provide the additional funds to achieve 90% coverage with childhood vaccines within the next 10 years.

Being a key member of public private partnerships, the IFPMA vaccine manufacturers collectively and individually are committed to increasing availability, affordability and access to vaccines, including those that are underused or newly introduced. Present and new alliances that build on a strong and longlasting partnership between vaccine manufacturers, governments, public health authorities, CSOs and international organizations, provide a sustainable pathway to controlling vaccine-preventable diseases and deliver on the promise of the Decade of Vaccines. Through such partnerships, children in poor countries benefit from lower vaccine prices, increased access, and a sustainable stream of innovative products.

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