A STRATEGIC ANALYSIS OF VACCINE ACCESS FOR DEVELOPING COUNTRIES

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Abstract

Vaccination has been one of the major successes in global health, providing a cost-effective method of reducing morbidity and mortality. However, middle- and low-income countries are often unable to access newer vaccines in a timely manner. This analysis outlines market-influenced solutions that address the inequity.

First, the current state of the vaccine industry and the roles of manufacturers are examined, and then the impact of innovation on the industry is assessed. High-, middle- and low-income country markets are compared. Finally, an assessment is made of the models that increase vaccine access. The industry, innovation impact, market and access model analyses lead to a proposal of a complementary strategic plan for improved vaccine access for developing countries. This analysis defines the key success factors for future vaccine development and manufacturing that will equilibrate vaccine use across the globe.

Dedication

We remember fondly biotechnology colleagues we lost too soon- David Fanning, Lee Adams and Cecelia Suragh.

This is also dedicated to our amazing parents, and to the memory of Aruna's father, who encouraged us in everything we do.

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List of Abbreviations

B- Billion
BMGF- Bill & Melinda Gates Foundation
BRIC- Brazil, Russia, India, China
CAGR- Compound Annual Growth Rate
DPT- Diphtheria, Tetanus, Pertussis combination vaccine
ECBT- Every Child By Two
EMEA-European Medicines Agency
EPI- Expanded Immunization Program
FDA- US Food and Drug Administration
GDP Gross Domestic Product
GAVI Global Alliance for Vaccine Initiative
GNI- Gross National Income
GMP- Good Manufacturing Practice
GPEI- Global Polio Eradication Initiative
GSK- Glaxo Smith Kline
Hep B- Hepatitis B
Hib- *Haemophilus Influenzae* Type B
HIV- Human Immunodeficiency Virus
HPV -Human Papillomavirus
IVI- International Vaccine Institute
JV- Joint ventures
M- Million
MPL- Monophosphoryl Lipid A
MVC- Multinational Vaccine Company
NFP- Not-For-Profit
NRA- National Regulatory Agency
PATH- Program for Appropriate Technology in Health
R&D- Research and Development
TB- Tuberculosis
UK- United Kingdom
UN- United Nations
UNICEF- The United Nations Children's Fund
US- United States
WHO- World Health Organization
VICP- Vaccine Injury Compensation Program
VLP- Virus-Like Particles

1: OVERVIEW

1.1 An Introduction to Vaccines

Vaccines are biological preparations used to prevent or limit disease. They trigger an immune response within the body. As a part of this response, an immune 'memory' is formed to respond to any future encounters with the disease agent. Vaccination began with Edward Jenner's use of cowpox, which protected against the related smallpox virus. In 1796, Jenner inoculated a young boy with cowpox from a lesion on a milkmaid's hand. He later administered smallpox to the child, who did not become infected with the second pathogen (Sprang, 2002). The results of similar treatments with 23 other individuals were published, giving widespread acceptance to this revolutionary medical technique. The root of the word vaccine comes from this first treatment, originating from the Latin word for cow, *vaca*.

The human immune system is a complex regulatory and surveillance network of interacting cells, tissues, and proteins, designed to respond and provide protection against foreign materials that enter the body. The immune system is stimulated by an encounter with an antigen. Antigens are components of disease causing agents, which can be introduced through immunization. When pathogens gain entry into the body for the first time, "antigen presenting cells" break them down and display components of the agent on their cell surface. In turn, antigens activate other immune cells, namely T and B-cells; they transform and seek to inactivate the intruder. In the first response to a pathogen, immune memory is created. This results in an enhanced response to subsequent exposure to the pathogen. In the event that a particular disease agent gains access to the body, the immune system responds specifically

within a matter of hours, rather than days or weeks. Immune memory is the basis for vaccination.

Though Jenner demonstrated the effectiveness of cowpox vaccination in protection against smallpox, development of additional vaccines did not materialize until almost 100 years after his discovery. In the late 1800s, Louis Pasteur and Robert Koch demonstrated that microorganisms cause infections in humans. They further demonstrated that unique microorganisms cause specific diseases. This understanding provided the rationale for using attenuated microorganisms to create vaccines. Attenuated vaccines are produced by culturing viruses or bacteria under conditions so that they lose their virulence, but still have the ability to invoke an immune response. Other vaccines utilize inactivated microorganisms or non-replicating components of the agent. Types of common vaccines include:

- Attenuated (weakened) live viruses
- Inactivated (killed) viruses and bacteria
- Toxoid vaccine (toxins produced by bacteria)
- Genetically engineered viral or bacterial components

An immune response to an infection can take several days or weeks. This delay can be long enough to allow the disease to manifest itself. However, if the agent or a component of it has previously challenged the immune system, the response is faster and stronger. The body can react before the disease is caused. Immune memory can last for years, but some vaccines need repeated doses to maintain the immunity after the initial vaccination. Today, there are over 30 vaccine-preventable diseases. The most common are listed in Table 1.

Table 1: Vaccine-Preventable Diseases (2009)

Cervical Cancer	Pneumococcal infections
Chicken Pox	Poliomyelitis
Cholera	Rabies
Diphtheria	Rotavirus
Haemophilus influenzae type B	Rubella
Hepatitis A and B	Shingles
Japanese Encephalitis	Smallpox
Influenza	Tetanus
Measles	Tuberculosis
Meningococcal group A & B	Typhoid fever
Mumps	Varicella
Pertussis	Yellow Fever

Source: Adapted from WHO, 2009a.

1.2 Social and Economical Benefits of Vaccines

As shown in Table 2, vaccination is one of the greatest public health achievements in the 20th century. Through immunization, smallpox has been completely eradicated. In addition, rubella, tetanus, measles, diphtheria, *Haemophilus influenzae* type B (Hib), and number of other infectious diseases have been controlled worldwide.

Table 2: Annual Infectious Disease Morbidity in 20th Century and 2008

Disease	20th Century Annual Morbidity	2008 Total	% Decrease
Diphtheria	175,885	0	100
Measles	503,282	132	99.9
Mumps	152,209	386	99.9
Polio (paralytic)	16,316	0	100
Rubella	47,745	17	99.9
Smallpox	48,164	0	100
Tetanus	1314	15	98.6

Source: Adapted from Red Book, 2009.

The social and economic benefits of vaccination are numerous. In addition to protection from death or severe acute illness, vaccination prevents the lifelong after effects of some diseases. Long-term morbidity is exemplified by polio, whose survivors often suffer from permanent paralysis. The Global Polio Eradication Initiative (GPEI) has already saved the lives of hundreds of thousands of children and has prevented additional children from developing serious disability from paralytic polio (GPEI, 2010). In countries where manual labour is the predominant form of livelihood, such a disability would completely curtail an individual's ability to earn a living, creating a significant burden to society as a whole. Supplementary human resources would be needed to support such individuals. Additional costs would be incurred, such as the cost of reduced quality of life and societal ostracism, both of which cannot be easily calculated in terms of monetary value. Successful vaccination programs can prevent other long-term morbidities. Measles infection can damage the brain, hindering a child's cognitive ability. Children free from such a disease could attend school regularly and would possess a greater potential for learning.

The cost-benefit analysis for vaccines compares the total costs and benefits to determine the net social advantage (Boardman, Greenberg, Vining & Weimer, 1996). Parameters include direct medical costs of disease treatment, indirect costs of lost productivity, and intangible costs such as pain and suffering against the medical costs of vaccine administration. Vaccination minimizes care costs and allows transfer of resources to the treatment of unpreventable diseases. The extension of life expectancy for vaccinated individual means that citizens are able to contribute for a longer period to the economic output of a nation. When child mortality drops, there is a concomitant drop in the birth rate. It costs less to treat children for illness who are not already sick with vaccine- preventable infections. Healthy communities and countries are in a better position to attract foreign investments and capital from tourism.

Lastly, immunization of a sufficient majority of the population –good 'vaccine coverage'- provides 'herd immunity' that prevents epidemic outbreak of diseases. Between 1967 and 1977, $1.35 B annually was saved worldwide through a smallpox eradication program (Barrett, 2004). In the US, every dollar spent on vaccines avoids $6.30 of direct medical cost, which, in aggregate for the nation, is $10.5 B. When potential indirect costs, loss of work, disability and death are included, this figure increases to $18.40, or an aggregated social benefit of $42 B (Every Child By Two, 2010). In 2000, when pneumococcal conjugate vaccine Prevnar 7 was first introduced, its cost-effectiveness analysis was projected. This study found that vaccination of healthy infants with Prevnar7 would prevent more than 12,000 cases of meningitis, 53,000 cases of pneumonia, 1 million episodes of otitis media, and 116 deaths. The analysis showed that the vaccination program will avoid US $342 M in medical treatment and $415 M for work-loss and indirect consequences of illness (Lieu et al., 2000).

Immunization is unparalleled in providing a cost-efficient improvement to overall welfare. Nevertheless, a drive towards universal vaccination coverage for all vaccine-preventable diseases will be a difficult task due to the high price of novel vaccines. Vaccines under patent protection can command supplier driven prices. Until 10 years ago, the only vaccines on the market were low-margin commodity products and many companies exited the business. Research and development (R&D) costs for current vaccine candidates are on the rise, as major causes of disease such as TB and HIV have eluded traditional methods of vaccine generation. This paper will review potential solutions to this problem of access.

1.3 Access in High-, Middle- and Low-Income Countries

Access to vaccines remains highly differentiated across the globe. The key factor of differentiation is the income level of the country. The World Bank classifies countries based on per capita Gross National Income (GNI) as follows: high-income, $12,196 or more; middle-income, $996 - $12,195; and low-income, $995 or less (World Bank, 2010a). In most high-income countries such as the US, public health initiatives are sufficiently supported to allow rapid incorporation of new vaccines into the public health plan. For example, GSK's Cervarix for the prevention of Human Papillomavirus (HPV) retails for approximately $125 /dose and yet received national government orders from both the UK and the Netherlands in 2009. The European Medicines Agency (EMEA) gave regulatory approval for sale of the vaccine in late 2007 (GSK, 2007).

In contrast, low- and middle-income countries have often gained access to new vaccines 10 or more years after their introduction in developed world markets. This is due to relatively limited medical infrastructure as well as the high initial cost of new vaccines. Most vaccines require both cold storage and medical staff who can administer them. New vaccines have been

introduced at prices that are as much as 1000 times the cost of older commodity vaccines (CDC, 2010c; UNICEF, 2010c).

Over the last 10 years, the Global Alliance for Vaccines Initiative (now the GAVI Alliance) has facilitated vaccine access for low-income countries. The mandate of GAVI was to improve vaccine access to new and underused vaccines in the developing world, and it has had significant success in this regard. The success of GAVI was achieved in part by consolidating vaccine purchases and leveraging the resultant buying power to negotiate lower prices on new vaccines. Some key manufacturers have been willing to price differentiate in exchange for access to a much larger market and stable demand.

GAVI only provides support for countries that had an annual GNI per capita of less than US $1000 in 2003. Some emerging economies may be just over this income threshold, but their limited healthcare budgets make purchasing newer vaccines impossible. Some more populous countries have been able to remedy this by negotiating intermediate prices due to a large market size. Others have developed competitive national vaccine industries able to reverse engineer vaccines at low margins. Nevertheless, many mid-income countries have had to forgo the purchase of newer vaccines in their public health budget. For these countries, citizens with sufficient income purchase innovative vaccines privately. In addition, GAVI has not yet provided support to any country for some of the newest vaccines, such as those protective against rotavirus. As a result, few low- or middle-income countries have had access to these vaccines.

1.4 Organization of This Analysis

This analysis will address methods to improve access to vaccines for low- and middle-income countries. An overview of the global vaccine industry will follow this chapter. There will be a high-level analysis of the five dominant Multinational Vaccine Companies (MVCs). The

chapter will also review a sampling of mid-size vaccine manufacturers who occupy uniquely valuable niches in the industry. We will then review current innovations in vaccines, and the strategic impact of innovation on the industry. As the focus of this paper is on models of improved vaccine access in low- and middle-income countries, an in-depth industry analysis will not be a component of the document. We will then review the different vaccine markets as defined by their income level. Lastly, we will move to an analysis of models for improved vaccine access in low- and middle-income countries, and propose a new model for the future.

2: THE VACCINE INDUSTRY

In this chapter, we will provide an overview of the vaccine industry. A brief history of the vaccine value chain and factors influencing the vaccine supply are discussed. Finally, we will introduce the five MVCs and a sampling of mid-size companies, looking at their products, innovations and collaborations. Aspects that pertain to developing world vaccine access will be highlighted.

2.1 Current Industry Overview

For much of the 1980s and 1990s, vaccines were low-margin commodity products. Low-cost vaccines designed to prevent childhood infectious diseases were predominant. The targets for these vaccines were for diseases such as diphtheria, polio, tetanus, mumps, rubella, and measles. These infections most acutely affected developing countries with a limited ability to purchase medication. Price pressure from governments and public-health organizations with strong buying power lowered revenue potential. A number of adverse events associated with vaccines generated negative publicity. Consequent litigation costs made the industry unattractive, and many firms exited as a result.

Over the last 10 years, a number of factors have begun to increase revenue potential and attract new entrants. Some of these factors include rapid uptake of new vaccines to disease agents affecting high-income countries, introduction of new technologies allowing competitive differentiation, and support or subsidy from wealthy governments for vaccine manufacturers. Today, vaccines are the fastest growing drug class, with predicted global revenue of US $52 B by 2016 and a compound annual growth rate (CAGR) of 11.5% (Taylor, 2010). Even with these

attractive attributes, the industry is highly concentrated. Five major pharmaceutical companies - GlaxoSmithKline (GSK), Merck, Novartis, Sanofi Pasteur, and Pfizer (formerly Wyeth) - hold 85% of the global vaccine market. Dominance by these five MVCs means that industry competition and turnover are low. With a limited number of firms producing the majority of vaccines, there is a high probability of fluctuating manufacturing capacity and vaccine shortages. This is most problematic when a single company produces a vaccine. In 2006, only one of the paediatric vaccines was made by more than two suppliers; seven of the vaccines were made by a single company (CBI, 2006).

2.1.1 Industry Downturn and Re-emergence

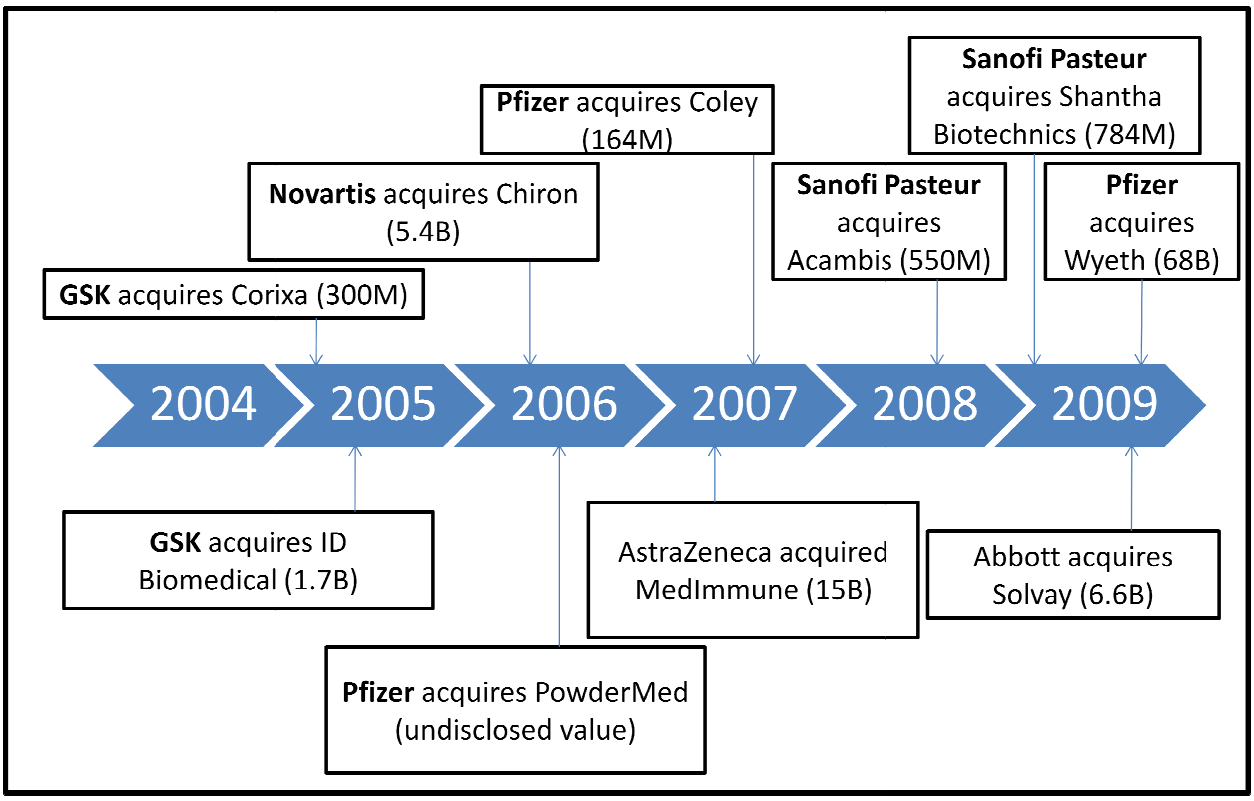
Just over thirty years ago, the landscape of the vaccine industry was markedly different. There were 25 vaccine companies serving the US market; 14 of these companies distributed their products internationally (Lancet Infectious Disease, 2004). Between 1988 and 2001, ten of the paediatric vaccine manufacturers reduced or completely halted production. Old vaccines lost margins as their manufacture was usually simple and barriers to market entry were low. It was not lucrative to develop new vaccines targeting diseases that predominantly affected low-income countries. These countries could not afford the margins typical for new pharmaceutical products. When neurological harm was linked to the DPT vaccine, the resultant lawsuits contributed to all but one of the major manufacturers exited the market (Sugarman, 2007). The combination of the threat of new entrants, rivalry among existing manufacturers, high buyer bargaining power led to an industry that was unattractive. Ann effective monopoly was created for several vaccine manufacturers (Porter, 2008).

In recent years, technological advances, interest in controlling health budgets and legislation protecting vaccine producers from liability has lead to renewed interest in the vaccine

industry. Two new vaccines, Prevnar and Gardasil, exceeded US $1 B in revenue; this new profit potential led to a surge in vaccine companies and the development of new vaccines (CNN Money, 2007). As major producers face the threat of new entrants, they have moved to strengthen their vaccine value chain by acquiring relatively mature vaccine related technologies from other companies.

Figure 1 shows the major acquisitions that took place within the past decade. Pfizer chose to enter into the vaccine industry through several major acquisitions; Powder Med, Coley, and the US $68 B acquisition of Wyeth in the last 5 years were all part of this strategy. When Pfizer's flagship drug *Lipitor* goes off patent in 2011, it will lose much of its annual US $12 B in revenue (Randall & Pettypiece, 2009). The acquisition of Wyeth's pneumococcal vaccine franchise will likely offset some of this loss. Prevnar 13, the second-generation pneumococcal vaccine, is Pfizer's biggest product launch for 2010 (EP Vantage, 2010). Novartis also entered the vaccine industry, with the acquisition of a significant vaccine manufacturer. Sanofi Pasteur's acquisition of India's Shantha Biotechnics meant access to manufacturing capabilities and market share in emerging economies for the MVC (Martino, 2009).

Figure 1: Vaccine Industry Major Acquisitions in the Past Five Years



Source: Adapted from acquisition press releases.

2.1.2 Factors Influencing Vaccine Research and Development

Despite improved market conditions, there remain significant factors discouraging vaccine development and manufacturing. These include high development costs for new vaccines, the re-emergences of liability issues, and price control by governments and supranational organizations.

Development of a vaccine can take 12 to 15 years and cost an estimated US $1 B. Once the vaccine is developed, manufacturing, storage, and cold chain management add considerable additional expense. Each type of vaccine needs unique manufacturing and fill/finish facilities; moreover, they must meet the standards set by one or more regulatory bodies. With this level

of stringency, the costs per unit also increase. The cost of building and maintenance is incurred regardless of the number of vaccine units produced. Vaccines are administered in a limited number of doses, reducing the market potential. Hence, the demand for a vaccine needs to be sufficiently large to justify the fixed-cost associated with it.

Healthy individuals receive vaccines. As a result, any temporally associated adverse events are likely to be attributed to the vaccine. Children are the most common recipients, and products that may cause them harm face severe response. In 1988, the US government set up a Vaccine Injury Compensation Program (VICP) to address claims against vaccine manufacturers. The "Vaccine Court" examines the claims for a true causal relationship to the vaccine. Compensation is awarded from a trust funded by an excise tax applied against each dose of the vaccine administered in the US (Sugarman, 2007). While this addressed the risks of litigation for some years, more recently, claimants have tried to circumvent the process. On March 8, 2010, the US Supreme Court agreed to hear a case in which the vaccine manufacturers were sued directly (USA Today, 2010). These lawsuits are mentioned in the annual reports of all the MVCs involved as a risk to their business.

Governments have increasingly stringent criteria that a pharmaceutical product must meet to be purchased for the public health system. In 2008, the UK government appeared to purchase Cervarix for HPV disease prevention due to its lower cost over Gardasil. This was despite the fact that Cervarix may have offered inferior protection (Boseley, 2008).

In this financial landscape, only well established multinational pharmaceutical companies have sufficient resources to take a novel vaccine through to the market. With high development costs, vaccine manufacturers need to charge a premium to recover the costs of their innovation. Demand therefore has to be strong in high-income countries. The result is that vaccine development by MVCs does not occur for diseases that predominantly affect medium

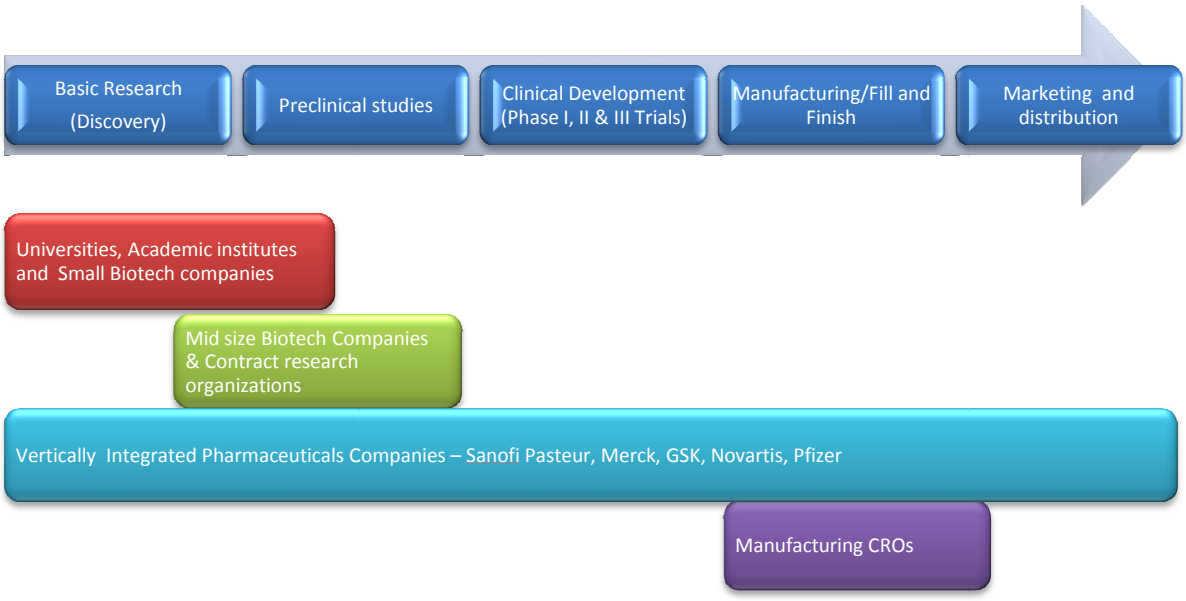
and low-income countries. In recent years, private philanthropies, governments, and public-private partnerships have attempted to remedy this by funding such vaccine R&D.

2.1.3 Vaccine Development Value Chain

Vaccines are complete pathogenic organisms or complex biological derivatives of an organism. They are designed to stimulate the immune system and prevent disease. Both drug and vaccines follow a complex development process. Each phase in this process is increasingly expensive; however, development risk decreases with each stage.

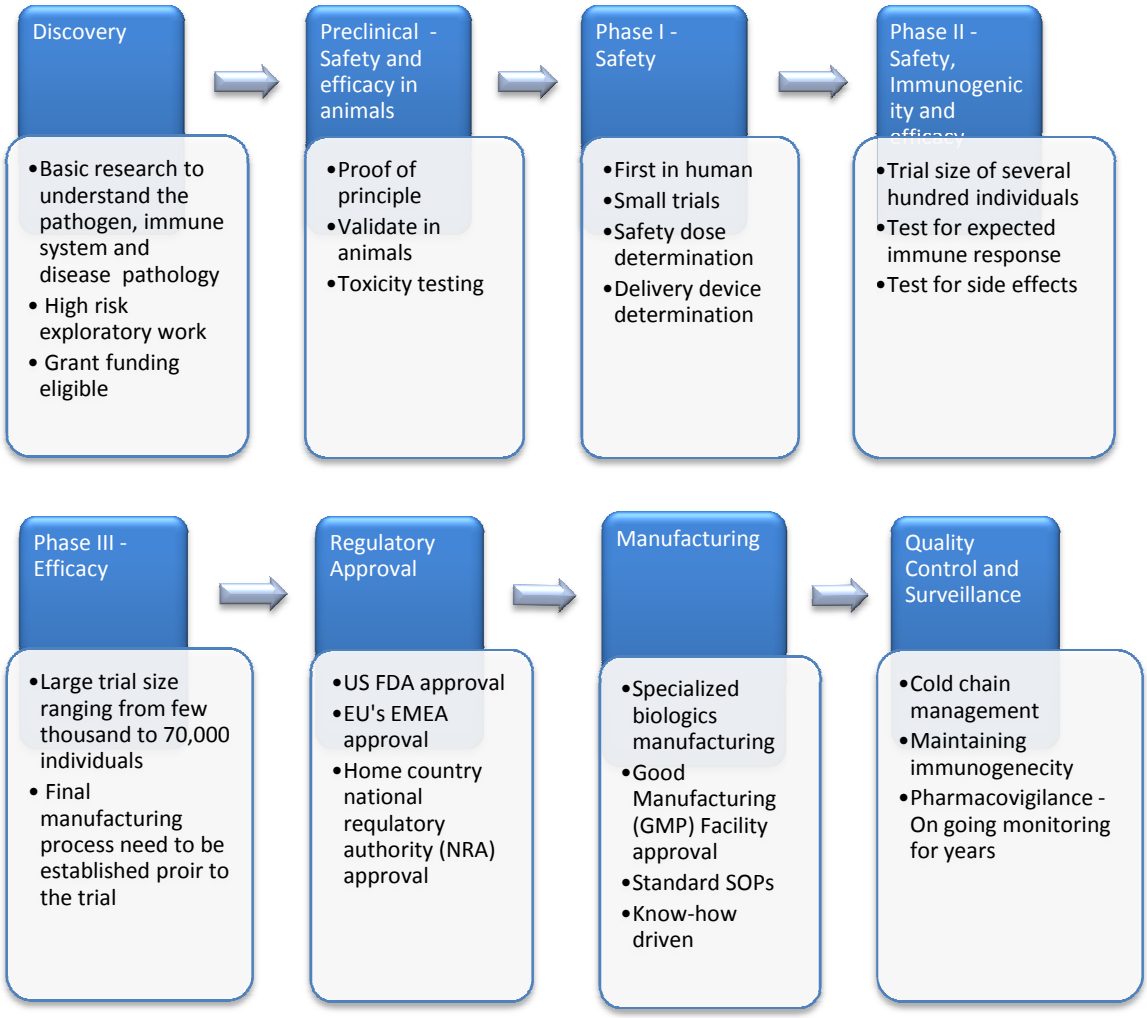
Five major companies have developed capabilities in each stage of the vaccine value chain (Figures 2 & 3). These firms possess resources and knowledge to take a vaccine from discovery stage to the clinic independently. However, public sector university and government laboratories often play a pivotal role in identifying potential vaccine candidates through basic research.

Figure 2: Vaccine Industry Value Chain



Source: Authors

Figure 3: Steps in Vaccine Development Process



Source: Authors

Small biotechnology companies also play an important role in the earliest stages of vaccine development. They may also contribute by translating discovery into a proof concept in preclinical cell line or animal models. Most of the development programs fail in the preclinical stage, increasing the risk of investments in the work. Biotechnology companies pose an innovation challenge to the MVCs in all aspects of vaccine development. In chapter 3, we will discuss their innovations in immunogens, and manufacturing and delivery devices. However,

most often the companies must collaborate with MVCs as they enter clinical trials. Similar to the pharmaceutical industry, these large companies depend on smaller biotechnology companies to fill the development pipeline. Most commonly, new vaccine development projects enter the MVC pipelines through partnerships or outright acquisitions. Usually, no more than two MVCs compete on a particular vaccine indication. However, there is competition between biotechnology companies for partnership or acquisition opportunities with MVCs.

The majority of biotechnology companies lack the resources or the skills needed to advance into the later phases of clinical trials. The size of clinical trials for vaccines can range from a few thousand to 70,000 people (IRIN, 2009; FDA, 2010). Most of these studies are in multiple countries. Clinical trials require the training of health care workers, recruiting test candidates, and managing test sites and trial data. All of these necessities are expensive and become even more complicated when the studies are run in different population demographics. Even with their internal capabilities, MVCs sometimes outsource trial management activities to specialized clinical trial CROs.

Manufacturing is another expensive and critical component of the value chain. Vaccine production must occur under Good Manufacturing Practices (GMP). Many countries have national GMP standards, and the WHO provides several guidance and training documents for products purchased by the WHO (WHO, 2010g). The International Conference on Harmonization works to standardize GMP guidelines globally, but different criterion fulfilment may be needed for different countries. The five MVCs can leverage their knowledge of GMP from their pharmaceutical product lines. For smaller entities, GMP requirements create another barrier to entry into the vaccine industry.

Vaccines require approval by national regulatory agencies (NRAs) before they are made available to the public; this regulatory process is very stringent. The product candidate must

clearly demonstrate efficacy, safety, quality, and good manufacturing processes in order to gain approval. The US Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) is always a first choice for MVCs. Mid-size vaccine producers often choose to gain approval from home country NRAs. Approval by a home country regulatory agency recognized by the WHO is a critical step towards entering the UN agencies Vaccine market. As UNICEF purchases 40% of the global vaccine doses for all diseases, this provides significant return potential (UNICEF, 2010a).

All vaccine development programs follow the process described above. Often, multiple public and private entities contribute to the vaccine value chain at specific steps. In the following section, we will examine how a constant vaccine supply is maintained.

2.1.4 Maintaining Vaccine Supply

In the 2000s, there was a shortage of eight of the eleven vaccines administered to children. In 2004, there was a major influenza vaccine shortage due to manufacturing problems at Chiron (CNN Money, 2004). These supply crises reflect the industry's high concentration of manufacturing capabilities. Vaccine manufacturing is a complex and sensitive process. Unlike manufacturing a chemically synthesized pharmaceutical agent, slight changes in raw materials or even the environment can pose threats to the production of biological molecules. One particularly illustrative example is the production of the influenza vaccine. This process includes injecting live viruses into fertilized chicken eggs, collecting the virus-infected liquid inside the egg and then inactivating the virus with formalin treatment. Viruses produced in such a manner are incapable of causing a natural infection but elicit an immune response. This process is inefficient, needing 6 months of production time and two eggs to produce a single dose. Furthermore, no two eggs will have the same production capacity (Bond, 2009). Different

strains of influenza may also require different conditions to be cultured efficiently in eggs; this was the primary reason for the significant delays in production of H1N1 pandemic vaccine in the fall of 2009. There are similar issues with the yeast system used for HPV vaccine, Gardasil. For these reasons, new technologies such as recombinant-protein-expression systems are being developed. With time, these new technologies will be integrated into the formulation for any new vaccine. These innovations will be assessed in more detail in Chapter 3.

Older vaccines are candidates for reformulation to improve potency, safety, and tolerability. In the case of inactivated polio vaccines, the addition of an immunostimulatory adjuvant may reduce the dose needed by 90% (PATH, 2010a). There is a 10% overfilling in vials to ensure a full dose is delivered. Some manufactures have been successful in reformulating vaccines into single dose delivery devices, extending the vaccine supply and strengthening the company's competitive advantage. Despite the benefits, reformulations require a change to the manufacturing process and even new facilities. Hence, new state-of-the-art manufacturing processes will be developed only if there is an attractive cost-benefit equation. The capital cost required for a manufacturing plant is an estimated 60% of vaccine production expense (Danzon, Pereira & Tejwani, 2005). MVCs have strong buying power and thus benefit from economies of scale on raw materials and services. Multinationals have built large production capacity for a chosen formulation and delivery device; therefore, switching costs are extremely high.

To date, Sanofi-Pasteur is the only MVC to have brought an old vaccine into a new delivery device. It was redesigned to differentiate the product in the competitive influenza vaccine market.

Contract Manufacturing Organizations (CMOs) play a significant role in the vaccine manufacturing industry. These CMOs has developed specialized proprietary manufacturing processes that can address unmet production needs. Companies who engage in CMO activities,

such as Crucell, have established partnerships with multiple MVCs due to the efficiency of their proprietary manufacturing process (Crucell, 2010a). Since there are a limited number of vaccines manufacturing CMOs, the demand for their services is high. Even though there are few companies able to provide this service, capital costs and operational complexities deter new companies from entering the market. Only a few CMOs are able to offer multiple services. This is particularly problematic for biotechnology companies with limited access to manufacturing. Manufacturing methods must be determined early in the development process because, once locked in, switching costs are high. Biotechnology companies must therefore risk purchasing services from a CMO or partner with a MVC to access their manufacturing capacity.

Some CMOs are beginning to reverse integrate on the vaccine value chain. CMOs in BRIC countries have built manufacturing capabilities over decades and are moving toward proprietary development of vaccines. India's Shantha and the China National Biotech Group are developing a new vaccine candidate for rotavirus in conjunction with the non-profit organization PATH (PATH, 2010b). Such ability to reverse integrate may limit contract capacity as CMOs favour their own candidates. Even when there is capacity available in other parts of the world, differences in regulatory standards can limit the ability to manufacture elsewhere.

The lack of additional capacity for vaccine manufacturing also limits an effective response in the case of a sudden need; this was evident during the recent shortages in the recent swine flu pandemic and the SARS outbreak in 2003. Capacity issues present a major challenge to vaccine supply, but currently the costs of switching to methods that are more efficient prevents MVCs from doing this without external subsidies.

Both MVCs and medium-sized companies in developing countries contribute to the current vaccine supply. In the following sections, we will examine the five MVCs and a selection of the mid-size companies. We will review the contribution of their marketed products to

supply, drugs in development, and the strategies they use to maximize profit given the forces that impact the vaccine industry.

2.2 Multinational Vaccine Companies

The five MVCs share several common characteristics. Their large infrastructure and relative financial security enable them to afford the large costs of vaccine development. Vaccines form a relatively small, but growing part of the companies' product portfolios. They are expanding their vaccine businesses as countries look to vaccines to ensure public health in a cost-efficient way. Below we describe the scale, focus and lead vaccine products of the MVCs.

2.2.1 Sanofi Pasteur

Sanofi Pasteur is the largest vaccine producer in the world. Its parent company, Sanofi-Aventis is the third largest pharmaceutical company in the world. The company headquarters are located in Lyon, France. Sanofi-Pasteur employs over 12,500 people in more than 150 countries. The company maintains full-scale development, manufacturing, and marketing capabilities. Multisite production facilities make it possible to access diversely skilled personal and utilize suppliers globally. The company owns eleven production and R&D sites in seven different countries, including India and China. Three new facilities are under development, two of them in emerging economies. Sanofi has accessed new capabilities and capacity through acquisitions (Sanofi Pasteur, 2010a). In 2008, they acquired the infectious disease vaccine developer Acambis plc for US $550 M (Martino, 2008). In 2009, the acquisition of Shantha Biotechnics of India for US $784 M allowed access to the emerging Indian market (Martino, 2009).

In 2009, Sanofi Pasteur produced and sold more than 1.6 billion vaccine doses. Their portfolio of products includes vaccines against 20 of the 26 bacterial and viral illnesses listed by

WHO as vaccine-preventable. By diversifying extensively, Sanofi has established a dominant position in the vaccine industry. Sanofi differentiates itself from other MVCs as a low-cost, high-volume producer (Sanofi Pasteur, 2010a).

Investment in innovation has been critical to Sanofi's success in new product development. Sanofi spends in excess of € 1 M per day on direct R&D activities. Currently, there are 28 new vaccines under development or at the approval stage. This pipeline includes vaccines for dengue and HIV, and next generation vaccines to replace existing suboptimal products for disease including Japanese encephalitis (Sanofi Pasteur, 2010b). In 2009, Sanofi received European marketing authorization for the first intradermal microinjection system for seasonal flu vaccine (PharmaNews, 2009). Whether working alone or with other partners, Sanofi is developing innovative vaccines and delivery mechanisms.

In Europe, Sanofi Pasteur markets their products through a joint venture with Merck and Company, while Aventis Pasteur was formed in 1994. This JV has enabled the two companies to create new combination vaccines by sourcing components from one of the two entities that the other did not produce. Aventis Pasteur MSD also markets the HPV vaccine in Europe (Silico, 2010). In 2008, this JV relationship allowed Sanofi to take more market share when production problems plagued Merck in 2008 (Edwards, 2009). The JV also prevented the issue of shortages that can occur when vaccines come from a single manufacturer.

To advance research initiatives, Sanofi has formed relationships with a wide range of universities, academic institutes, biopharmaceutical companies, and a number of public health organizations. Sanofi is a major partner in the Global Polio Eradication Initiative (GPEI). Since 1988, they have donated 120 million doses of oral polio vaccines towards this initiative. Over the past 30 years, Sanofi has been the sole international vaccine provider for meningitis, which causes large outbreaks in Africa annually (Sanofi-Aventis, 2010a). By leveraging the partnerships

with organizations such as UNICEF, the WHO and GAVI, Sanofi is able to access populations throughout the world for enrolment in vaccine clinical trials.

Along with becoming a major supplier of vaccines to UNICEF, Sanofi has gained access to sales directly from developing countries. With a first mover advantage, Sanofi has successfully established partnerships and production facilities within BRIC countries. The successful acquisition of India's Shantha Biotechnics was attributed to years of relationship building in the country.

In 2009, Sanofi-Aventis reported total vaccine revenue of €3.5 B, a 19.2% increase at constant exchange rate from the previous year. Lead revenue generating products included influenza vaccines with total revenue of €1 B, paediatric and polio vaccine with €968 M, meningitis/pneumonia vaccines with revenue of €538 M, adult booster vaccines at €406 M, and travel/other vaccines at €509 M (Sanofi-Aventis 2010b).

2.2.2 Merck & Co. Inc.

Merck & Co. Inc. is one of world's dominant pharmaceutical companies. The company, headquartered in New Jersey, USA, employs over 55,000 people worldwide. As a global research driven pharmaceutical company, Merck maintains all the functions of the vaccine value chain. Though company's main focus has been pharmaceutical drugs, in recent years it has increased development efforts for vaccines. In 2009, the company had a 25% share of the world's vaccine revenue. Strong research capabilities and global access to suppliers have enabled Merck to bring high-value vaccines to market (Merck 2010a).

Merck has an extensive portfolio of vaccine products and many products in its development pipeline. Merck is the first and only company to have developed a vaccine against shingles. Zostavax is a live vaccine that reduced the incidence of shingles by 51.3% in a clinical trial of over 38,000 adults. Currently, Zostavax is recommended for adults over the age of 60,

including individuals who have suffered from prior episodes of shingles (Medical News Today, 2005a).

In developing RotaTeq, a vaccine against rotavirus, Merck conducted a clinical trial with 70,000 subjects to prove statistically that this vaccine is safe. This was one of the largest clinical trials ever conducted. A post licensure three-year study with 44,000 children also monitored any adverse effects associated with the vaccine. Large trial size and long-term monitoring stem from tighten regulatory guidelines resulting from Wyeth's withdrawal of Rotashield vaccine. Rotashield had a suspected association with intussusceptions, a rare condition leading to blockage or twisting of the small intestine (Margaret & Rennels, 2000). No small- or mid-size vaccine development company could have afforded to run such a large trial. Due to Merck's efforts, the FDA granted approval for RotaTeq in 2006; the product had sales of US$ 523 M in 2009 (Merck, 2010b).

Merck's Gardasil, the vaccine against the human papillomavirus (HPV) is one of the recent success stories in vaccines that have reawakened interest in the industry. Infection by HPV is a known cause of cervical cancer. In the US alone, there were 11,270 new cases of cervical cancer in 2009. Clinical trials demonstrated that Gardasil prevented more than 70% of these cases. Health care authorities quickly began to include Gardasil as part of national immunization schedules, contributing to rapid market penetration. Gardasil gained FDA and EMEA approval in 2006 and is now approved in over 100 countries worldwide. Due to the high cost of the vaccine regimen, it has still not reached low-income countries. GSK released a competing HPV vaccine in 2007, but Merck's first-to-market advantage created revenue of almost US $2 B that year. The basis of the Merck's HPV vaccines are the patent rights obtained from a cross licensing agreement with GSK in 2005 (Grimes, 2006). This strategic alliance had enabled Merck to build a lucrative HPV vaccine franchise.

Merck's vaccine pipeline includes a next generation HPV vaccine, currently in phase III trials. The candidate, V503, protects against nine strains of the HPV virus. The development work for V503 is being carried out under licensing partnerships with several companies; this includes a relationship with CSL Ltd., an Australian vaccine manufacturer who originally developed the Gardasil vaccine. Merck also manufactures and sells this vaccine in Europe through its joint venture with Sanofi-Pasteur, Sanofi-Pasteur MSD.

Merck has several other promising alliances and licenses that enrich its vaccine pipeline. In 2004, Merck and Intercell formed a worldwide, exclusive commercial alliance to develop a bacterial vaccine against methicillin-resistant *Staphylococcus aureus* (MRSA) infections. A second, licensing and collaborative agreement with Dynavax is aimed at developing a new investigational Hepatitis b (Hep B) vaccine, Heplisav. This vaccine is currently in phase III trials. With this agreement, Merck funds all the developmental activities in return for worldwide exclusive right to the vaccine, if Dynavax is successful.

In addition to successes, in recent years Merck has experienced manufacturing difficulties related to Varicella, which is required for the production of Varicella Zoster virus-containing vaccines, such as Varivax, ProQuad and Zostavax. Merck has struggled with ongoing shortages of Zostavax since 2008 (CDC, 2010a). The company has also had sterility issues with Hib and Hep B vaccines (Edwards, 2008). Merck will need to engage in partnerships and acquisitions to attract new technologies and build manufacturing capacity in these areas.

Merck has been relatively slow in engaging in such relationships within developing countries. The company established a joint venture in 2009 with The Wellcome Trust, to form MSD Welcome Trust Hilleman Laboratories in India. Hilleman Labs focuses on developing low-cost affordable vaccines for diseases affecting people in the poorest regions of the world. In

addition, Merck has provided *RotaTeq* to countries eligible for the GAVI Fund at cost (Merck, 2010c).

Merck has successfully differentiated with a vaccine portfolio that commands high market prices. This has enabled Merck to capture almost the same market share as Sanofi-Pasteur, with a much lower number of vaccine doses sold. In 2009, Merck & Co reported total revenue of US $27.4 B, which included US $3.6 B vaccine revenues. This was a 12.2% decrease from the previous year and due in part to Gardasil's decrease in revenue from US $1.4 B to $1.1 B. This loss can be attributed to competition from GSK's Cervarix, as well as market saturation amongst the target population for vaccination. ProQuqdéM-M-R II/Varivax was the highest revenue generator at US $1.3B.

2.2.3 GlaxoSmithKline plc (GSK)

In 2000, Glaxo Wellcome PLC and SmithKline Beecham PLC merged to form the UK-based company GlaxoSmithKline plc (GSK). GSK employs over 100,000 people worldwide in 116 countries. 1,600 scientists work on vaccine R&D. Currently, the company holds 16 different vaccines in clinical development and 25 different vaccines in the market. In 2009, GSK produced 1.4 billion doses of vaccines; 1 billion were sold in the developing world. GSK sells some of these vaccines at differential prices in lower-income markets. GSK supplied 21.2% of the world vaccines needs in 2009(GSK, 2010a).

Vaccine development work primarily occurs in the biologics centre, located in Rixensart, Belgium. Three other GSK sites and two joint ventures in China and Russia support additional large-scale manufacturing.

Two key acquisitions in 2005, ID Biomedical (ID) for $1.7 B and Corixa for $300 M increased GSK's manufacturing capacity and added innovative vaccine complements (DrugResearcher.com, 2005). ID developed innovative vaccines and had large manufacturing

capacity. In 2004, ID acquired the influenza vaccine related assets of Shire Pharmaceuticals. This transaction included a 200,000 square foot influenza vaccine manufacturing and fill/finish facility in Quebec with production capacity of 40-50 million doses per year. A 68,000 square foot vaccine research centre in Quebec and a vaccine development and pilot manufacturing facility in Massachusetts were also acquired in the agreement. The ID acquisition significantly increased GSK's vaccine manufacturing capacity in North America (Medical News Today, 2005b).

The second company acquired in 2005 had previously collaborated with GSK to discover cancer and infectious disease antigens for vaccines. Corixa developed and produced Monophosphoryl Lipid A (MPL), a novel adjuvant used in many of the vaccines in GSK's development pipeline at that time (DrugResearcher.com, 2005). Adjuvants can reduce the amount of vaccine needed for a protective immune response by as much as 90%, allowing significant cost of goods savings. GSK's HPV vaccine, Cervarix included MPL and was the first vaccine with a new adjuvant approved by the FDA. This was a significant milestone for the vaccine industry, as the FDA was very conservative about the new adjuvant. RTS,S , a MPL containing vaccine targeting the malaria is currently in phase III clinical trials.

In the past two decades, GSK has invested over US $300 M for developing a vaccine against malaria. RTS,S is the most developed vaccine candidate to malaria . RTS,S has a lower efficacy than required of most other vaccines, but given that an estimated 300 million people are infected with malaria annually, the lower efficacy is still valuable and the market large. GSK hopes to receive regulatory approval for RTS,S vaccine in 2012 (GSK, 2010b).

GSK has been conducting HIV vaccine research for the past two decades. In collaboration with the Pasteur Institute, GSK's strategy is to develop a vaccine by fusing HIV genes with a highly potent measles vaccine. While this collaboration is in progress, GSK is developing their own candidate F4co, which is currently in phase I and II clinical development.

The company has also established extramural R&D collaborations to identify HIV envelope-based proteins for which vaccines can be developed (GSK, 2010b). Hence, the company's clear strategy is to build a pipeline with both internal and external developmental programs.

GSK has taken an active role in technology transfer and partnership formation in the developing countries. Currently there is a network of 13 vaccine production sites in 12 different countries working with GSK. A long-term partnership with Brazil's Oswaldo Cruz Foundation (Fiocruz) had provided technology to manufacture vaccines for public health priorities in Brazil including polio, Hib, measles, mumps, rubella, rotavirus, and most recently pneumococcal disease. In return, GSK has gained exclusive access to the Brazilian market. Since 2007, 50 million doses of GSK's Rotarix vaccine have been delivered through the technology transfer agreement with Fiocruz. Since 2009, GSK had made inroads into the Chinese vaccine market through a joint venture with Shenzhen Neptunus Interlong Bio-Technique Co. Ltd (Shenzhen Neptunus). This joint venture will focus on developing and manufacturing influenza vaccines for the Chinese market. Both companies will benefit through building joint expertise in vaccine development. GSK will provide access to its adjuvant, while Shenzhen Neptunus will provide local manufacturing capacity and R&D expertise (GSK, 2010c).

GSK became one of the first vaccine manufactures to sign an agreement with the GAVI Alliance on an Advanced Market Commitment (AMC) program for pneumococcal vaccine. GSK committed to the supply of 300 million doses of the pneumococcal vaccine Synflorix over 10 years. A newly built US $600 M vaccine manufacturing plant in Singapore will manufacture the majority of this pneumococcal vaccine, starting in 2011 (Medical News Today, 2009a). The Singapore site was built because of the guaranteed demand provided by the AMC.

In 2009, GSK reported £3.7 B in vaccine revenue, a 30% increase at constant exchange rates from 2008. Pandemic influenza vaccines were the main revenue generator, contributing

£883 M. Hepatitis vaccine revenue fell 11% to £665 M. Infanrix/Pediarix also fell by 15% to £649 M because of competing multivalent vaccine products. Cervarix, the competing product of Merck's Gardasil, increased market penetration with a 38% increase in revenues to £187 M, in part due to sales from their exclusive supply agreement with Brazil. Rotarix increased sales 50% to generate £282 M. Since 2007, GSK has invested over £1 B in expanding influenza vaccine manufacturing capacity as part of signing the largest pandemic flu vaccine contract in history with the UK government (GSK, 2010d).

2.2.4 Pfizer

Pfizer, with corporate headquarters in New York City, US and 116,500 employees worldwide, is the world's largest pharmaceutical company (Pfizer, 2010a). Revenues in 2009 were US $50 B. Despite their dominance in the drug industry, Pfizer does not have a history of developing vaccines. This began to change in 2006 with their acquisition of PowderMed, a company with a DNA-based vaccine technology. At the time of the PowderMed acquisition, Pfizer publicly stated that further vaccine related acquisitions would be forthcoming (Pollack, 2006). In 2008, Pfizer acquired Coley Pharmaceutical Group for US $230 M. Coley had two key values, a vaccine adjuvant technology and a new class of immunomodulatory drug candidates (The Medical News, 2007). Their most notable acquisition was Wyeth; purchased for US $68 B in 2009, this was the largest pharmaceutical acquisition in history. With this purchase, Pfizer gained its first marketed vaccine, Prevnar 7.

The acquisition of Wyeth gave the new organization manufacturing facilities in 10 different countries. In May 2010, the company announced a workforce reduction of 6000 employees in manufacturing to increase operational efficiency. Though the company reaffirmed its commitment to growing biopharmaceuticals and vaccines, it stated:

"…the company also proposes changes at its sites that manufacture vaccines and large molecule medicines to improve efficiencies, capitalize on process and productivity improvements and new technology, and to simplify the supply chain." (Pfizer, 2010b)

The authors see this as part of a larger effort to find ways to reduce the significant cost of manufacturing vaccines.

Worldwide sales for Prevnar 7, a vaccine used to prevent pneumococcal disease in children, was US $2.9 B in 2009. In 2010, the company gained regulatory approval from the FDA for their second-generation vaccine against pneumococcal disease, Prevnar-13. As of March 2010, 40 countries have approved Prevnar-13 for use (Pfizer, 2010c). This vaccine is considered to be the most complex ever marketed, with 13 different molecules each requiring individual formulation and attachment to immunostimulants. This is reflected in its market cost of over US $400 for the standard 4-dose immunization. This vaccine is undergoing trials for prevention of pneumococcal disease in adults, an indication that could add another US $1.5 B to annual revenues (Wilson, 2010). Pfizer has no other marketed vaccines, but does have vaccines in phase 1 against *Staphylococcus aureus* and phase II trial against meningococcal B vaccine in infants (Pfizer, 2010d).

Pfizer's history with the developing countries has been limited. They have donated antibiotics to countries for the prevention of river blindness through the International Trachoma Initiative. In 2008, Pfizer entered into collaboration with Grameen Bank of Bangladesh to address unmet medical needs in the country (Pfizer, 2010e). The company formed an Emerging Markets Business Unit during their reorganization after the Wyeth organization. However, their first foray into differential pricing of their products for low- or middle-income countries occurred in March of this year, when they signed a contract with the GAVI Alliance's Pneumococcal AMC. This program provides initial subsidy to the manufacturer in exchange for the commitment of long-term production and lower prices overall. Pfizer committed to produce

30 million doses for the AMC over the next 10 years. In Pfizer's press release regarding the AMC commitment, they state that they will increase manufacturing capacity for the vaccine to meet the commitment (Pfizer, 2010b; Pfizer, 2010c). Acquisitions in emerging markets and freestanding differential pricing agreements have not yet formed part of Pfizer's strategy, but the Emerging Markets Business may change this.

2.2.5 Novartis

Novartis, founded in 1895 and based in Basel, Switzerland, is a global pharmaceutical company with over 99,800 employees in 140 countries worldwide. The company operates four divisions: pharmaceuticals, vaccines and diagnostics, generics and biosimilars, and consumer health. Novartis holds 8% of the vaccine market.

The vaccines and diagnostics division was established following Novartis's 2006 acquisition of Chiron Corporation for US $5.4 B. At the time of acquisition, Chiron was the fifth largest vaccine developer and the second largest influenza vaccine producer in the world, with manufacturing facilities in Europe, the United States, and Asia (Medical News Today, 2006).

The current portfolio of products includes vaccines to prevent influenza, meningitis, Hib, rabies, Japanese encephalitis, tick-borne encephalitis, polio, diphtheria, tetanus, and pertussis (whooping cough). Novartis' vaccines in development include two-phase II vaccines and five phase III products (Novartis, 2010a). In March of 2010, Novartis received European approval for a Menveo, the first quadrivalent conjugate vaccine against meningococcal disease. The FDA approved this vaccine targeting preventable *N. Meningitidis* serogroups A, C, W-135 and Y in February of 2010 (Novartis, 2010b).

Novartis is the first company in the world that commercially produces vaccines by utilizing mammalian cell cultures; this technology uses their proprietary cell line to produce viral components. In 2007, Novartis received the European approval for Optaflu, an influenza vaccine

manufactured by mammalian cell culture. Clinical trials showed equivalency to egg produced influenza vaccines in terms of efficacy, safety, and tolerability. According to Novartis, this is the first major innovation in the influenza vaccine manufacturing process. This system enabled Novartis to respond with faster and more flexible manufacturing in to the recent H1N1 pandemic. Celtura, which was produced with this technology, was one of the first H1N1 vaccines to be marketed in 2009 (Novartis, 2010a). Cell culture manufacturing is carried out in Marburg, Germany, while a new facility is being built in North Carolina, US. We will discuss the importance of this innovation further in Chapter 3.

Novartis has also pioneered reverse vaccinology (Rinaudo, 2009); this technology uses sequence information of pathogens to identify targets that other antigen identification methods cannot. It may find antigens that produce a protective response even if the individual is later infected with a different variant of the pathogen. Novartis's meningitis B candidate was developed using this technology. This vaccine is currently in phase III trials in adults and phase II in infants.

Like all the other MVCs, Novartis formed strategic partnerships to gain new product candidates and technologies. In 2008, Novartis entered into a partnership with AlphaVax, giving it exclusive global rights to AlphaVax's investigational Cytomegalovirus (CMV) vaccine program. This agreement also gave Novartis first rights to AlphaVax's preclinical respiratory syncytial virus (RSV) program (Novartis, 2008). The CMV vaccine is currently undergoing phase II clinical trials.

In recent years, Novartis has taken an active role in fighting disease affecting the developing world. Through partnerships with the WHO, UNICEF, and the Pan American Health Organization (PAHO), Novartis has provided millions of vaccine doses to developing countries at an affordable cost through price differentiation. Around 70% of the 800 million vaccines doses produced annually are destined for developing world countries. Since 2006, 100 million doses of

Quinvaxem have been distributed in 50 developing countries. This vaccine was developed through a partnership with United Nations and Crucell. It is one of the few vaccines designed by a MVC for the developing world. Quinvaxem is used to protect infants and toddlers against diphtheria, tetanus, pertussis (whooping cough), Hep b, and Hib. A commitment towards fighting disease affecting developing countries is further evident from the Novartis Vaccines Institute for Global Health (NVGH). This NFP organization collaborates with scientists globally to develop vaccines against neglected disease (Novartis, 2010c).

In 2009, the Novartis Vaccine & Diagnostics Division reported revenue of US $2.4 B. This was a 39% increase at constant exchange rates from 2008. The pandemic vaccine for H1N1 was the main revenue generator, contributing US $790 M to revenue (Novartis, 2010d).

2.3 Mid-Size Vaccine Companies

While the five multinational companies described above account for most of the revenue from the vaccine industry, mid-size vaccine firms can occupy profitable specialist niches that also benefit emerging economies.

In the developed world, a few smaller vaccine manufacturers have avoided acquisition by MVCs. These firms tend to form partnerships with several of the MVCs, which would complicate acquisition by any one firm. Their strategic relationships with the five MVCS are based on proprietary innovations of the smaller partner. These innovations often lower the cost of production or ease of use of the vaccine, and therefore have utility for the developing world. .

Over the last 25 years, many emerging economies have built national vaccine manufacturing infrastructure. Today, India, China, and Brazil each have multiple vaccine manufacturers that supply vaccines to their large domestic markets. These companies typically produce low-cost vaccines that are second-generation products based on MVC products. The

WHO recognizes both Brazilian and Indian NRAs. Manufacturers in these countries can now apply for WHO pre-qualification so that they may also sell their vaccines to UNICEF, which purchases 40% of all vaccines manufactured worldwide.

Middle-income country manufacturers are just beginning to innovate in vaccine development. Sales from India and other emerging economies to UNICEF have placed innovation and price pressures on MVCs based in high-income countries. As an example, the average cost of the pentavalent vaccine in 2010, after two Indian manufacturers began sales to UNICEF, dropped by an estimated 20% from that paid in 2004 (Singh, 2009). Some MVCs have responded to this threat by forming long-term strategic alliances or made acquisitions with vaccine manufacturers in these emerging economies.

2.3.1 Developed Country Producers

2.3.1.1 Crucell

Crucell is headquartered in the Netherlands. The company achieved revenues of € 358M and a net profit of € 23.9M in 2009. The company has a proprietary high-yield production process for biological compound drugs. They also manufacture their own vaccines and proteins. Crucell has strategic alliances with Merck, Novartis, Sanofi-Pasteur, and Wyeth for vaccine manufacture using the Per.C6 production technology. Crucell's vaccine production is focussed on production of vaccines that meet developing world needs. Quinvaxem is Crucell's lead vaccine product, with 64.3 million doses sold in 2009. The vaccine is made in collaboration with Novartis, who manufacturers 4 of the 5 components of the vaccine. Final production occurs in Crucell's Korean manufacturing facilities. Quinvaxem is part of the WHO Expanded Program on Immunization (EPI) and received a renewal procurement contract with UNICEF for product worth an estimated US $300 M over the period of 2010-2012. There is no quantity obligation

for UNICEF in this agreement, and the amount is US $200 M less than Crucell received for the procurement period of 2007-2009. This occurred as two Indian manufacturers gained prequalification for their pentavalent formulations. UNICEF offered tenders to these new entrants to reduce the risk of sufficient procurement of the vaccine and to lower the vaccine price. UNICEF is the major purchaser of this vaccine. Crucell shares fell after UNICEF's bid to Indian manufacturers was announced (Block, 2009). However, in May, UNICEF recommended the recall of Shantha's pentavalent vaccine due to manufacturing problems; Crucell gained an additional US $110 M contract concurrently with this announcement. While this has alleviated concerns about competition in the short term, emerging country manufacturers will continue to place competitive pressure on Crucell's lead product.

While Crucell is headquartered in the Netherlands, the main manufacturing site is in Korea. While this country is now considered high-income by GNI, the company has found it financially beneficial to be situated there. The company completed construction of its manufacturing facility in the Incheon Free Economic Zone in Korea this year. Investment at this site allows 'tax holidays', reducing deferred tax liabilities by €2.1 million (Crucell, 2010b).

2.3.1.2 Intercell

This mid-sized vaccine manufacturer is based in Vienna, Austria, with manufacturing facilities in Scotland. The company achieved revenues of € 61.7 M in 2009, with a net loss of €18.4 M. Novartis AG owns 14.9% of shares and markets Intercell's first approved vaccine. They also have a strategic alliance with GSK for their vaccine patch technology and are developing vaccines with Merck.

Their Japanese Encephalitis vaccine, IXIARO, gained regulatory approval from both the FDA and EMEA in the first quarter of 2010. In May, they signed a five-year exclusive contract for

the supply of the vaccine to the US Department of Defence. IXIARO generated € 7.7 M in revenue in 2009. Intercell has also generated an agreement with the manufacturer Biological E., to manufacture a product based on IXIARO that will be marketed in India and other neighbouring countries (Intercell, 2010). Japanese encephalitis is endemic to India and many other emerging economies, so this agreement allows Intercell to access a lower-margin, but higher volume market.

In addition to a focus on sales to the military, the company is targeting their products towards the general travellers market. This includes a vaccine for traveller's diarrhoea, a vaccine in phase III trials that uses a needle free patch method of administration. This delivery innovation was the basis of a strategic alliance agreement signed with GSK at the end of 2009. The companies will also develop needle-free, patch-based vaccines from GSK's pipeline of new clinical candidates. GSK paid €33.6 M upfront for this agreement, and may invest up to €84 M additionally (Intercell, 2010). Vaccine patches also have the potential for high demand in low- and middle- income countries; we will their benefit in more detail in Chapter 3.

2.3.2 Indian Vaccine Industry Overview

Indian vaccine companies have repeatedly entered the market with low-price vaccine offerings that have forced significant discounting of MVC product in the country. National manufacturers often release competitor vaccines to the same disease within a few weeks of each other. There is the intense vaccine manufacturing competition within the country. With the recent achievement of WHO prequalification status by multiple Indian companies, price competition is now appearing for products of interest to the world's largest vaccine purchaser, UNICEF. Below we will describe the largest vaccine manufacturers in India, their current products and the influence on pricing.

2.3.2.1 Serum Institute of India (SII)

Founded in 1966 to increase access to vaccines within the country, SII has grown to become the world's largest supplier of measles, mumps, and rubella (MMR) combination vaccines as well as DTP. Two out of every three children in the world have received a vaccine generated at SII. The company exports to over 140 countries (Serum Institute, 2009). Within India, the institute is the largest supplier of vaccines paid for by the Indian government. In 2007, the organization launched a proprietary Hib vaccine. They began selling the product at US $8 per dose, which undercut the price of global manufacturers Wyeth, GSK and Sanofi by 50-70% (Unnikrishnan, 2007).

2.3.2.2 Panacea

Panacea developed their first vaccine production plant in 1988, and in 2002, they built a facility for recombinant vaccine production. In 2004, the company formed a joint venture with Chiron (now Novartis) to market vaccines within India. Panacea's Hep B vaccine and several of their multivalent vaccine types are WHO prequalified. In 2009, they also received a UNICEF tender for production of pentavalent vaccine, worth US $222 M. The company's vaccine department had revenues of Rupees 66.8 B (approx. US $1.6 B) in the fiscal year ending March 31st, 2010. Panacea is the second largest manufacturer of vaccines in India. The completion of their formulations facility in Baddi, India in 2009 has allowed a capacity of 1 billion vaccine doses annually (Panacea, 2009). Table 3 summarizes the capabilities of Panacea's vaccine production facilities. Their volume capacity and variety of manufacturing technologies rivals that of any MVC.

Table 3: Panacea Vaccine Manufacturing Facilities

Panacea Facility name	Vaccine Capabilities	Notes
Baddi- Vaccine Formulation	Several filling lines with WHO compliance	capacity of 1B doses/year
	Filling line for prefilled syringes	
New Delhi- Vaccine formulation	Two vial filling lines for OPV	
	One vial filling line for Hepatitis B Vaccine and combination vaccines	WHO Prequalification expected 2010
	One line ready for pre-filled injection devices	
Lalru- Bulk Vaccines Facility 1	Recombinant antigen production- Hepatitis B	
	Pneumococcal polysaccharide production for candidate vaccine	
Lalru- Bulk Vaccines Facility 2	Production of tetanus toxoid for conjugation	
	Production of bacterial vaccine antigens- diptheria toxoid, pertussis	

Source, Panacea, 2009

2.3.2.3 Shantha

Shantha was founded in 1993 with a mandate to be the first Indian manufacturer to produce a proprietary vaccine. The successful launch of this Hep B vaccine occurred in 1997. Shantha sold the product at one tenth of the price of products from multinational manufacturers, profoundly affecting market price for competitive formulations. Today, the company supplies almost 50% of the global Hep B vaccine demand.

In 2007, the NFP organization PATH approached Shantha to develop a rotavirus vaccine that could be purchased in India and other emerging markets. PATH chose Shantha due to its technological and business abilities, as well as the organization's prior success with achieving WHO prequalification status for their vaccines (Business Standard, 2007). In 2009, Shantha was awarded a three year contract with UNICEF for its SHAN5 pentavalent vaccine worth an estimated US $340 M. This contract was the lasted demonstration of the sophistication of Shantha's vaccine formulation expertise, though the product has since been under scrutiny for manufacturing irregularities.

In 2008, Shantha achieved revenues of US $33 M (Biotechnology Journal, 2009). The Merieux Alliance acquired a 60% stake in the company in 2006, and in 2009, Sanofi-Aventis

acquired Shantha from Merieux for US $784 M. This was the first acquisition of an Indian manufacturer by an MVC, but it is likely others will follow to access low-cost manufacturing.

2.3.2.4 Indian Immunologicals

This company is one of only a few nationally owned vaccine manufacturers in India. It is a subsidiary of the National Dairy Development Board, and develops vaccines for veterinary and medical purposes. While not WHO prequalified, the company sells its rabies vaccine, Abhayrab directly to over 30 countries (Indian Immunologicals Ltd., 2010). To maximize demand of the vaccine, the company supplies over 1500 clinics in India with fridges for proper cold storage, and is expanding this system to other rural Indian communities and countries (Frew et al., 2007).

2.3.3 Chinese Vaccine Industry

This government owned company is the largest vaccine manufacturer in China. It is comprised of six Institutes of Biological Products and two trading companies. They produce blood derivatives, biopharmaceuticals and diagnostics in addition to vaccines. The National Vaccine and Serum Institute subsidiary was formed in 1919. The corporation produced 800 million doses of vaccine and made worldwide revenues of US $372 M in 2005 (DCVMN, 2007). More recent information is not published. The company has development collaborations for rotavirus and pneumococcal vaccines with PATH (PATH, 2007; PATH, 2009). In 1988, the Chengdu Institute of Biological Products began to market a vaccine against Japanese encephalitis within China. For the last 10 years, the company has sold this vaccine to other countries where JE is endemic, including Nepal and South Korea. Recently, price differentiation was established to allow low-income countries to access the vaccine. Filing for WHO prequalification has been submitted; pending approval, this vaccine may receive demand from

global travellers and military markets, creating an opportunity for high-margin sales (PATH, 2008).

2.3.3.1 China National Biotec Group (CNBG)

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2.3.3.2 Sinovac

Sinovac is a privately owned vaccine manufacturer registered on the NASDAQ in the US. It has a demonstrated capacity for innovation, collaborating with the US CDC to develop a SARS and H5N1 influenza vaccine. In 2009, the company realized a gross profit of US $64 M (Sinovac, 2010).

2.3.4 Brazilian Vaccine Industry

Brazil has a long history of nationalized vaccine production. The country gained expertise in yellow fever vaccine generation over 70 years ago when they received a technology transfer from the Rockefeller Foundation. The drive for national vaccine production capacity continued with the initiation of the National Program for Self-Sufficiency in Immunobiologicals (PASNI) in 1983 (Homma, 2008). This program was designed to increase the percentage of vaccines produced within the country's borders by investing in vaccine manufacturing infrastructure. Brazil is very progressive in adopting vaccines; in 2006, it became the first country to include GSK's new oral rotavirus vaccine into their public health program (Wecker, 2006). Today, Brazil has two dominant state-owned vaccine manufacturers that supply the public market - Bio Manguinhos and the Butantan Institute. The two organizations are under legal obligation not to compete with one another so that a greater variety of vaccines are manufactured in the country.

2.3.4.1 Bio Manguinhos

Brazil's efforts to develop manufacturing expertise through PASNI has paid dividends, with Bio Manguinhos receiving WHO prequalification status in 2001 for yellow fever vaccine. This allowed sale of yellow fever vaccine to the supranational organization, which is one of the globe's largest purchasers of vaccines. As of 2007, Brazil produced over 80% of yellow fever vaccine supplies for the world with an estimated 16 million units sold that year (Fiocruz, 2007b); More recent sales statistics are not available. Bio Manguinhos is also prequalified to produce the meningococcal A&C vaccine (Homma, 2009).

In 2008, Bio Manguinhos signed a technology transfer agreement with GSK for their pneumococcal vaccine, Synflorix. In return for the technology transfer, Brazil committed to purchase Synflorix at pre-determined prices over the next 8 years providing a large market for

the vaccine (Neto & Jayaraman, 2009). This marked the fourth such agreement that had been signed between the pharmaceutical company and Bio Manguinhos for vaccines since 1985; prior agreements covered oral poliomyelitis vaccine, Hib and a measles, mumps, and rubella trivalent vaccine (Fiocruz, 2008). GSK's historical relationship with Brazil's nationalized manufacturers gave an advantage to the manufacturer for this negotiation. This was especially positive for GSK, as Pfizer has just gained US approval for Prevnar-13, a pneumococcal vaccine that provides protection against 3 additional strains of the bacteria that Synflorix does not cover. Bio also cited GSK's willingness to negotiate on price as key to forming this partnership (Neto & Jayaraman, 2009). As this is a nationalized vaccine manufacturer, sales figures are not available.

2.3.5 Other Emerging Country Vaccine Manufacturers

2.3.5.1 PT Bio Farma

PT Bio Farma is a nationally owned firm with the predominant mandate of producing vaccine for the domestic market. Most of Bio Farma's vaccines produced are WHO prequalified. The company has manufacturing capacity of over 1 billion doses per year. In 2000, the company completed development of a facility to produce a novel delivery device, Uniject. This innovation came from a partnership with Becton Dickinson, UNICEF and Programs for Appropriate Technology in Health (PATH). Today, the company produces tetanus toxoid and Hep B vaccines in Uniject (PT Bio Farma, 2010). On June 18, 2010, PT signed a memorandum of understanding to develop vaccines with Medicago of Singapore. This company has a 'virus-like' particle technology that is one of the newest technology platforms for vaccine development (Biospectrum, 2010).

2.4 Summary

Over the last 10 years, the value of vaccines has been reconsidered by the pharmaceutical industry. Firms of sufficient size to manage the massive clinical trials and capital investment demands of manufacturing have yielded high returns on their marketed vaccines. These profits often last well beyond patent expiry, as manufacturing expertise is rare enough that generics have not yet become a threat. Today's vaccine profits remain highly concentrated amongst these firms. Through partnerships and acquisition of small- and medium-size companies, MVCs are further expanding into the industry. These activities were once limited to developed country markets, but today MVCs are making some inroads into emerging economies.

While MVCs have the highest profit margins, manufacturers in emerging economies surpass them in doses produced. Moreover, emerging country manufacturers are starting to broaden their value chains both backwards - into research and development - and forward, into clinical trials and marketing. These additional value chain links will enable them to compete against the current MVCs. Where emerging country manufacturers develop vaccines to regionally endemic diseases, they may dominate regional market share. Other countries with middle-class private buyers, in addition to demand from military and foreign travellers may allow high profit margins for 'regional disease' vaccines. In addition to the development of new vaccines, MVCS and smaller companies alike are developing new techniques for vaccine manufacture and formulations that will dramatically lower cost of goods. This will in turn, open up new market segments. Innovations may lower barriers to entry and change the trend towards industry consolidation. We will discuss the impact of innovation on the industry in Chapter 3.

3: INNOVATION AS A DRIVER OF THE VACCINE INDUSTRY

Scientific and technological innovations have advanced the re-emergence of the vaccine industry. These advances include a better understanding of the human immune system, increased screening capabilities for antigen identification and improved formulations. The aim of this chapter is to gain an understanding of innovations and technological improvements in vaccine development and manufacturing processes. We will also introduce new vaccine formulations and delivery methods that are adding value and increasing accessibility to vaccines.

When Wyeth marketed Prevnar in 2000, the vaccine's multibillion-dollar annual revenues motivated other companies to enter the industry. Because of their importance for public health, wealthy governments have also invested heavily in innovations that improve vaccine supply. Today there are innovations occurring in all segments of the vaccine value chain. The majority of commoditized vaccines have been successfully developed through simple manufacturing processes. However, vaccine development for many of the current pathogens is difficult and expensive. While there are sustained innovations for improving or extending the life cycle of current vaccine products, new disruptive technologies can revolutionize the industry by enabling products that developing countries can afford (Bower & Christensen, 1997). DNA vaccines, discussed below, are a likely candidate for disruptive innovation in this industry.

The book *Open Innovation* (Chesbrough, 2003) describes the paradigm shift from a closed-innovation to an open-innovation model. In the closed model, R&D projects are launched based on the knowledge and technology base of the company. The beginning and end of projects are also determined internally. In this model, technology development projects can

only originate within the company. Economies of scale and scope of internal innovation give rise to vertically integrated companies that internalize the entire value chain. More recently, companies have been following an open model of innovation. Here, technology development can originate from either internal or external sources. Importantly, innovations can be captured from many sources including technology transfer, licensing and partnerships. Open innovation is apparent in the vaccine industry today. The majority of MVCs are looking to smaller biotechnology firms to gain access to new vaccine development projects, research techniques and newer manufacturing processes. The MVC's own research allows them to absorb the inflow of knowledge from external sources. Intellectual property is used as a class of assets that simultaneously generate revenue and develop new technologies.

Given that one company cannot develop all the expertise and capacity themselves, strategic alliances or 'networks of innovation' are being used (Bakkers, Duysters & Verspagen 2002). Knowledge 'spillovers' - between companies and with universities - are fuelling these networks (Colyvas et al., 2002). Technologies that lack an initial value path within an organization can find an external fit where it fulfills the demand of different industries. The re-emergence of the vaccine industry can be attributed to a combination of new technological developments and a build-up of networks utilizing new knowledge to full potential. This chapter will examine some of the sustaining, incremental, and disruptive innovations taking place in the vaccine industry.

In the following sections, we will examine innovation taking place in the vaccine industry. Some of these are incremental innovations while others are disruptive innovations. For example, research-grade recombinant DNA techniques are now being used to create a completely new class of vaccines.

3.1 Multivalent Vaccines: Old Vaccines, New Combinations

Whether in the developing or developed world, the increasing number of vaccines recommended for children places challenges on the vaccination system. There is a risk of patient fatigue as families make multiple visits to a medical facility for immunization. The risk of an associated adverse event also increases, whether temporal or causal in nature. In remote communities, those who wish to be vaccinated may not be able to visit a clinic on the day that a trained medical worker is available to perform the vaccination. A solution to these issues is to vaccinate against multiple pathogens in a single dose. There are number of companies that have successfully created such multivalent vaccines. In 2006, both GSK and Crucell received prequalification from the WHO for pentavalent vaccines of the following formulation: diphtheria, tetanus, pertussis (whole cell), Hib and Hep B. UNICEF alone purchases an estimated 400 million pentavalent doses annually. In 2008, Shantha and Panacea accessed the UN market by receiving prequalification status. Serum Institute of India (SII) has received prequalification status in 2010, indicating that this innovation continues to be financially beneficial for companies that adopt it.

In the developed world, new multivalent vaccines have also seen great success. These incremental innovations have extended the product life cycle of older vaccines, enabling companies to generate additional revenues. In 2008, sales of Sanofi's Pentacel increased 21% over the previous year and gained 50% of market share within a few months. Pentacel is a pentavalent vaccine with antigens from five disease agents; diphtheria, acellular pertussis, tetanus, inactivated poliovirus and Hib. The use of this combination vaccine reduced by seven the number of injections recommended for children aged 0-2 years of age in the US vaccination schedule (Sanofi-Aventis, 2009). The "crowded schedule" of childhood vaccines in the western world is an impediment to the successful uptake of new vaccines (Graham, Legerwood & Nabel,

2009). Reducing vaccination visits appears to have been a major factor in the rapid adoption of Pentacel in the US market.

3.2 Formulation

Older vaccines used killed whole cell or attenuated pathogen to induce an immune response. Though these vaccines normally induce a strong immune response, they have a risk of causing the disease that they should prevent. Vaccines in their ideal formulation would catalyze a long-term protective response in a single dose, while having no associated risk of adverse effects. There are several pathogens for which vaccine development has not yet been successful. These diseases include malaria, HIV, dengue and tuberculosis, which together affect hundreds of millions of people worldwide. New formulation technologies hold promise for fulfilling this unmet need.

3.2.1 Reverse Genetics

With reverse genetics technology, genes that code for proteins are isolated from the pathogen. These genes are inserted into a small circle of DNA known as a plasmid. Once the plasmids are introduced into a mammalian cell, viral proteins are made and assembled into "virus like" particles (Neumann, Hatta & Kawaoka, 2003). These viruses are not able to replicate and, hence non-pathogenic. This method of vaccine production eliminates the chance of vaccine-induced disease.

Some pathogens are difficult to grow under culture conditions. Other viruses such as HIV pose a significant safety risk by regaining virulence during culture. Reverse genetics can be effectively used to develop vaccines for these difficult pathogens. Add-on technologies that can increase the efficiency of introducing plasmids into cells will simplify and shorten the manufacturing process. With the use of correct combination of surface and internal proteins

from different pathogenic species, a multivalent vaccine can be developed. Novartis's meningitis B candidate that is currently in phase III trials was formulated with this technology.

3.2.2 DNA Vaccines

DNA vaccines are the most recent vaccine formulation technology. Genetically engineered gene sequences of pathogens are used instead of pathogenic proteins or the whole organism. Antigen-presenting cells of the vaccinated individual take up the foreign DNA and produce the associated protein. The immune system detects the proteins as foreign, resulting in an immune response. Recently, researchers demonstrated that a single dose of HIV DNA vaccine induced a lasting immune response in non-human primates (Arrode-Brusés et al., 2010). This study will provide insight in designing future vaccines against HIV.

DNA vaccines have a number of advantages. Unlike attenuated or killed pathogen vaccines, there is no risk of infection. Antigen-presenting cells that incorporate the pathogen genes will provide a long-term antigen source that could eliminate the need for booster doses. Since these vaccines strongly stimulate the immune system, potentially toxic adjuvants are not needed. As discussed further in the manufacturing section, recombinant DNA is relatively easy and inexpensive to produce. The quality control burden will be reduced, as there is no need for conjugation or other secondary manufacturing steps. DNA is stable at room temperatures for longer periods, reducing the need for refrigeration during transport and storage. This last point is particularly valuable for developing country vaccine supply, since in infrastructure-limited environments, cold-chain control is not readily available.

DNA vaccine technology has many of the characteristics of a disruptive innovation (Christensen, Baumann, Ruggles & Sadtler, 2006). Unlike existing vaccine formulations, DNA vaccines are much simpler and less costly. Genes from different pathogens can be transferred using the same plasmid system to induce an immune response, so the technology can be used

for many diseases. If successful, this technology will replace some of the current, complex vaccines as well as address future demand for new vaccines.

DNA vaccines are becoming attractive to investors and entrepreneurs because of the numerous differentiators. With further technology improvements and proof of efficacy in human trials, this industry segment is likely to expand dramatically. Biotechnology companies currently dominate the DNA vaccine field. There are a large number of small firms competing with proprietary technologies. Inovio Pharmaceuticals Inc. is a Pennsylvania-based company developing both DNA-vaccines and safe DNA transfer technologies. Their current vaccine pipeline includes one completed phase I study, six phase I studies in progress and three preclinical studies. In 2004, Merck & Co. licensed Inovio's proprietary DNA transfer technology along with DNA-vaccine candidates to a variety of cancers. The deal included upfront and milestone payments, development fees, royalties, and a supply agreement. Inovio's other partnerships include a collaboration with ChronTech Pharma of Sweden. ChronTech's therapeutic vaccine against chronic hepatitis C infection will shortly be starting phase I with Inovio's DNA transfer technology (ChronTech, 2010a). Inovio's DNA vaccine development platform is also under assessment by the PATH Malaria Vaccine Initiative (ChronTech, 2010b). Vical Inc. of San Diego, CA is another company that has been successful in developing DNA vaccine technologies. Vical's CMV vaccine TransVax had shown promising results in their initial analysis of phase II trial results. The company is set to release final data in the third quarter of 2010 (Vical, 2010).

3.3 Thermostability

The majority of vaccines are refrigerated to ensure stability. Transport and storage of vaccines in this 'cold-chain' adds an estimated 14% to the cost of vaccines (IRIN, 2010). Old

fridges can cause accidental freezing, which destroys any vaccine containing alum adjuvant. The US CDC estimates that $20 M per year in vaccines is wasted due to improper refrigeration in their Vaccines for Children program alone (Welte, 2007). In low-income countries, the limited cold-chain is under greater strain due to the increasing number of vaccines provided in single dose, bulky formats; vaccine wastage rates are as high as 10% for single dose vials (Parmar et al., 2010).

Demand for improved thermostability has come from countries of all incomes. Cambridge Biostability had been developing two different stabilization technologies. Sugar glassification was under development by the company and competitors. This technology is based on observations of a drought resistant 'Resurrection Plant'. To protect against drought, the resurrection plant produces a thermostable form of sugar. Upon re-encountering water, the plant recovers almost immediately. Viruses dried in sugar glass also retained their functionality upon reconstitution. However, there were serious concerns raised about environmental impact of the formulation process (Quested, 2009).

In December of 2006, the company announced the formation of a joint venture with Panacea of India. Panacea purchased a 10% share in the company for £1.9 M. The focus of the JV was on the creation of multivalent thermostable liquid formulations (Panacea, 2006). This is the first known example of an investment by an Indian firm in a developed world company technology. While Cambridge Biostability recently declared insolvency, this JV demonstrates the increasing buying power and strategic initiative of the Indian vaccine manufacturing industry. (Quested, 2009).

In 2003, Medimmune gained FDA approval for their influenza vaccine, Flumist. Despite the innovative nasal delivery method, Medimmune did not achieve significant market uptake at launch. The vaccine required storage at negative 20C. This temperature requires special freezer

storage, a unique requirement amongst influenza vaccines. Medimmune soon reformulated the vaccine to be thermostable at 4C; in 2007, the FDA approved this vaccine format (FDA, 2007). This case is clearly illustrative of the power of market forces to drive innovation. If a financial analysis showed a compelling benefit for vaccines stable at room temperatures, the industry would rapidly move to innovate. Emerging country manufacturers may provide pressure for broader adoption of thermostable vaccines by creating a thermostable influenza vaccine, where there is a competitive market in the developed world.

3.4 Manufacturing

The current method for production of many virus-based vaccines is by culture in fertilized chicken eggs. Although this manufacturing technology has evolved over 60 years of sustained-incremental gain of knowledge and experience, the unpredictable nature of egg incubation and viral culture continues to constrain production levels. This was evident in the 2009 H1N1 response when manufacturers produced only 32 million of a planned 161 million doses by the onset of the flu season (Burns, 2009). This pandemic and concerns about the potential of the H5N1 virus to evolve to a pandemic strain have reawakened interest in alternate production methods. Mammalian cell, plant and bacterial antigen expression systems are under development, often with significant support from wealthy countries concerned about national health security (Faster Vaccines, 2009). The US Health Biomedical Advanced Research and Development Authority (BARDA) has awarded US $1.3 B for manufacturer development plants over the last 5 years (Wechsler, 2010). The goal of this government investment is to help ensure reliable vaccine supply through development and integration of new vaccine manufacturing technologies. Without external subsidy, it may be prohibitive for a company to make the significant capital investment required for new manufacturing technologies.

3.4.1 Mammalian Cell Culture

Mammalian cell-culture vaccine technology produces viruses, “virus like particles” or combinations of pathogen derived proteins in a controlled cell culture system. After production, vaccine components are isolated from the culture media or by lysing the cells. In case of influenza, cells are inoculated with the three strains of influenza viruses identified by the WHO as most likely to be circulating in that season. Mammalian cells used for viral culture can be stored frozen and can be rapidly recovered. Hence, the response rate during an outbreak is faster and production is scalable based on the need. Since vaccines are produced in regulated machinery, the quality is monitored and maintained to the highest standards. Use of cell culture methods to produce protein and viruses is not a new technology as it has been widely applied in basic life science research. However, it is a newly adopted technology for the vaccine manufacturing industry.

Novartis‘s influenza vaccine Optaflu was the first cell-based influenza vaccine to reach the European market. In 2009, Novartis received a US $490 M grant from US Department of Health and Human Services (HHS) to build a cell-culture vaccine plant in Holly Springs, North Carolina. This plant is the first large scale cell culture-based vaccine manufacturing facility in the US. Other companies such as Baxter and Protein Science Corporation are also developing mammalian cell culture vaccines (BioPharm, 2010). As the industry develops new knowledge of how to build efficient cell culture-based manufacturing technologies, facilities and production costs will decrease. This will allow new entrants. The initial production cost may be higher due to capital investment, but over time, efficiency gains will reduce costs and create a higher return on investment.

3.4.2 DNA Vaccine Manufacturing

Upgrading research-grade plasmid production technologies allows the manufacture of plasmids to use as DNA vaccines. Plasmids are circles of DNA. For vaccine manufacturing, they contain genes from the pathogen, which is transferred into bacterial cells. These bacteria are then cultured within bioreactors to produce large volumes of plasmid. Lastly, the pathogen's genes along with the plasmid DNA are harvested.

DNA vaccine bioreactors can be assembled with 'off the shelf' components as the machinery is widely used. Clean room facilities are added for clinical use to prevent contamination. Once a sufficient quantity is produced, plasmids are biochemically purified from the bacterial culture for vaccine formulation. In comparison to traditional vaccines, much smaller doses of DNA vaccines are needed. A DNA manufacturing plant can have many small bioreactors operating independently. Individual bioreactors can be shut down or brought online as demand warrants. The capital investment cost for a DNA manufacturing facility is significantly less than a traditional egg-vaccine production facility. This allows smaller biotechnology companies an opportunity to establish their own production facilities. For example, Inovio has a 500L cGMP manufacturing plant in Texas and a 3000L plasmid manufacturing facility in Korea (Inovio, 2008).

3.4.3 Plant Organism Manufacturing

Plant-based vaccine manufacturing is carried out in two different ways. In the whole plant method, transgenic field crops express the pathogen proteins. One of the major drawbacks of this method is that it is difficult to regulate the environmental conditions. The transgenic protein is expressed in all parts of the plant while the plant interacts with its surrounding environment. There is not an established regulatory path for determining the safety of proteins isolated from these plants.

The second method involves plant cell culture manufacturing. This process uses salt, sugar and water to culture plant cells in a highly regulated environment. A single cell is transformed with the pathogen gene of interest and this cell multiplies to transform into a protein production apparatus. Cells can only grow in the contained environment, eliminating external environmental factors. In 2006, Dow Agrosciences received FDA approval for the world's first plant-based vaccine for use in animals (In-Pharma-Technologist, 2006). In February of this year, a consortium was formed to demonstrate proof of concept for plant-generated human vaccines (Texas A&M, 2010). The US Defence Advanced Research Project Agency primarily funds this project, suggesting the organization recognizes the potential of plant-generated vaccine technology.

3.4.4 Disposable and Modular Manufacturing Components

A time-intensive step in conjugate vaccine production is fractionation of polysaccharides for attachment -conjugation- to proteins. Conjugate vaccines include the sales blockbuster, Prevnar. This fractionation process has traditionally used beaded resin columns made on site, which is difficult and time-consuming. The introduction of disposable materials has an important role in increasing efficiency, speed, quality and safety during vaccine manufacturing. Disposable, pre-packed membrane columns eliminate the need for custom column packing. A pre-pack column such as Pall's Mustang ion exchange membrane can remove contaminants 100 times faster than conventional resin columns (Pall 2010). Disposable materials reduce time lost to error and allow switching processes in a timely manner. Cleaning and decontamination processes are reduced, which simplifies adherence to regulatory requirements. Given that quality and safety control issues comprise 70% of production time, these disposable technologies can make a significant impact on manufacturing speed.

Smaller autonomous robotic systems for manufacturing and fill/finish of vaccines can also help with efficiencies in manufacturing. According to Christopher Procyshyn, CEO of Vanrx PharmaSystems in Vancouver, demand is increasing for automated filling technologies. Fill and finish expertise is limited to a relatively small number of specialists. This constitutes a significant barrier to entry. The majority of vaccine shortages have been caused by contamination during manufacturing or fill/finish steps. Automated technologies remove the human factors that may lead to contamination. Unpredictability of vaccine demand is a major problem for large manufacturing plants. However, these smaller modular manufacturing and fill/finish units can be brought into use based on demand; they also allow redundancy for uninterrupted production in the case that one unit fails. Dr. Procyshyn sees the greatest demand for robotic systems from smaller biotechnology companies that have the need for smaller, cheaper manufacturing capacity. He envisions future technology transfer as “vaccine in a box”, where vaccine manufacturing and fill/finish machinery is packaged together for local manufacturers in developing countries.

3.4.5 Manufacturing Summary

The vaccine manufacturing industry must follow the significant safely requirements set forth by regulatory agencies, and so there is caution about the adoption of new manufacturing infrastructure. Even GMP approved technologies have taken decades to gain industry-wide adoption, as manufacturers have typically invested significant capital in older manufacturing processes. Though the adoption of new technologies increases manufacturing costs in the short term, efficiency and consistency savings accrue over time. High-income countries, especially the US, have also demonstrated a willingness to support expensive manufacturing facility construction. This has encouraged some MVCs to build new technology manufacturing plants.

3.5 Delivery Technologies

In 1885, Louis Pasteur used a hypodermic syringe to vaccinate against rabies; this remains the most common vaccine delivery system today (NMAH, 2010). One of the major problems with needle-based vaccine delivery is patients' fear of needles. This fear has been estimated to affect 10 % or more of the US population and plays a role in the negative publicity that vaccines receive (Hamilton, 1995). Additionally, some studies have shown that over 85% of healthcare workers experience an accidental needle stick per year, placing them at risk for exposure to hepatitis and HIV (Lee, Bottman, Xanthakos and Nicklasson, 2005). In the developing world, needles are often reused with insufficient disinfection. 40% of Hep B and C infections and 5% of HIV infections are attributable to improper needle reuse (Nundy, 2010). Unsafe disposal of needles has also created a public health hazard for people (often children) who scavenge landfills for their livelihood. This additional disease burden places a strain on fragile health care systems.

Though trained healthcare workers are necessary for proper use of syringes, the devices' low cost has meant that they have remained the dominant delivery method. Needle and syringe manufacturing is strongly embedded within the vaccine industry, limiting the adoption of other devices. As a result, new devices are only beginning to be available. Sanofi gained EU marketing approval for an influenza vaccine with delivery by microneedle technology in early 2009. This device methodology provides a differentiator for a vaccine that has significant market competition. Similarly, the product life cycle of commoditized vaccine can be lengthened through incorporating a new delivery device.

3.5.1 Edible Vaccines

In the past decade, scientists have examined delivering vaccines through edible plants. Plant cells produce pathogen proteins through a vector-based method similar to that used in DNA vaccines. This method has been successful in developing plants that are resistant to pests and pesticides. Researchers have also developed plants that produce immunogens. Rice, corn, potatoes and tomatoes have been used to produce vaccines.

There are a number of major advantages to an edible plant base vaccine; it is a safer method of administration than by needle, cold chain requirements are eliminated, and plants can be easily reproduced in large quantities using low-cost manufacturing mechanisms. In addition to providing healthcare savings, plant-based vaccine manufacturing could stimulate agriculture-based economies in the developing world.

The world's first clinical trial for edible vaccines was conducted in 1997. In this trial, 19 out of 20 people who ate potatoes containing *E. coli* antigens developed a protective antibody responses, with no adverse reactions reported (Tacket et al., 1998). Hepatitis B surface antigen (Mason, Lam & Arntzen, 1992), heat-labile enterotoxin B subunit (Tacket et al., 2004), and Norwalk virus particles (Zhang et al., 2006) have all been produced in plants. These vaccines are still in development stage.

There are a number of technical challenges for plant-based vaccines. Since processing or cooking plant material can destroy the antigens, it is important to select plants that are edible when raw. Therefore, there is a need for alternatives to vaccine production in rice and potatoes. Determining the actual vaccine dose will be difficult as the protein expression level can be variable. Lastly, but most importantly, this delivery method will be challenging for infant vaccines. As typical immunization schedules have six vaccinations in the first 2 months of life, this is a significant limitation (CDC, 2010b).

3.5.2 Intranasal Delivery

The majority of pathogens enter the body through the upper respiratory tract and the mouth. It is therefore plausible that stimulating these mucosal membranes to create immunological memory may be the best way to prevent disease. Vaccination via nasal mucosa rapidly induces strong systemic and local mucosal immunity. The large number of fine blood vessels in the nasal mucosal membrane facilitate rapid uptake of the vaccine. Direct introduction to the blood is also more effective than oral delivery as the liver does not process the vaccine.

One intranasal delivery vaccine reached the market in 2003. MedImmune developed FluMist, the first nasal spray vaccine approved by FDA. The vaccine is directly delivered to the nasal mucosa in the form of a mist. However, in 2008, revenues were only US $104 M. This is due to several limitations. Flumist must be stored at negative 20°C, while traditional flu vaccines are stored at 4°C, so that cold-chain and storage requirements are greater. The cost of a dose is four times greater than a traditional flu vaccine. The FDA only permitted a restricted age group, 5-49 years old, to receive the vaccine.

Today there are a number of biotechnology companies developing nasal vaccine delivery technologies. NanoBio Corporation of Michigan has developed a 'nanoemulsion'-based vaccine delivery system. This platform supports intranasal vaccines to gain a robust immune responses in animals vaccinated against influenza, pneumococcal, Hep B, HIV, RSV, anthrax, and smallpox. Successes of the technology in animals indicate further development in to human trials (NanoBio, 2010).

As cold-chain storage is increasingly strained, companies are focusing on creating heat-stable nasal delivery technologies. A lyophilized or spray-dried intranasal vaccine powder would allow room temperature storage. A complete delivery solution would be created if the vaccine

were reconstituted immediately prior to injection within the delivery device. This capability would eliminate the current use of sterile vials for mixing. It would also reduce the risk of using the wrong diluents and vaccine contamination during devices filling. The VRx2™ delivery platform of Mystic Pharmaceuticals contains these auto-reconstitution capabilities. Sterile blisters containing freeze-dried vaccine and the sterile diluent solution are stored in separate reservoirs. At the point of use, the vaccine powder is mixed with the diluent to *in situ* reconstitute within the delivery system, followed by intranasal delivery (Mystic 2010). There are a number of factors that determine the success of intranasal vaccine delivery technologies, listed below. Though the device is designed to deliver exact dose every time, there is no guarantee that the right dose will be absorbed to the blood stream. Furthermore, penetration through the mucosal membranes will require live vaccines or killed vaccines with adjuvants, which can pose a risk of infection. There is also a slight risk of vaccine contact with the nervous system causing other unknown side effects. Lastly, nasal administration of an effective dose in infants may not be possible.

3.5.3 Vaccine Patches

Vaccine patch technologies use the strong immune surveillance system of the skin to stimulate the immune response. With controlled release of antigen through the patch, a constant dose can be administered over an extended time, mimicking a booster effect. The advantages of vaccine patches include their ease of use, potential temperature stability, and small volume. These last two features could dramatically reduce transport and storage costs for vaccines.

Vaccine patches in development are being marketed to travellers and developing world markets. In 2008, Iomia Corporation reported a successful phase I trial against severe diarrhoea for the travellers' market (Bloomberg, 2008). In 2009, the Austrian vaccine manufacturer

Intercell acquired Iomia. They have continued development and are currently conducting phase III trials (Intercell, 2010b). Intercell is further developing the trans-dermal patch to enable the delivery of antigens for other indications, including influenza. The development program for pandemic flu vaccine patches is funded in part by the U.S. Department of Health and Human Services. In 2009, Intercell formed a strategic alliance with GSK to further develop and commercialize the technology.

3.5.4 Prefilled Needle Delivery Devices

In current practice, most vaccines are produced and packaged into single or multi-dose vials. The vaccine is administered by filling a syringe and then injecting the dose by needle. While standard syringe and needle pairs cost only a few cents, they have significant drawbacks. Specially trained healthcare workers must understand the appropriate storage conditions, diluent and dose for each vaccine. In remote areas, medical staff may not be available, preventing vaccine use for residents of small communities and travellers. In the developing world, resources to train healthcare worker has always been limited.

One drawback associated with multi-dose vials is that the vaccine typically must be used the day it is reconstituted. If only multi-dose vials are available when a vaccination is requested, the remaining supply is wasted if not used. This has led to multi-dose vaccine wastage rates as high as 80% (Guichard, 2010). One solution to these problems is to use pre-filled single dose syringes.

Several companies have developed needle-based devices that can be used safely without significant medical training. PATH's Uniject is an example of such a device, which is distributed worldwide by the licence holder Becton Dickinson and Company (BD). With this device, pressing the pre-filled blister releases the contents through an attached needle. This single-use device is non-refillable to prevent re-use. The Indonesian company PT Bio Farma has

built a fill and finish line specifically for Uniject. Since 2001, the company fills their Hep B vaccine into the devices for the Indonesian Ministry of Health (Nelson, Widjaya & Wittet, 2002). The vaccine is administered at birth in the case of home deliveries, where a medical worker with extensive knowledge of needle use might not be present. This device has removed the requirement for trained healthcare workers and made the vaccination process simple, which is a major advantage in increasing access to vaccines in developing countries. Shantha Biotechnics introduced their Hep B vaccine, Shanvac-B in a Uniject device in 2005; as a major Indian manufacturer, this has allowed the birth-dose strategy to be used in India as well (Bioportfolio, 2005).

Prefilled reconstitution devices contain a dry powder and liquid in separate blisters that are reconstituted by pressing on the liquid. The single dose of vaccine is delivered though an integrated needle. AktiVax and Aktiv-Dry are two technology companies combining their capabilities to develop the Immunoject delivery device (AktiVax, 2010). Aktiv-Dry has developed the technology to convert vaccines into dry powder (Dubin, 2010). The device is similar in shape to a small credit card. The needle is disabled after a single dose usage by folding the card in on itself. Graphic instructions for use of the device are printed on the card for additional ease of use. One of the major advantages of this technology over liquid prefilled devices should be the removal of vaccines from the cold-chain. This product has not been tested in clinical trials.

Uniject was licensed to the syringe manufacturer BD in 1995 (PATH, 2005). However, market acceptance has been relatively slow. All the MVCs have invested hundreds of millions of dollars in capital equipment for their proprietary filling lines. While fulfilling new technology requests from high-income country markets might be financially beneficial, demand for Uniject comes from markets that typically purchase vaccines at lower profit margins. However, there has been adoption of Uniject by Pfizer for Depo-Provera, a contraceptive drug that is

administered repeatedly, so that capital costs may be amortized more quickly (PATH, 2009b). If the company gains regulatory approval for the new formulation with the device, Pfizer may expand the use of Uniject to other products including vaccines.

3.5.5 Intradermal Administration

In 2009, the first intradermally delivered influenza vaccine was approved for use in a major market. The intradermal method of delivery deposits the vaccine in the dermal layer of skin. The high number of immune cells in this layer means that the immune response is strong so that the dose required is less. Sanofi has targeted Intanza to individuals over 60 years of age. Due to aging of the immune system, these individuals do not always generate a sufficient response to influenza vaccines delivered by needle and syringe. Sanofi had sales of over €1 B in influenza vaccines in 2009; with Intanza, they have the opportunity to gain another market segment through differentiation. Intanza will also be a delivery option for those with phobia of needles, as the delivery device is 1.5mm in length, 1/10 the length of traditional syringes (BD Worldwide, 2009).

Governments are also interested in delivery of vaccines by intradermal administration due to their ability to lower the dose required. An effective immune response can be generated with as little as 20% of the dose needed for conventional subcutaneous injection. This would be immensely helpful in the case of a vaccine shortage. Biojector 2000, by Bioject Medical Technologies Inc., was chosen by Centers for Disease Control and Prevention (CDC) for influenza clinical trials just completed (Businesswire, 2010). The results of this study are still pending. If successful, this innovative technology will provide reduced costs per dose to the purchaser.

3.6 The Strategic Importance of Innovation

The vaccine industry has undergone remarkable growth in the past decade. Investments in R&D for new vaccines have increased primarily because of the profits gained through wealthy governments' purchase of expensive vaccines in the early 2000s.

Wealthy government concerns over vaccine shortages have meant that they have also provided extensive financial support for manufacturing innovations. As described in the section on manufacturing, small and large vaccine manufacturing companies alike have accessed these funds, reducing initial capital costs. As infrastructure can comprise as much as 60% of the total price of vaccine production, the opportunity to reduce these expenses has a significant economic benefit (Danzon, Pereira & Tejwani, 2005).

Adoption of new modular vaccine manufacturing and fill/finish technologies is allowing small companies to afford manufacturing in their own value chain, enabling vertical integration by smaller firms. Replacing old egg-based technology with cell culture manufacture will increase efficiency while reducing cost. Innovations in manufacturing processes and equipment improve vaccine production security.

The majority of innovation in the industry has been for influenza vaccines, where the highest competition for market share exists. There are multiple influenza vaccine producers, and so product differentiation plays a key part in maximizing profits. The recent H1N1 pandemic, flu vaccine shortages and buyers in the developed world who are willing to pay for a device that meets their unique needs, are all factors driving companies to innovate for flu vaccines. The device used in the recently approved Intanza provides a dose sparing benefit that would be of use for many other market segments. Adoption of successful innovations from influenza vaccines into other products will further strengthen vaccine access, safety, and supply.

MVCs are starting to incorporate these delivery devices to differentiate their older vaccines from competition. This strategy is likely to generate higher net profit margins through higher pricing power created by perceived uniqueness of the vaccine. In an industry where the majority of the end users are not the buyers, governments' and supranational organizations' willingness to pay for differentiated vaccine products such as pentavalent formulations will be robust if the social benefit of increased vaccine coverage (defined as the percentage of the population who have been vaccinated) is clear.

The diversity of vaccine related innovations had gone beyond the capabilities of any individual company, forcing collaboration to reduce the uncertainties associated with innovation development. As a result, the vaccine industry has "positive sum" competition that translates successful innovations in one vaccine to others, meeting the needs of different groups of customers. Multivalent vaccines designed to address different regional needs exemplify this trend. As emerging country and other smaller vaccine companies produce competitor vaccines for other indications than influenza, they will innovate to differentiate their process costs or product features. Any innovation that results in a differentiation for the vaccine producer and benefits vaccine supply stability will be rapidly adopted by the industry.

Innovations in vaccines are reviving the once stagnant, commoditized industry and adding value to vaccine products. The advances in development, manufacturing, and delivery technologies that we discussed here are helping to increase efficiency in gaining access to disease preventing vaccines. As the newer technology becomes mature, the cost of development and manufacturing will decrease. DNA vaccine manufacture will likely not have high adoption costs, giving this class of vaccines the potential to be a disruptive technology. Reduced cost and increased production is necessary to address future vaccine demands.

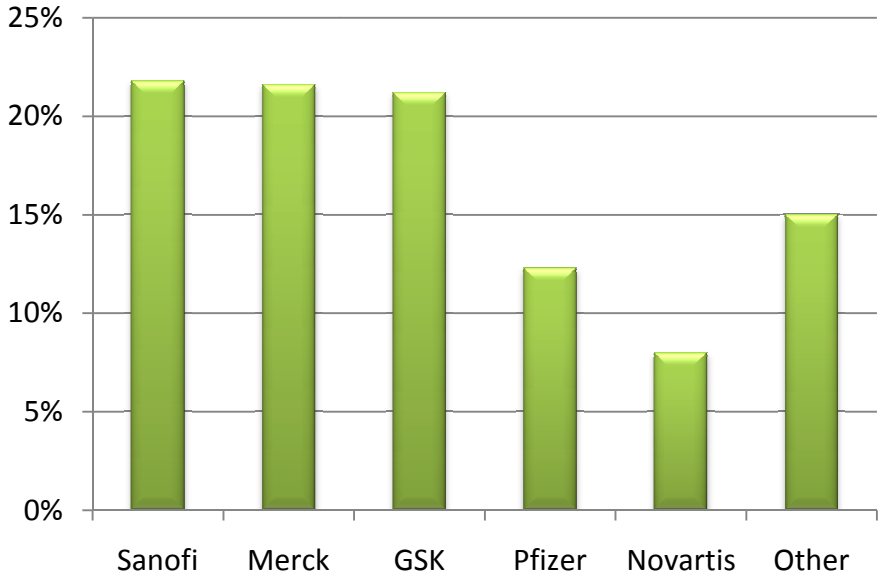
4: DEMAND FOR VACCINES

The demand for vaccines changes based on demographic factors, and disease prevalence in the country region. In this chapter, we will analyze drivers behind high-, middle- and low-income country demand for vaccines. We will further examine demand-forecasting strategies that will help vaccine access to middle- and low-income countries.

4.1 Introduction

In 2009, the global vaccine industry reported US $27 B in revenue (Pr-inside, 2010). This was a 50% increase over 2007, during which there was $18.5 B in revenue; the exceptional revenue yield was in part due to increased influenza vaccine sales in the year of the H1N1 pandemic (Maggon, 2009). Predicted growth continues to be robust, with a calculated compound annual rate of 11.5% during 2008-2016, reaching total annual revenues of $52 B in 2016 (Taylor, 2010). Currently, the five MVCs control 85% of total market share (Figure 4); Sanofi, Merck and GSK alone held 74.5% of the market. By 2012, vaccine revenues are expected to represent 10% of total pharmaceutical sales. The rapid market uptake of high-cost vaccines in the developed world has driven this trend. As the MVCs lose further margins on basic paediatrics vaccines, they will look to increase profits with new vaccines in niche markets.

Figure 4: Vaccine Market Share in 2008



Source: 2009 Annual Reports, Sanofi-Aventis, Merck, GSK, Pfizer, Novartis

The WHO reports that 106 million infants were vaccinated in 2008 (WHO, 2009b). This is the highest level of vaccination reported so far. However, access to vaccines has varied by prices of new vaccines and the income level of the country. In Table 4, we enumerate the World Bank country members by annual GNI per capita.

Table 4: World-Bank Country Income Classification and Annual Births

	High-Income	Upper-Middle-Income	Lower- Middle-Income	Low- Income
Per Capita GNI/year, US $	>12,195	3,946-12,195	996-3,945	<996
Annual Births	13,098,086	17,013,026	75,482,114	28,043,073
Number of countries	69	48	56	40

Source: Adapted from World Bank, 2010b

The number of annual births from 2005-2010 for these income levels was 13.1 million in high-income countries, versus over 75 million in low-income countries. Thus, price sensitivities and

demand volumes at each income level differ widely. In addition, variability in immunization coverage rates, introduction rate of new vaccines, and predictability of demand forecasting further complicate the global market for vaccines.

In this chapter, we will discuss the differences in calculating demand for countries with different economic capacity. We will then discuss the specific vaccine markets of representative countries from each income level, looking at countries that in total comprise over half of the world's population.

4.2 High-Income Markets

In high-income countries such as the US, Japan, and Canada, vaccines costing several hundred dollars per course are usually accepted by government purchasers for the paediatric market. There is an ability and willingness to pay for vaccines. However, population growth also has a direct impact on vaccine industry profitability. With a declining fertility rate in the developed world, the demand for paediatric vaccines is also decreasing. Japan will decline from the current population of 127 million to 100 million by 2050 (Indexmundi, 2010). Therefore, the vaccine industry will have to generate revenues in the high-income markets through new vaccines for other market niches. They will create demand for these expensive vaccines through innovation, marketing strategies, and lobbying to public health officials.

The demand for influenza vaccines has been steadily increasing for the past few years. Concerns about H5N1 bird flu and the H1N1 pandemic have contributed to increased knowledge about influenza in the developed countries. There are now surveillance systems that can accurately predict the demand for flu vaccines. Annually, 50,000 people die from seasonal influenza and over 200,000 people need hospitalization (Cohen and McKee, 2010). An epidemic can cause up to $1 B in healthcare costs. These effects could be mitigated by vaccinating the

majority of the population. However, the US only achieved a 20% vaccination rate amongst 18-49 year olds in 2008. This is the highest rate recorded in the previous 20 years (National Health Interview Survey, 2009). This relatively low uptake is likely because influenza vaccines are one of the few vaccines that are not typically paid for by the government. However, during the 2009 influenza pandemic scare, the US purchased 240 million doses of H1N1 vaccine (Market Research Media, 2009). As concerns of the impact of a pandemic grow, even countries with predominantly private medical systems will likely purchase influenza vaccines to protect their populations. This is one of the segments where the high-income markets will have growth in the future. As a result, MVCs are competing through product differentiation with influenza vaccines.

The vaccine market for international travelers from high-income countries will also expand in the coming years. Dengue, malaria, typhoid and Japanese encephalitis vaccines will have a market for both travelers and developing countries. The RTS,S vaccine candidate is forecast to have a market of US $419 M by 2025 (Businesswire, 2009). Almost all of this value will come from high-margin sales to travelers and the military, as GSK has agreed to sell the vaccine slightly above cost of goods in the developing world.

4.2.1 United States

The US is the largest vaccine market in the world. This is due to a) fast uptake of high-price vaccines by the government, b) a relatively large population of 304 million people in 2008, and c) some of the highest prices in the world for vaccines due to the predominantly private medical system. The CDC vaccine price is often half that paid by private buyers in the US (CDC, 2010c). In 2009, the US accounted for more than 50% of combined vaccines sales of Merck, GSK, Pfizer and Novartis, a trend that is likely to continue (Merck, 2010a; GSK 2010d; Pfizer, 2010a; Novartis 2010d). The US government has made vaccination a public health priority. In 1977, the American Academy of Paediatrics (AAP) called for a universal childhood immunization program

that would be comprehensive and conducted in a timely manner (Paediatrics, 2010). The success of this policy is evident from the 90% or better coverage rates of vaccines to diphtheria, pertussis, tetanus, Hep B, measles, Hib and polio (Childinfo, 2010). In the US, financing vaccines is a joint responsibility between the private and public sector. Childhood vaccines are typically purchased through the federal government's Vaccines for Children (VFC) program, which has an annual US $2 B budget (Welte, 2007). Vaccines for children bought privately are reimbursed through third-party payers. However, the public healthcare system has a minimal role in purchasing adult vaccines. Adult vaccines are largely purchased privately.

4.2.2 Japan

Japan had 127 million residents in 2008. The Japanese vaccination schedule covers fewer paediatric vaccines than in the US and Europe. Hepatitis A & B, influenza, varicella, and mumps are still voluntary vaccines. Even during the recent influenza pandemic, the Japanese paid for the vaccines out-of-pocket (Doshi & Akabayashi, 2010). As the country's vaccination program develops, other vaccines are expected to be included in the national program. The current annual vaccine market in Japan is US $600 M (Vaczine-analytics, 2009). Because of this, Novartis, GSK and Merck are setting up collaborations and facilities in Japan.

4.3 Middle- and Low-Income Country Markets

As the populations of the US and Japan age and birthrates continue to decrease, sales of paediatric doses stagnate in high-income countries. For this reason, vaccine manufacturers are looking to low- and middle-income countries for future revenues. As all these nations gain economic strength, their demand for vaccines also grows.

Middle-income countries are classified by the World Bank as those with GNI per capita above US $950. Though Brazil, China, and India are considered middle-income, their economic

differences are great. Indian's GNI per capita was 1/7th that of Brazil in 2008 and much more similar to Bangladesh, which is classified as low-income (World Bank, 2010a). The markets for vaccine are similarly disparate, in both the access to newer vaccines and who pays for those products. We will discuss the market for vaccines in the most populated countries of each income level: Brazil, for the upper-middle income, China and India for lower-middle income, and Bangladesh for low-income.

4.3.1 Brazil

Brazil had a population of 191 million and an estimated annual birthrate of 3.1 million infants in 2008 (World Bank, 2010c). The public health system pays for most vaccines. The national budget for vaccine purchases in 2008 was an estimated US $550 M (Homma, 2009). Additionally, the government has rapidly adopted additional vaccines to the public vaccination schedule. In 2006, Brazil became the first nation in the world to introduce rotavirus vaccines into the public health program (Wecker, 2006). A second-generation pneumococcal vaccine was introduced to the country in 2010. Both of these early adoptions were part of technology transfer agreements between GSK and the government-controlled vaccine manufacturers in the country. The government generally does not pay for vaccines unless they are manufactured within the country. National manufacturers supply 83% of vaccines for the Brazil's public health system. Brazil is an emerging economy with a growing middle class able to purchase newly developed vaccines on the private market. However, there are few vaccines that are not part of the public health system, so profits from private sales are likely small.

4.3.2 China

China is the world's most populous country, with 1.3 billion individuals in 2008 (World, Bank, 2010c). Due to the one-child policy, China's annual birth rate is roughly 16 million. In 2007,

China was the world's fourth largest vaccine market, with an estimated CAGR of 15% (Zhou, 2007). The Chinese public health system provides scheduled vaccines for TB, polio, DTP, measles and Hep B as well as *ad hoc* vaccination for diseases such as JE. The national producer, CNBG, produces 90% of the doses required for planned immunization programs. The restricted foreign import market is estimated to be only 10% of the total.

However, the private market is expected to increase. 25% of the world's cervical cancer cases are diagnosed in China. Because limited medical infrastructure in rural areas may preclude routine testing for cervical cancer, prevention by vaccination may be more cost-effective than in developed countries. The import value of vaccines in 2008 was calculated to be US $526 M (Research in China, 2009).

4.3.3 India

India's population of 1.1 billion people makes it the second most populated country in the world. Like Brazil, the country's population is young. The country has the largest birth cohort in the world, with 26 million births per year (World Bank, 2010c). India covers the six vaccines under the 1979 EPI under the public health plan. However, in some states, vaccine coverage rates are below 50%; given the large population, if vaccination were to increase only for EPI vaccines, dose demand could double. Like Brazil, an emerging middle class with the ability to afford vaccine purchase is creating a private market. However, due to the limited public coverage for vaccines, there is a much larger potential for this segment in India.

India's middle class is expected to grow from 50 million in 2007 to 583 million in 2025, an estimated 41% of the population. With the expansion of the middle class, the demand for high quality, complex vaccines will also increase as the willingness to pay increases. This is advantageous to the vaccine industry as 80% of Indian healthcare delivery is managed by the

private sector (Mukherji, 2005). Expensive vaccines such as HPV will be in high demand as, like China, nearly 25% of the world's cervical cancer patients live in India (Esciencenews, 2010).

4.3.4 Bangladesh

Bangladesh is the seventh most populous country in the world, with an estimated 160 million residents in 2008 and 3.4 million births (World Bank, 2010c). Its population density is one of the highest in the world, increasing the risk of rapid spread of infectious disease.

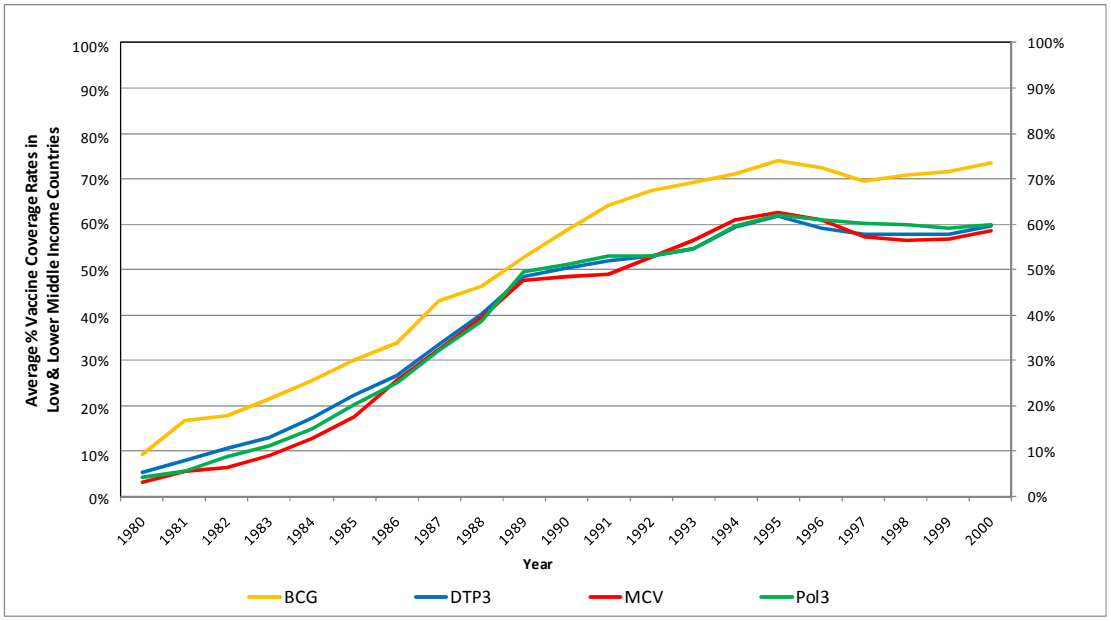
In collaboration with the WHO, Bangladesh has built a robust vaccination infrastructure. Between 1985 and 1995, vaccination coverage of children increased from 2% to 76%. Bangladesh's vaccination schedule for infants includes BCG (to prevent non-pulmonary TB), measles vaccine, OPV, DPT and Hep B, which was added in 2008 with GAVI support. Although this introduction came many years after Hep B was available in the western world, access to other newer vaccines should be more rapid; Bangladesh's multiyear vaccination plan also intended the introduction of pentavalent vaccines containing Hib in 2008, the first time this vaccine would be part of the national vaccination program. The country spent US $7.3 on each of 3.7 million infants in 2010. Almost half of the cost of the coverage was borne by the country (WHO Bangladesh, 2010).

Bangladesh is comprised mostly of low-lying plains susceptible to floods. Pools of stagnant water are a by-product of the environment and the ideal breeding ground for mosquitoes, the vector for both dengue and malaria. Cholera is also endemic to the country. IVI tested their cholera vaccine candidate in the capital of Bangladesh (IVI, 2010c). The World Bank predicts that Bangladesh may become a middle-income country by 2016. If the economic growth continues, any vaccines to these diseases that have reached the market may be purchased by a growing middle class on the private market.

4.4 Calculating Demand for Low- and Middle- Income Countries

Because low- and middle- income countries have limited resources for medical infrastructure, assessing the need for vaccines can be problematic. One method for calculating vaccine demand is to enumerate the number of births and surviving infants in each country. However, the percentage of individuals receiving vaccines in developing countries has been very low. Over the past two decades, the global health community has worked with countries to improve coverage rates to the levels of 80% in most countries (Figure 5). The majority of the world's population resides in low- and middle-income countries. With increased immunization coverage rates for newer vaccines, these countries could demand very high volumes of vaccine.

Figure 5: Vaccine Coverage Rates in Low- and Lower Middle-Income Countries from 1980-2000

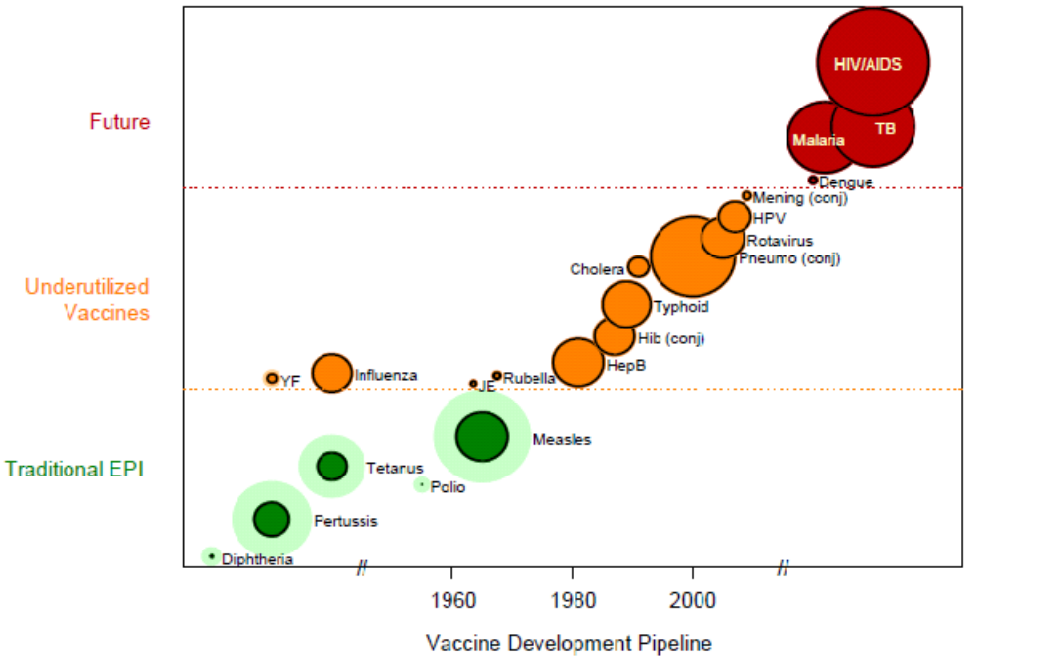


Source: Adapted from WHO, 2010a.

4.4.1 Priority Vaccines

In 2007, the WHO selected a group of disease experts to prioritize infectious agents based on ten criteria including mortality, economic impact, disease incidence, and long-term sequelae. The analysis revealed diseases that should be global health priorities. The WHO defined these disease areas as recommended areas of investment in vaccine R&D (WHO, 2007b). These were re-categorized by GAVI to reflect those with the biggest impact in the developing country perspective, illustrated in Figure 6 (WHO, 2008).

Figure 6: Evolving Vaccine Pipeline for Developing Countries



Sources: Adapted from GAVI Alliance, 2008; WHO, 2010a.

Meningococcal B, influenza, varicella, and hepatitis E were not included on the priority list for GAVI-eligible countries. Similarly, MVCs removed many of the diseases specific to

developing countries from their vaccine R&D pipelines. The common interest of MVCs and developing country manufacturers, which has been advantageous for developing country markets, is to produce vaccines for diseases that are prevalent globally. However, as vaccines to these diseases reach the market worldwide, the product pipeline of HICs begins to diverge from that of LICs. MVCs are demanding incentives to develop products that will not serve the public sector high-income markets. The need for low-cost developing country manufacturers with an interest in developing vaccines that are not appealing to MVCS will increase.

4.4.2 Demand Forecasting for Low- and Middle-Income Countries

Challenges with information exchange and knowledge dissemination in the developing world currently limit demand for vaccines. Once disease evidence and potential vaccine impact data has been generated, those that make the decision to purchase must understand the economic impact and funding alternatives related to introducing a new vaccine. These decisions need to account for the availability of donor funding, infrastructure requirements, and many more fluctuating variables. Thus, a decision to adopt a new vaccine must be considered very carefully and action can therefore take months or years.

Introduction of vaccines is often slow. The initiation of the GAVI Alliance and demand creation efforts through Product Development Partnerships (PDPs) have accelerated vaccine introduction (GAVI, 2008). In order to continue this trend, increased donor financing and significant increases in vaccine production efficiencies will be required.

As the number of vaccines available increases, financial and capacity restraints will further complicate adoption decisions. Many companies, including MVCs, will focus on generating vaccines for low-volume, high-price markets when demand uncertainty exists (Levine, Kremer & Albright, 2005). Therefore, the importance of regional manufacturers in developing countries to provide vaccine solutions for their local markets is critical.

Over time, the global health community has applied knowledge from earlier vaccine introductions to reduce the time until vaccines are available in developing countries. As a result, newer vaccines are entering low- and middle-income countries earlier in the product's lifecycle. Adoption of new and novel vaccine products may have a great impact on morbidity and mortality; however, the products may not have been formulated with optimal levels of immunogenicity, dosing, formulation, or duration of effectiveness. Therefore, new vaccines may require high dosing requirements, multiple boosts, or administration to older children or adults who are not part of the standard vaccination system. The requirements will further complicate immunization practices where there is limited medical infrastructure, further affecting the confidence of demand forecasting. This uncertainty makes negotiations to lower vaccine price difficult, and for high-cost vaccines, manufacturers may not engage in price negotiation at all.

5: THE CHALLENGES TO VACCINE ACCESS FOR LOW- AND MIDDLE-INCOME COUNTRIES

As we have outlined in the previous chapter, there is a large demand for vaccines in low- and middle-income countries. The key differential between such countries and high-income nations is the degree to which the free market meets demand. Access to medical intervention is unequal between the developing and developed worlds. While vaccination rates for old vaccines generally approach that of the US and Europe, this is not the case for new vaccines. The lag between vaccine licensure in the US or Europe and distribution in poor countries is typically 10-15 years (Breitstien, 2009). This exacerbates differences in disease specific mortalities by income level, as illustrated in Table 5. For example, the current use of vaccines against diarrhoeal diseases in high-income countries means that there are 1.3 deaths for every 100,000 individuals. In contrast, in low-income countries, almost none of whom have access to rotavirus vaccines, there are 55 deaths per 1000,000 people per year due to diarrhoeal disease. Collectively, greater than 76% of deaths related to these diseases occur in lower- middle-income and low-income countries.

Table 5: Projected mortality by cause and income group, 2008

YEAR OF VACCINE AVAILABILITY (WHO PQ)	CAUSE	HIGH-INCOME	UPPER-MIDDLE INCOME	LOWER-MIDDLE-INCOME	LOW-INCOME
2016	HIV/AIDS	29,239	453,681	189,832	1,569,845
2015	Dengue	125	209	5,160	7,405
2014	Malaria	193	2,039	39,542	795,850
2012	Typhoid*	13,341	28,095	224,958	1,420,821
2009	Cholera*	13,341	28,095	224,958	1,420,821
2009	Japanese encephalitis	19	166	3,911	9,461
2009	Meningitis	2,998	8,317	47,119	211,689
2004	Rotavirus*	13,341	28,095	224,958	1,420,821
1981	Hepatitis B	6,144	3,554	31,694	47,259
1963	Measles	15	582	24,617	302,527
1963	Polio	628	33	95	339
1948	Tetanus	118	262	14,032	113,847
1948	Diphtheria	0	67	195	3,672
1948	Pertussis	39	856	7,229	185,972
1926	Tuberculosis	13,463	64,977	356,349	815,184
	Population (000)	990,793	588,913	2,526,554	2,594,318

*Total deaths due to diarrhoeal diseases

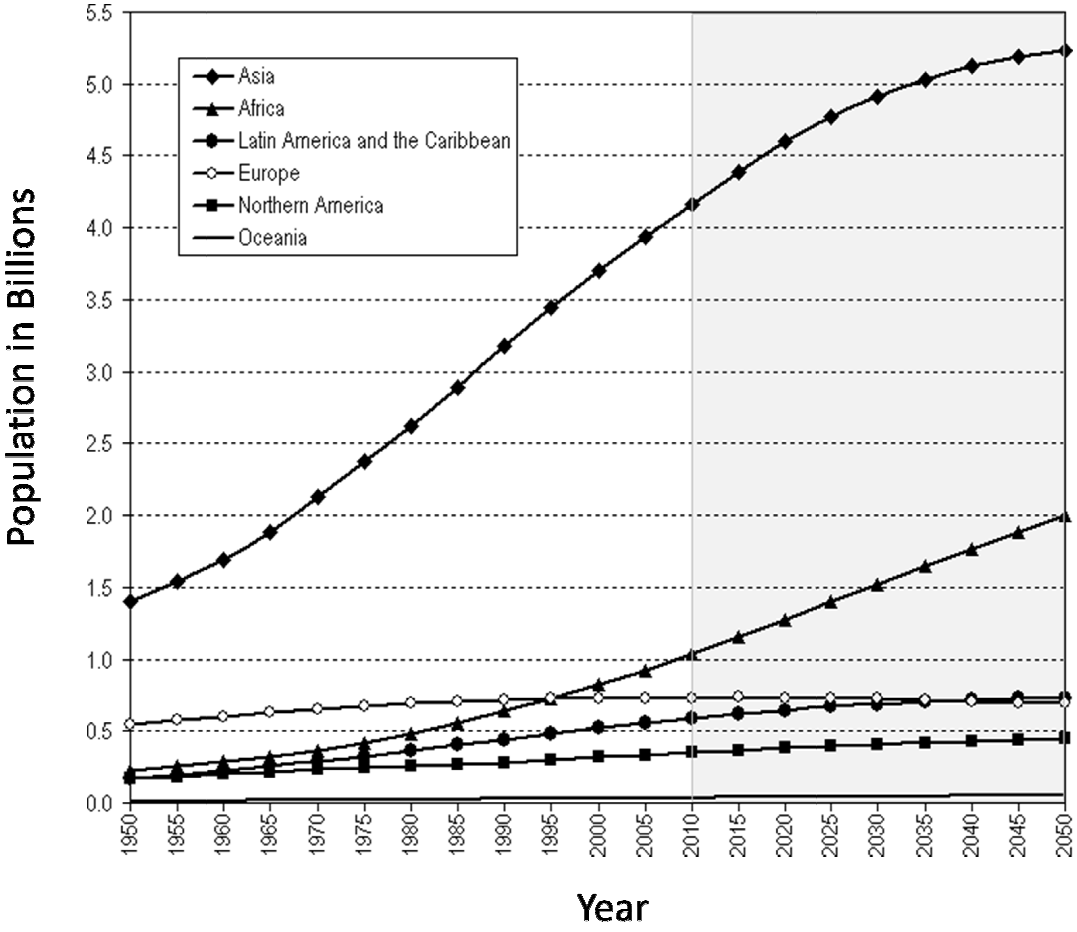
Sources: Adapted from WHO, 2010b.

The reasons for this inequity are many. Firstly, the very classification of countries as low- and middle-income highlights their limited ability to pay for medication. While vaccination is one of the most cost-efficient medical interventions available, the high price demanded for innovation means that new vaccines can cost as much as 1000 times that of old vaccines. While the five MVCs have engaged in some differential pricing for low- and middle-income countries, to date direct-country negotiation has only regularly occurred with countries where there are other incentives for the MVC, such as exclusive access to a large population. When MVCs do price negotiate with individual developing countries, they typically do not disclose the agreed price publicly. Therefore, countries with similar per-capita incomes may pay very different prices. As a result, countries may be reluctant to negotiate at all. If they do, they may be unable

to commit to multi-year purchases due to economic volatility. Political instability in some emerging countries also limits the ability to guarantee purchases, contributing to MVC reluctance to participate in developing world markets.

As illustrated in figure 7, vaccine supply is not keeping pace with the population growth predicted for the next 40 years. Asia and Africa is forecast to have a population of ~7.25 billion, but current vaccine production levels are not even sufficient to support the current demands. The majority of the world's population lives in developing countries; birth cohorts are also a proportionally larger percentage of the population.

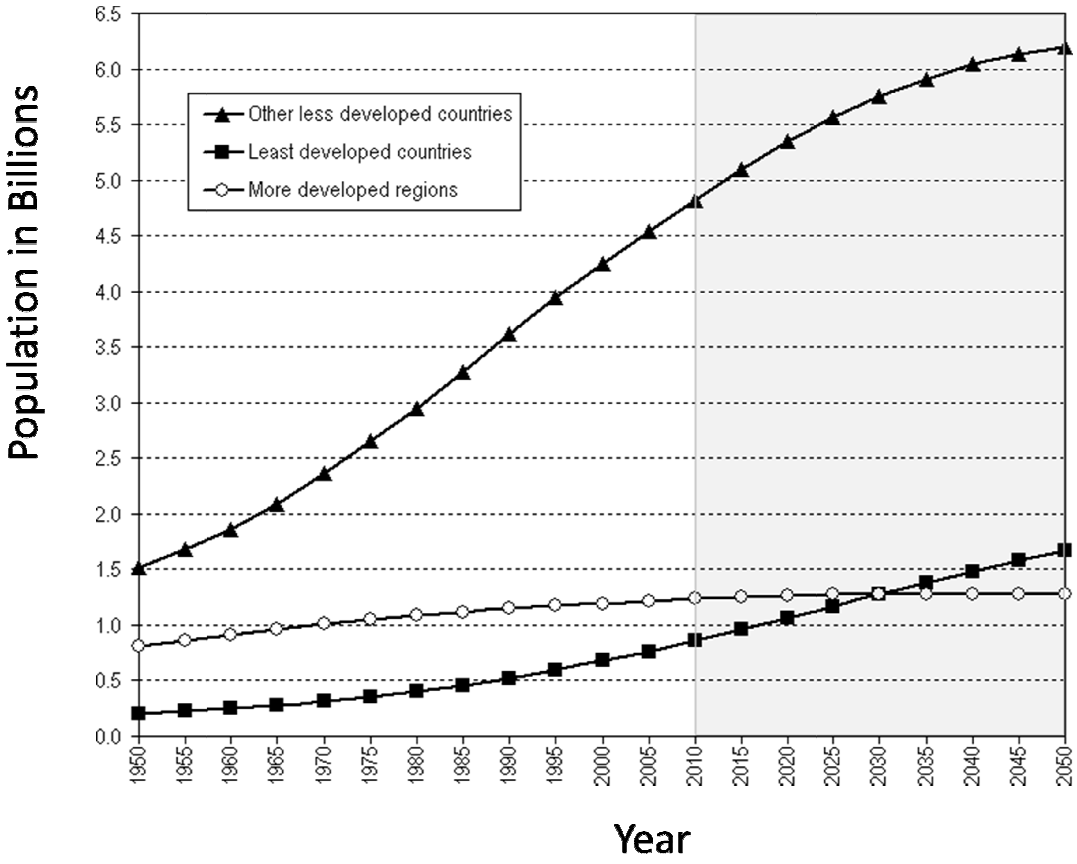
Figure 7: Population by major geographical region, 1950-2050(in billions)



Source: United Nations, 2009a

Therefore, the number of vaccine doses required by developing countries vastly exceeds production, as demonstrated in Figure 8. MVCS often do not have the capacity to produce the total worldwide doses required. As the global population continues to increase, ability to meet future demand will be even more limited. Because of the relatively low margins from vaccines bought by low- and middle- income countries, there is often not sufficient incentive for MVCs to expand capacity.

Figure 8: Population by development region, 1950-2050(in billions)



Source: United Nations, 2009b

By 2050, there will be 6 billion more people in developing countries than the in the developed world (Figure 8). The demand created by this population is unlikely to filled by the MVCs. Infrastructure in the destination countries for contracting out the manufacturing process

is limited. Vaccine shortages like the H1N1 pandemic influenza in 2009-2010 will continue if current capacity is not increased, and they will disproportionally affect poor countries.

Even when the capacity is available, the format of vaccine doses used in the developed world often does not meet the needs of the developing world. As outlined in Chapter 3, the MVCs have no incentive to invest in innovations unless the resulting differentiation increases profit margin or accesses to another market segment in high-income countries. The risk of unstable markets and low margins also deter MVCs from investing in new vaccine development for diseases that predominate in developing countries. Local suppliers in developing countries usually have limited R&D experience and financial resources to develop these vaccines independently. With international travel as a commonplace event, and changes to global climate, some of these diseases will expand to become global concerns unless there is near-term intervention.

Population growth in the developing world illustrates the need for increased vaccine supply to low- and middle-income countries. Though the challenges to adequate supply in the free market are many, the public-health benefit of vaccines has meant that there are many innovative incentives available for improved vaccine development and access. While such market support is clearly needed, the pace of change is still insufficient. In Chapters 6 & 7, we will evaluate the current models used to improve vaccine supply. We will assess their cost as well as their ability to build sustainable vaccine industry infrastructure and recommend whether they should be continued, modified or abandoned. We will propose models not yet in practice. Finally, we will make strategic recommendations on a complementary model to improve vaccine development and access for the future.

6: ESTABLISHED VACCINE ACCESS SYSTEMS

Equitable vaccine access for the developing world has been supported since the 1930s, when the Rockefeller Institute in New York transferred technology for the manufacture of yellow fever vaccine to Brazil (Neto & Jayaraman, 2009). In the 1970s, organizations such as the WHO have developed international programs to improve vaccine use in low- and middle-income countries. There have also been longstanding free-market practices that have allowed eventual access to vaccines, and some MVCs have donated doses under specific circumstances. In this chapter, we will provide a brief history of longstanding vaccine access systems, and analyze the strengths and weaknesses of ongoing programs from supranational organizations.

6.1 History of Supranational Support for Vaccines

Until 2000, the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) led the management of global vaccination initiatives. In 1974, the WHO launched the Expanded Program on Immunization (EPI). This program gave global guidelines for recommended childhood vaccines and a schedule for their administration. The expanded list added polio, measles and tuberculosis vaccinations to those against already suggested for diphtheria, pertussis and tetanus (GAVI, 2010). Smallpox was eradicated after an intensified vaccination eradication effort between 1967 and 1977.

6.2 Supranational Programs

For decades, the UN has played a central role in providing access to vaccines for low-resource economies across the globe. With the influence of the BMGF over the last 15 years, the

UN now also works in partnership with private and NFP organizations. Their predominant role is in procurement and health systems strengthening for the developing world. Significant UN programs that aid access to high-quality vaccines are described below.

6.2.1 UNICEF Procurement

The UNICEF Supply Division purchases vaccines using funds from a variety of sources. These include GAVI funds and contributions from recipient nations. In 2007, UNICEF spent approximately $620 M on vaccines for children in almost 100 countries (UNICEF, 2010b). Because UNICEF procures mostly low-cost vaccines and receives differential pricing from suppliers, this money purchases 40% of the total global vaccine doses used annually. The UNICEF Supply Division generally procures for all low- and middle-income countries eligible for GAVI funding, unless the nation is able to procure through Pan American Health Organization (PAHO's) Revolving Fund. Both GAVI and PAHO are described below. UNICEF charges a handling fee of 3-4.5% for vaccine procurement, depending on the vaccine type and country income level. The total funds for the vaccine must be deposited with UNICEF before the vaccines are purchased. This can be an onerous requirement for poor countries.

UNICEF also tries, where possible, to purchase from multiple manufacturers to strengthen the security of vaccine supply (IAVI, 2008b). As an example, they procured from all the prequalified manufacturers of pentavalent vaccine in their last purchasing cycle. While this approach is commendable for ensuring a consistent supply, it can prevent recipient countries from receiving the formulation of the vaccine best suited to the needs of the country.

6.2.2 PAHO Procurement

PAHO's "Revolving Fund" for vaccine procurement was created in 1979 to assist in stabilizing vaccine access for the Americas. There are 37 member states in PAHO, most of whose

annual GDP excludes them from gaining access to GAVI funding (IAVI, 2008b). The PAHO Revolving Fund offers several advantages over UNICEF's procurement process. Firstly, unless the country requires a large amount of doses, funds need not be deposited into the Revolving Fund before procurement begins. Secondly, the administrative fees are lower than of UNICEF. As shown in Table 6, PAHO's bulk procurement has lowered prices for its members. Prices are now often equivalent to those received by GAVI.

Table 6: Vaccine Price Per Dose Comparison 2010, US $

Vaccine	US CDC	GAVI	PAHO
Pentavalent, fully liquid	n/a	3.01	3.20
Hib	8.83	3.40	2.25
Pneumococcal conjugate	91.75	7.00	20.00
Yellow Fever-10	n/a	0.90	1.15
Rotavirus 2 dose scheme	83.75	n/a	7.50

Sources: CDC, 2010c; UNICEF, 2010c; PAHO, 2010

Recently, PAHO's vaccine procurement prices have been challenged. The organization's mandate is to receive the lowest price possible for vaccines. GAVI also demands the same. However, the majority of the countries that the PAHO serves are middle-income countries. MVCs recognize that middle-income countries may be their best source of profit growth, and are no longer willing to discount their prices for PAHO at the same level as they would for GAVI-funded low-income countries. This is problematic because there is often income inequity within the PAHO countries, so that some regions or individuals cannot afford an increase in vaccine

price. PAHO is now re-evaluating their procurement strategy. This will ideally allow price differentiation between low- and middle-income countries while still allowing robust vaccination coverage rates in countries of both income level (Medical News Today, 2009c).

Despite this negotiating issue, PAHO has benefited its 37 member states by pooling vaccine requests to maximize negotiating power and to standardize annual demand. We believe this model may work well for other geographic regions that contain middle-income countries who cannot procure through GAVI.

6.2.3 WHO Programs

Since 1989, the WHO has had a program to assess the safety of vaccines supplied to UN agencies and other supranational partners (WHO, 2006). A prequalification process for delivery devices was initiated in 2005 (IAVI, 2008b).

The WHO provides extensive guidelines that must be met for a vaccine to be considered for prequalification. For countries that produce vaccines, the NRA must carry out the following six functions independently, with the power to enforce:

- a published set of requirements for licensing;
- surveillance of vaccine field performance;
- system of lot release;
- use of laboratory when needed;
- regular inspections for GMP, and
- evaluation of clinical performance (WHO, 2010c).

The recognized NRA must approve the vaccine for domestic use before the manufacturer can apply for prequalification.

The prequalification process includes inspections of the vaccine production facilities additional to those done by the NRA. These inspections focus on adherence to Good Manufacturing Practices (GMP). This is a set of guidelines internationally recognized by manufacturers and regulatory authorities as necessary for the quality manufacture of medicines. Another criterion is batch testing of samples from at least three lots of the vaccine for consistency. Prequalification is awarded for a period of 2 years, but can be extended to five if no manufacturing issues have occurred in the two-year period.

The WHO also has a mandate to strengthen NRAs across the globe. This has included the WHO-initiated formation of the Developing Countries' Vaccine Regulators Network, which is a group of representatives from fully functional NRAs that discuss trials appropriate for vaccines in their countries. This has proven uniquely valuable as the network identified a potential interaction issue between the rotavirus vaccine and oral polio vaccine; since OPV is not used in developed countries, this consideration would not have been made by those NRAs (Nishioka, 2008). The WHO also offers a training network for vaccine quality; to date, more than 300 vaccine industry affiliates have participated (WHO, 2010d). The country that produces the most vaccines, China, does not have a recognized NRA, and for this reason cannot sell their vaccines to UNICEF. The WHO is assisting China in building internal capabilities to establish an NRA. Given China's manufacturing dose capacity, building regulatory capability could dramatically increase vaccine supply. This process should be continued.

6.3 Differential Pricing

Differential or tiered pricing has greatly facilitated vaccine access for low- and middle-income countries. All the MVCs engage in differential pricing (Plahte, 2005). The concept of differential pricing is to charge customers based on their ability or willingness to pay. Differential

pricing is a widely accepted method of revenue maximization (Miravete, 2005). For vaccines, high-income countries generate the maximum profits (Plahte, 2005). Additional revenues are made on lower margins from lower income countries. Pricing has been significantly differentiated for vaccines purchased through UNICEF and PAHO, where large volume purchases also facilitate buyer power. Prices for the six basic vaccines recommended by the EPI and procured through UNICEF and PAHO are less than 10% by high-income countries.

There are two main factors affecting the vaccine price: production volume and product life- cycle stage. Given that manufacturing costs are predominantly fixed, the higher the volume of production, the lower the cost. New vaccines always have initial high prices, to recover the investment on R&D, clinical trials, manufacturing facility and marketing. In the past, vaccine prices only dropped to a level of affordability for low- and middle-income markets after recovering the cost of investment. Typically, it would take 15-20 years for a vaccine to reach a life cycle stage where developing countries could afford it. With low returns on older vaccines, MVCs are switching to production of higher value vaccines. These often have complex manufacturing processes that diminish production capacity, resulting in higher prices. Additionally, vaccines for diseases that are not endemic in the developed world will not be candidates for differential pricing. This further highlights the need for regional vaccine development programs.

Bulk procurement by UNICEF means lower transaction costs and lower vaccine prices. UNICEF, PAHO and other pooled procurement organizations should work together to develop joint strategies to maintain and broaden differential pricing policy. The bids by MVCs for the pneumococcal AMC, described in section 7.1.12, suggest that guaranteed demand over the long-term facilitates differential pricing.

Maintenance of differential pricing will be especially important in the near term, as some lower-middle-income countries are about to become ineligible for GAVI support and access to GAVI vaccine prices.

6.4 Vaccine Donations

In 2007, Merck provided the first donation of a vaccine that had been licensed for high-income country markets in the same year. In 2005, there was an outbreak of rotavirus in Nicaragua. While the country could not afford the new vaccine, they agreed to be a partner in assessing the outcome of a vaccination program in an environment with limited medical infrastructure. Merck, in turn, donated three year's worth of Rotateq to the country. In 2009, Wyeth contributed a newer vaccine for another significant disease agent. 3.1 million doses of Prevnar 7 were donated through GAVI to the Gambia and Rwanda, the first two countries in Africa to introduce this vaccine (GAVI, 2009). Recognizing the seriousness of pandemic influenza, in 2007, GSK and Sanofi donated a combined 110 million doses of H5N1 vaccine to the WHO's stockpile initiative. These vaccines were distributed to low-income countries (Medical News Today, 2007; Johnson, 2009).

While these donations are significant, they are predominately for the purpose of demonstration. For newer vaccines, the ultimate purpose is to model successful vaccine usage in low resource settings in order to facilitate uptake in other low- and middle-income nations. Merck explicitly discussed assessment of the public health benefits of early adoption as a component of the project (Merck, 2009). While it is highly commendable that Merck and other manufacturers engage in long-term donations to make the benefits and limitations of vaccine use transparent, it is not a sustainable model for ongoing vaccine access to the broader low-income market, as it is dependent on the need of the manufacturer to make a case for

purchasing the vaccine. It may also have the unintended consequence of delaying introduction to other low-resource countries until the benefits are 'proven'. While we recognize the value of vaccine donations for modelling efficacy in low-resource settings, we recommend that phase III trials be run concurrently with ones in high-income countries, so that speed to access can be optimal.

In the long-term, dependence on donations is not a viable mechanism for improving vaccine access. In seasonal products, such as flu vaccines and commoditized vaccines, MVCs can donate at relatively little net cost. Donation is not a reliable source of vaccines as this is often dependent on an oversupply from the free market. It is unlikely that newer vaccines will be donated until developmental and capital costs are recovered. Lastly, vaccine donations contribute little to capacity in developing countries or to strengthening global vaccine supply.

The established mechanisms for vaccine supply are generally positive and should be continued. However, in their current form and capacity, they have not truly equalized access to vaccines. In the next section, we will examine newer initiatives that are working to increase access to vaccines.

7: ALTERNATIVE ACCESS MODELS

In addition to long-term efforts from MVCs and supranational organizations, there are other newer models intended to provide vaccine access to low- and middle-income countries. In this chapter, we analyse such models to understand their strategic importance. Furthermore, we will propose and discuss a new model that can support sustainable vaccine development that meets developing country demands.

7.1 Public – Private Partnerships

A Public-Private-Partnership (PPP) is a relationship between at least one public and one private organization, where both groups share the risks and benefits (Widdus, 2003; Buse & Walt, 2000). Vaccine development by public entities dates back to US President Roosevelt's "The March of Dimes" foundation, which supported the successful development of the first polio vaccine (March of Dimes, 2010). Since then, there have been number of PPPs that have delivered cost-effective vaccines for the developing world. Partnerships are economically efficient as they share risk and cost between the parties involved.

The global health community is greatly interested in the development of new vaccines against malaria, tuberculosis, diarrheal diseases, and HIV/AIDS. While these diseases kill thousands of people each day, the most affected countries lack sufficient purchasing power to incent robust efforts for vaccine development. The need for PPPs to generate such vaccines is due to the lack of traditional free market forces that encourage market-based innovation, or market failure (Rangan, Van Wassenhove & Samii, 2003). Private-sector investment in R&D

efforts is unlikely when the financial returns are low and even unpredictable (Sciencebase, 2010).

Economic theory assumes that a perfectly competitive market is driven by self-regulated mechanisms of supply and demand. However, the vaccine market fails for developing countries as it suffers from information asymmetry (the manufacturer has more information than the purchaser), bounded rationality (not all problems are known and can be accounted for), and potential opportunism (promotion of perceived self-interest, for example, MVC set high prices that make vaccines unaffordable) (Rice, 1998; Slater and Tonkiss, 2001). The extent of these problems leads to very high transactions costs in developing new vaccines for the developing world, where private companies are not willing to take on the burden. PPPs are useful when there is a significant public benefit and profit uncertainty is high for private companies. A public partner can minimize the high transaction costs of governance, contract management, intellectual property management, clinical trial management, and regulatory affairs using public resources (Rangan, Van Wassenhove & Samii, 2003). For diseases such as malaria and AIDS/HIV with particularly heavy disease burden, there should be a near-term global response with both public and the private sector working together. MVCs are beginning to place value on neglected diseases drug development. The companies see benefits in fulfilling increased public demand for corporate social responsibility, strengthening their access to low-cost resources and highly skilled researchers in the near-term and increasing margins as the economies develop over the long-term. As emerging economies strengthen, free market vaccine development may be able to predominate.

Unlike in infrastructure PPPs where governments are looking to transfer risk to private companies (Vining & Boardman, 2008), vaccine PPPs take on risk to encourage private companies to develop new disease prevention solutions. Their mandate is often to fund high-

risk and high-cost projects to develop vaccines targeting the developing world demand. A well-developed PPP with clear objectives and strategies will help to ensure returns for both public and private partners. This is especially important for global vaccine PPPs initiatives, where governments and companies from many nations are involved.

The most appropriate place to conduct research and clinical trials for vaccines targeting the developing world is in the disease-affected regions. Vaccine efficacy can vary dramatically for those with underlying health issues such as malnutrition or chronic endemic infections. However, a major obstacle for clinical trials in many developing countries is poor medical facilities and lack of regulatory systems to oversee safety practices. The participation of global health organizations brings a diverse set of expertise and resources. They can bridge the gap between free-market industry and emerging economies to reach a common goal of delivering vaccines for neglected, preventable diseases.

It is also important to recognize that PPPs may not be desirable when there is inequity and ethical dilemmas related to the population that they intend to benefit. There is concern that some countries are chosen because of favourable geographical, social and political considerations (Walt & Buse, 2000). Therefore, it is imperative that the developing country partner selection process is governed by ethical and social principles.

One of the major concerns about vaccination related PPPs is the drive towards cost-effective, rapid results. While this seems positive in many aspects, there is a risk that the focus will be on short-term interventions rather than long-term improvement for the health care system as a whole. Therefore, PPPs have to consider sustainability when developing project goals (Martens, 2007). The funding has to be carefully allocated in order to gain the maximum benefit. There are two types of PPPs that contribute to vaccine access: financing and product development partnerships.

7.1.1 Financing Partnerships: GAVI

Recognizing a desire to provide more rapid access to vaccines in the developing world, the Global Alliance for Vaccine Initiative (GAVI) was begun in 2000 (Diamond, 2005). A US $750 M grant from the Bill and Melinda Gates Foundation (BMGF) seeded the organization; within 5 years, donor funds from wealthy governments and matching funds from private donors matched the initial amount. In addition to BMGF, GAVI membership included the WHO and UNICEF, government representatives, and for-profit vaccine manufacturers. The Alliance's initial focus was to improve access to vaccines beyond those in the 1974 EPI, including yellow fever, Hib and Hep B vaccines. While the price of the three 'original' vaccines combined was less than $1, Hib and Hep B cost significantly more, putting them out of reach for low-income countries. Financing of vaccines became GAVI's key mandate while UNICEF continued to procure the majority of vaccines with funds from GAVI.

GAVI has provided support to countries based on their 2003 GNI. However, their criteria are about to change. Eligibility for assistance will be limited to countries with per capita GNI less than US $1500 (GAVI, 2010). This change reduces the number of eligible countries from 72 to 58, excluding countries such as India. However, the latest poverty report from UNDP shows that with 421 million poor people, India has more individuals below the poverty line than all the African countries combined. The GAVI policy will challenge access to current differential vaccine prices and may even risk current supply levels (BBC, 2010).

Over the past decade, GAVI has created several initiatives that utilize market forces to fund these efforts. They are as follows:

7.1.1.1 International Finance Facility for Immunization (IFFIm)

This program launched in 2006. The IFFIm issues bonds that are based on legally binding long-term financial commitments from high-income country governments, transforming the

pledges into immediate cash. As of the third quarter of 2009, the IFFIm raised over US $2 B, of which GAVI has disbursed $1.2 B. This has doubled the organization's purchasing power (IFFIm, 2009). Highlights of funding allocation include:

a) Purchase of reformulated multivalent vaccines;

b) Polio vaccine purchase as part of efforts to complete eradication of the disease

c) 1/3 of the funds were allocated to purchase of new and underused vaccines

Despite concerns about the impact of the global recession on the IFFIm, four countries initiated or added funds for the IFFIm in 2009; US $1.1 B was raised on bond issuances.

7.1.1.2 Advanced Market Commitments

The Advanced Market Commitment (AMC) program is a mechanism designed to 'pull' vaccine development into the market. It encourages the development of vaccines for the developing world through long-term financial commitment. It also reduces the lag time before a new vaccine reaches the developing country markets. Bidding manufacturers commit a set amount of supply over a number of years. Manufacturers receive a higher price per dose in the early years of the commitment, and lower per-dose prices once AMC funds are depleted. Pneumococcal vaccines were chosen for an AMC pilot study. In February of 2007, five donor countries - Canada, Italy, Russia, Norway, and the UK, as well as the BMGF - contributed a combined $1.5 B to the pneumococcal AMC. In 2009, requests for manufacturing offers were made. Four manufacturers placed bids within a month of the initial request: GSK, Pfizer, Serum Institute of India, and Panacea Biotec. In March of 2010, GSK and Pfizer were each awarded contracts to produce up to 30 million doses per year for 10 years. Under the terms of the contract, they will be paid $7 per dose until AMC funds are depleted; this will then drop to $3.50 per dose for the remainder of the contract. In developed countries, pneumococcal vaccines sell for $50-60 / dose. The AMC provided immunogenicity, formulation, and delivery specifications

in a target product profile prior to soliciting manufacturing bids (AMC, 2008). This suggests the significant buying power afforded when purchases are made in high volume. Additionally, GSK announced that it would open a second manufacturing plant for Synflorix in Singapore shortly after receiving the AMC contract.

The AMC has come under criticism for failing to negotiate vaccine prices to be low enough to allow purchase by LICs (Pollack, 2010). In 2009, Brazil and GSK signed a pneumococcal vaccine purchase agreement where the vaccine was discounted to $17.50/dose in exchange for a long-term commitment to purchase, suggesting that the $3.50 price per dose will approach affordability for all but the poorest countries (Neto & Jayaraman, 2009).

The AMC has also been criticized for providing financial incentive exclusively at the post-marketing stage, rather than encouraging vaccine R&D for unaddressed diseases. It is also not clear why the two MVCs were awarded AMC funds before the Indian manufacturers. If the pilot is successful in accelerating access to developing countries, the choice of the next disease target will address or heighten this concern. A malaria vaccine AMC has been proposed. If vaccines for this disease were to be the next candidate for AMC funds, funding should not go to manufacturers who have also received 'push' funding through the Malaria Vaccine Initiative for their R&D.

7.2 Product Development Partnerships (PDPs)

A Product Development Partnership (PDP) is a specific type of PPP mandated to develop a new drug or vaccine. Often, no single entity has the resources, intellectual property, and knowledge to undertake all activities in the value chain for vaccine development. However, collaborations within a group can achieve more by pooling resources (Bazzoli et al., 1997). In a

PPP, the public partner typically provides funding incentives to the private partner in exchange for access to their drug development knowledge and infrastructure.

Push and pull funding mechanisms are drivers of successful PDPs. Push mechanisms operate in the research and development stages of the value chain. Public partners contribute policy assistance and direct research funding to reduce the risk to the private entity. Companies can focus on early-stage discovery activities where their expenses are reduced in a way that is attractive to shareholders. They can also conduct expensive late-stage development activities in collaboration with the public partner. Pull mechanisms operate in later development stages through creating market opportunities. Pull mechanisms include assured priority regulatory review by robust NRAs and guaranteed procurement contracts upon licensing approval. These funding mechanisms are considered "social venture capital" that brings affordable treatments and preventive mechanisms to the developing country markets (Wheeler & Berkley, 2001). Like true venture capital contracts, deals structures are designed to align investments with project goals. PDP partners are accountable for their actions and financial management.

The main goal of a PDP is to develop a new vaccine or a delivery technology that has been neglected by the free market. This is achieved through funding MVCs to develop new vaccines or building a specific PDP consisting of private companies and public entities. The development process can also build vaccine development capacity within a developing country or region. PDPs can assemble bridging social and financial capital from various parts of the world for a common goal (Szreter & Woolcock, 2004). This can provide sustainable infrastructure for future development, innovation, and economic growth.

7.2.1 Funding MVC Programs- Malaria Vaccine Initiative RTS,S

MVCs have little interest in developing vaccines for a market where the returns might not justify the investment. The drug industry often abandons such products due to the lack of

commercial market. PDPs with funding from public sources can re-initiate development on such products. Work prior to PDP investment often means that the path to licensure is shorter and less risky than for *de novo* development. PDPs with MVCs are strategically important in accessing potentially successful vaccine candidates for late stage development. The partnership between the Malaria Vaccine Initiative (MVI) and GSK is an example of a PDP that has re-initiated development on a vaccine candidate (Malaria Vaccine, 2010).

MVI is a PATH initiative established with a US $200 M grant from the Gates Foundation to accelerate the discovery of a malaria vaccine. MVI also has the mandate to make the vaccine available at an affordable price to low-income countries. In 1987, GSK invented the anti-malaria RTS,S vaccine candidate (Ballou & Cahill, 2007). However, this project progressed at a very slow pace until GSK and PATH signed a collaboration agreement in 2001 to pursue the paediatric clinical development of RTS,S in Africa.

There were 247 million reported cases and nearly a million deaths attributed to malaria in 2008 (WHO, 2010e). Malarial disease disproportionally affects children. In Africa alone, a child dies every 45 seconds from malaria, accounting for 20% of all childhood deaths. The morbidity associated with the illness has a profound economic and social impact, impeding normal childhood development. Given these facts, an urgent solution is required.

MVI is providing finances and trial expertise for phase III trials in Africa to support GSK's development efforts. African researchers and collaborating institutions in seven countries have joined the partnership. Under the current plans, RTS,S will be submitted for regulatory approval in 2012 with marketing in 2013 (GSK, 2010e). Under the partnership, GSK has agreed to set the price just above the cost. The small return will be invested in next generation malaria-vaccine research. GSK recently announced that at least 12.5 million doses would be donated to PATH for distribution in developing countries (PATH, 2010c).

Initial phase II results demonstrated a reduction of clinical malaria episodes by 53% over an 8 month follow-up period (Sciencecodex, 2009). This is a low efficacy rate compared to other marketed vaccines. However, considering the social and economic impact of malaria in the African continent, this is the best option for medical intervention in malaria today. If the vaccine is licensed, GSK has the opportunity to sell to travellers and the military, which are both high margin markets.

The MVI is also supporting earlier vaccine candidates that may provide greater efficacy or lower cost. A significant benefit for these second-generation vaccines is that tests often have been designed to correlate a biomarker with successful protective immunity for the first vaccine. If such a correlate assay is available, then other vaccines are usually assessed against the correlate, rather than waiting for months or years to see if vaccinated individuals become infected with the disease agent. Trials can therefore be smaller and shorter.

The success of the partnership with GSK will be clearer if and when the RTS,S vaccine is licensed. PDPs can often be more effective when the partnership occurs at an earlier development stage, as there is more ability to negotiate the target product profile. The development process may also be streamlined if public partner involvement facilitates application for accelerated regulatory review, etc. We will explore some of these examples in the next section.

7.2.2 Developing Products and Capacity through Emerging Economy Partnerships

Vaccine development for neglected diseases is best achieved by collaborating with local companies. Global health organizations and wealthy government agencies have the best knowledge about these types of disease conditions and patient management. These groups have the resources and knowledge to work in regions where certain diseases are prevalent and develop evidence-based policy recommendations. Because of experience working with

communities, public organizations are well equipped to train personnel, recruit trial candidates, and manage clinical trials. Private companies hold a complementary set of skills required for vaccine innovation. Companies are stronger in scientific knowledge, technical and research capabilities, preclinical trial experience, manufacturing expertise, and commercialization capabilities. Combining these complementary strengths leads to rapid vaccine development. Though we make the distinction of different strengths brought to the partnership by public and private entities, both may be proficient in all parts of the vaccine development value chain. The roles each partner in a PDP changes over time as the vaccine progresses through the value chain. The partner who has the stronger skills set at a particular stage will take on a dominant role. Through realistic timelines and open communication of expectations and setbacks, PDPs can achieve major developmental milestones.

Capacity building is the major by-product of PDPs. There are several examples where the developing country private partner gained capabilities that enabled competition in the free market. Knowledge exchange and infrastructure support have been the main benefits for developing economies (Hovland, 2003). In the past, international development work has focused on infrastructure support and training programs with a short-term vision. We believe that knowledge transfer has a long-term impact. Promoting local science and innovation will create economic growth and industrial competitiveness (Nuyens, 2007). However, capacity building is not limited to scientific training, but also requires physical infrastructure, management and organizational capacity, political, economical, and social support (Csazzar & Lal, 2004). In the following sections, we examine different areas of capacity building in the vaccine value chain and highlight where capacity building has occurred in several PDP cases.

7.2.2.1 Research and Development

R&D is the driving force behind any innovative company. Without innovation, companies lose competitive advantage. R&D capabilities in the emerging economies are limited in comparison with the developed world (Nuyens, 2007). The disparity makes it difficult for these countries to compete with developed countries. As a majority of the early stage discoveries take place in academic and government institutes, these organizations also need assistance with capacity building. In order to ensure that disease research focused on vaccine development is maintained, research should be carried out within a region affected by the disease. Therefore, indigenizing vaccine R&D is an essential component for improving healthcare and economic status.

PDPs have been successful in integrating academic and industry partner capabilities in a way that develops an expanded set of skills useful beyond the scope of a single project. Academic collaborations can lead to discoveries for other neglected diseases that were not in the original scope of the project. Accumulating a critical mass of knowledge and expertise will help to make a sustainable research industry for these diseases.

Developing regional disease vaccines is critical public health goal (Scidev, 2009). For example, different types of meningococcal sub-species exist in different regions of the world. While three manufacturers sell a vaccine for the meningococcal strain that predominates in Europe since 2001, development of a vaccine against the strain predominant in sub-Saharan Africa required a PDP involvement, as described in section 7.2.2.6 (Jodar et al., 2003). Building early stage research capacity through PDPs is essential to identify pathogens in the native environment with the help of local experts. PPPs such as the International Vaccine Initiative (IVI), described below, are actively involved in building on local talent with knowledge exchange and infrastructure support.

7.2.2.2 Manufacturing

As we have discussed previously, vaccine-manufacturing facilities are the main capital cost in the vaccine value chain. As GMP and regulatory standards evolve, these costs continue to rise. Historically, the lack of reliable vaccine demand forecasting from developing countries had made it risky for the MVCs to make investments specific to those countries. One way to address this issue is by building manufacturing capacity within developing countries. Access to technologies required for newer complex vaccines are not readily available. Though some developing country manufacturers in India, China and Brazil are investing more resources towards closing this technological gap, their capabilities still lag the MVCs. Because vaccines are comprised of biological materials, there is no generic regulatory pathway and similar vaccines must be tested in new clinical trials. Technology and expertise is specific for each manufacturing process. In addition, intellectual property barriers may delay developing country manufactures gaining capabilities for an extended period (Milstein, Gaule & Kaddar, 2007).

Through PDPs, private companies can gain access to technologies and expertise that will give capabilities to manufacture newer vaccines. Technology transfer or innovation partnerships can help developing companies in bridging the technology and build manufacturing capabilities. Furthermore, public entities can be successful in providing resources and assistance to carry out R&D work to improve older vaccine technologies. Ideally, PDPs help private companies gain manufacturing capabilities that extend beyond the partnership period. As discussed in the case analysis of PATH's MVP project below, the Serum Institute of India gained a new manufacturing technology in the partnership.

Unfortunately, some PDPs are engaged in *ad hoc* knowledge transfer of expertise and infrastructure (Ziemba, 2005). There is little coordination between different vaccine development projects to maximize the value of their resources. There is an opportunity for

PDPs to exploit other PDP infrastructure while assisting local governments to develop regulatory and ethical review capacity

7.2.2.3 Clinical Trial Infrastructure

Clinical trials must always be conducted with participants from the region where the target disease in prevalent, especially if there are differences in the sub-species of the pathogen. HIV/AIDS vaccine trials against non-clade B strains of the virus are best conducted in the African continent, where these clades predominate. Clinical trials can be effectively managed by training and building local expertise to recruit patients, administer the vaccine, monitor the subjects and collect data. Knowledgeable local teams have a better understanding of the diseases that affect the region as well as cultural norms important for appropriate interactions with those that volunteer for trial studies (Timmermans, 2005). Since the main links between the test vaccine and the study participants are local doctors and healthcare workers, successful recruitment and monitoring requires local cultural intelligence. Once a particular vaccine project is completed, the trial capacity left behind is invaluable for other vaccine or drug development projects. For example, IAVI has actively built clinical trial sites for many of its vaccine development programs. These resources stimulate the local economy, as well as building expertise for the testing of future vaccine candidates.

7.2.2.4 Regulatory

Safety standards for vaccines have become extremely stringent in the past couple of decades. Developed countries are more concerned and increasingly intolerant to vaccine side effects even if exceedingly rare. It is important to consider that the acceptable risk profile for developing countries may be different, where a disease is more prevalent and the disease outcome more severe. However, maintaining different safely standards for developed and

developing countries is problematic. A good example of this is Wyeth's rotavirus vaccine, RotaShield. One year after approval in US, the vaccine was withdrawn from market after 15 children developed serious side effects. Because of this safely concern, developing countries were also unwilling to use the vaccine although an estimated 1.5 M children die from rotavirus infection annually in low- and lower- middle- income countries (WHO, 2010b).

Any vaccine sold in a foreign country must gain approval from the NRA of the country of manufacture. Vaccines procured through UN organizations have to meet additional regulatory standards. To gain WHO prequalification status, the manufacturing processes need to meet WHO regulatory standards. However, many middle- and low-income countries do not have the regulatory bodies that meet global standards nor have the expertise to gain such status. Global health public partners are well positioned access regulatory expertise for vaccines. Organizations such as IAVI and PATH are actively engaged in helping developing countries gain regulatory expertise. PDPs and WHO programs can focus capacity building through achievable goals such as harmonized regulatory guidelines for clinical trials and streamlined licensing procedures.

7.2.2.5 Commercialization

Vaccine commercialization can be a difficult task for a developing country manufacturer. Usually, the Ministry of Health in each country manages demand generation in developing country markets and UNICEF procures the vaccines. Global public health organizations have built relationships with the Ministries of Health and supranational organizations. By leveraging these relationships, PDPs can provide market information to the private company partners. To create demand, it is important to increase awareness of vaccine value at the highest decision-making levels in governments. The cost- effectiveness of vaccines in both in public health and economic terms must be highlighted. Pilot studies, are often necessary for evidence-based demonstration

of the benefits. In most cases, emerging economy companies lack the capacity or the expertise to undertake cost-benefit analysis and disease surveillance work. Unless PDPs help the private companies, they do not have the reach or resources to undertake these activities.

Vaccine prices for most of the developing world are determined through complex negotiations with UNICEF. The downward pressure on pricing is strong, as available donor funding for vaccine purchases are limited. This is counterbalanced by the need of procurement agencies to encourage multiple suppliers to maintain an uninterrupted vaccine supply. PDP expertise can navigate through complex negotiations to reach a fair price and the market share for the company and country. PDPs provide companies a bridge to gain market assessment and price negotiation capabilities.

7.2.2.6 Case Studies

In the following case studies, we will highlight specific capacity building that was achieved through PDPs. Since most PDPs contribute to all aspects of capacity-building types, the cases are chosen to highlight stronger capability of each PDP

Meningitis Vaccine Project (MVP)

Meningitis is a bacterial or viral infection of the meninges, the layer that surrounds the brain and the spinal cord. The viral infection is less damaging and resolved without any specific treatment. However, the bacterial form is much more serious and carries a high risk of mortality. There are also debilitating side effects such as deafness, mental defects and epilepsy common to the disease survivors. Hib bacterium *was* the leading cause of meningitis infection prior to 1990, which was controlled by a paediatric vaccine. Since then, *Streptococcus pneumoniae* and *Neisseria meningitides* (meningococcus) have been the leading causes of bacterial meningitis.

In the 1990s, over 100,000 people died in sub-Saharan Africa from meningitis caused by meningococcal A infection. At the same time 1,000 died in United Kingdom from meningococcal C infection. By 2001, three vaccines were developed against type A infection, while there were none developed against C type (Jódar et al., 2003). Finally, because of a successful PDP, in June 2010 MenAfriVac vaccine against type A received WHO prequalification status.

The Meningitis Vaccine Project (MVP) brought four unique organizations together in the partnership. CynCo Bio Partners of Netherlands supplied the meningococcal A polysaccharide, the Serum Institute of India (SII) supplied the tetanus toxoid and scale up manufacturing capacity, the US Food and Drug Administration agency provided the conjugation technology and PATH managed all aspects of the partnership and funding. One of the key benefits of this project is that SIIL has gained capabilities from technology and knowledge transfer in return for negotiated low price and long-term supply commitments. PATH formed an experience technical team to address and technical and standardization issues related to scale-up production, who worked closely with SII. This conjugation technology and manufacturing expertise transfer benefited SII as an emerging country supplier to build capacity in both vaccine development and manufacturing (Brooke, Harner-Jay, Lasher & Jacoby, 2007).

From the beginning, the focus was to develop a vaccine that would be affordable to African countries. Initial evaluation indicated that the vaccine should be priced at no more than US $0.40 per dose. The partnership package gave enough other incentives to agree to this pricing, which aligned with SII's high-volume, low-margin business model.

Several other key factors contributed to the success of the MVP model. A related conjugate meningococcal C vaccine had already been developed. This knowledge made identifying antigen candidates simple and kept developmental costs low. The total projected R&D cost for this vaccine is US $65 M, which is significantly lower than industry standards. As

demonstrated by the MVP successes, this model of vaccine development is well suited for development of similar variants of existing vaccines. Many diseases vary sub-species by region, so it is likely such a model will have use in the future

The International AIDS Vaccine Initiative (IAVI)

Today, over 33 million people are infected with HIV, two-thirds of them in Sub-Saharan Africa. IAVI was formed in 1996 to address the lack of financial incentive for market driven vaccine development. This was especially problematic for HIV strains that predominate in developing countries. IAVI offered grants to private companies who were developing such vaccine candidates to lower their investment risk. In exchange for the funding, the company would agree either to differentiate pricing or to grant a license to IAVI to sell a successful vaccine in the developing world (Grossman & Ross, 2010).

Early on, IAVI build R&D infrastructure and capacity in Africa to gain access to virus strains that predominated in the region. With the advances in development program, they have built clinical trial infrastructure in the region. They ran their first clinical trial in collaboration with the Kenyan AIDS Vaccine Initiative and completing trials in 11 countries by 2008. Sites were chosen, in the words of IAVI's CMO, as follows: "The most important thing we were looking for was African leadership. Next was HIV rate- you have to go where the risk is-and after that came willingness of the researchers, government and community to work with us" (Case Studies for Global Health, 2009). IAVI's Human Immunology Laboratory in London and the University of Witwatersrand Contract Laboratory Services in Johannesburg coordinate the training. As of late 2009, the organization had three clinical phase II trials that are partnered with high-income country companies, and one phase one trial with the Indian Department of Health (Innovation Bridge, 2009).

Building good laboratory facilities and providing training has resulted in increase in research efforts in these communities. The Ugandan Virus Research Unit now performs basic research on the HIV virus that has informed the design of new vaccine candidates (Case Studies for Global Health, 2009). It is also IAVI's policy to partner with local community organizations to build trust between researchers and communities that is critical for participation in basic research and clinical trials.

Recently, the organization has created several HIV research consortiums that consist of academic leaders in the HIV research community. They have also invested in infrastructure for their own research facilities in the US. This includes a US $30M commitment to new facilities at Scripps Research Institute in San Diego (Grossman & Ross, 2010). These two efforts have distanced the organization from their earlier efforts to build infrastructure in the developing world. It remains to be seen how this will influence their access to patients and local researchers in Africa.

International Vaccine Institute (IVI)

The International Vaccine Institute (IVI) is an organization completely dedicated to development of vaccines for developing countries. With a United Nations mandate, IVI was formally established in 1997 and first laboratory operations began in 2003 in Seoul, Korea. Over the past 12 years, IVI has established major research programs in 28 developing countries. IVI works to fill gaps that exist in translational research, basic research, development, manufacturing, technical support and capacity building in developing countries so that regional vaccine development can take place. One of the major strengths of IVI is research and development capacity building in developing countries (IVI 2010a).

As a part of knowledge building, IVI has established the only international vaccinology course in the Asia Pacific region. In-house research facilities and field sites attract numerous

researchers who come to learn about vaccine development. These training programs are the basis for strengthening scientific research capabilities in developing countries. No other public organization in vaccine field is combining research programs and broad training activities to build capacity in the developing world (Access to Pharmaceuticals, 2010).

IVI has strong record of accomplishment of designing and development of vaccines against shigellosis, cholera, and typhoid fever, diseases that are predominant in most impoverished developing countries in the region. With funding assistance from the Gates Foundation, the Government of Korea and the Swedish International Development Cooperation Agency (SIDA), IVI scientists recently developed a cholera vaccine. This vaccine is a modified form of a cholera vaccine that is produced Vietnam under GMP standards and WHO production guidelines. After successful clinical trials in India and Vietnam, manufacturing partner Shantha Biotechics has taken over production and distribution (IVI, 2010b). Supporting regional companies will build capabilities that increase local manufacturing capacity.

Japanese Encephalitis Project

JE is a mosquito-borne viral disease that endemic to much of Asia. 50,000 cases are reported each year, though the numbers affected are thought to be much higher due to incomplete reporting. JE kills 20-35% of those infected and leaves 2/3rds of survivors with serious neurological damage (WHO, 2010f).

In 2005, an outbreak of JE in Nepal and India galvanized the Indian government to initiate a vaccination program in their country. PATH had already identified an ideal vaccine candidate produced by the Chengdu Institute of Biological Products (CDIBP) branch of the China National Biotech Group. The vaccine had been used in China for over 15 years with 200 million children vaccinated. A single dose was required to generate immunological protection, making it ideal for administration in remote and resource poor settings (PATH, 2010d). However, the

vaccine had never been administered outside of China. It was not accessible through UN organizations, as China, to date, does not have a recognized NRA. PATH initiated a relationship with CDIBP to bring the vaccine outside of the country. PATH's work with the organization included:

1. Assessment of market size for the vaccine,
2. establishing a differential pricing structure based on annual gross national product,
3. strengthening of GMP and regulatory infrastructure in China to accelerate the path to WHO pre-qualification for the vaccine , and
4. clinical trial setup outside of China to support introduction to new countries affected by the disease (Yaich, 2009).

The potential for increasing access to vaccines expands much beyond the candidate for JE in this collaboration. Because of China's enormous population, it has the world's largest national vaccine manufacturing capacity. Enabling robust Chinese manufacturers to sell their products globally could dramatically increase the number of providers available for any one product. A desire to expand market share may further accelerate adoption of global GMP standards and regulatory infrastructure. Improved communication with Chinese manufacturers may also uncover other inexpensive, effective vaccines with utility for global health.

7.2.3 Challenges for PDPs and Recommendations

The successes of PDPs are not without many challenges. These partnerships are complex and difficult to establish. Even with public sector assurances, the private sector sees an uncertain return on the investment. Complex management and organization issues can distract from the ultimate goal. The structure of these partnerships is not always balanced with financial resources and knowledge, which are indicators of power. Lack of formal internal governance is cited as a major risk to PPP success. As an example, the external evaluation of the "Roll Back

Malaria Project" project found that the loose governance structure made the concept of partnership and the roles of each partner unclear (Yamey, 2002; Feachem et al., 2002). This power imbalance is one of the major factors for information asymmetry, bounded rationality and opportunism that lead to vaccine market failure.

PDP partnerships must also manage the differences in motivations between the public sector and the private sector. The motivation for the public sector is primarily social benefit while profit-generating opportunities motivate the private sector. If there is no common ground within these goals, motivations can pose a hindrance to the process, influencing developmental time, cost and quality of the product.

PDPs are often focused on developing a single product. This focus ignores the context of the health care system in which it must operate. Other complementary resources require for successful launch of the vaccine, such as medical infrastructure, need consideration. In addition, the public partner invests significant resources in the form of funds, expertise and logistical support to build a successful partnership. However, if such an investment is utilized for a single vaccine or device candidate, the same investment must be re-initiated in the next partnership. Instead, public sector should seek to maximize the return of investment by forming vaccine pipeline associated with each partnership.

PDPs are designed to stop or cure a neglected disease through a product solution. Attention is paid to finding a quick solution at a cost-effective manner. The successors are measured by quantifiable outputs, while processors and process capacity is neglected. With the increasing demand for vaccine solution (and other healthcare solutions) for neglected disease, there to be a policy change towards inclusion of processors and process capacity as measurable successors. Lessons learned in one PDP can be applied to reduce the time and financial cost of another PDP. Public organizations need to find a way to work together to maximize capacity

built within developing countries. This is the best way to maximize funds donated by the global community.

There is a significant push from funding organizations to reducing vaccine prices as close as possible to the cost of production. This is a genuine policy to increase vaccine access to the low-income countries; however, the long-term sustainability is questionable. Specifically, the privet entity needs to be able to re-invest in facilities, update technologies and make some profits in the long-term. These reinvest mechanisms are important to develop next generation vaccines without further dependence on donor organizations. There should be a policy alternative to the current cost structure that would invite other private companies to establish sustainable manufacturing capabilities in the middle- and low-income markets.

7.3 Technology Licensing

We define technology licensing as a free-market transfer of vaccine production expertise from a developed country manufacturer to one in a low- or middle- income country manufacturer. The fact that such agreements have existed without support from NFP organizations indicates that the model is attractive to both parties. In these agreements, it has been essential that the market access the MVC receives is large enough to warrant the investment, and that good vaccine support infrastructure- i.e., a NRA- is present in the technology-recipient country.

7.3.1 Synflorix for Brazil

Brazil exemplifies the possibility of unsupported technology transfers from MVCs. Since 1985, Bio Manguinhos, Brazil's major nationalized manufacturer, has signed five technology transfer deals. The most recent was for GSK's pneumococcal vaccine, Synflorix. This agreement covers a period of 8 years. In exchange for stepwise technology transfer from GSK backwards

through the value chain, the country has agreed to purchase Synflorix exclusively over the period. As described by the director of Bio Manguinhos, there must be a win-win situation for both parties to engage in an involved business relationship like a technology transfer (Homma, 2009). For Bio Manguinhos, the agreement means that the country accesses this vaccine relatively quickly after adoption in high-income countries; it also brings in a conjugation technology, a critical formulation innovation used in many vaccine candidates. For GSK, the company has a committed market for 8 years and a price point that is higher than that paid by the AMC. Moreover, they have insulated against competition from Prevnar-13 in a large market. Pfizer's pneumococcal vaccine provides protection against more strains of the bacteria, and had revenues of almost US $3 B relative to Synflorix, with revenues of £73 M in the last three quarters of 2009.

The Brazilian government, in an effort to encourage other technology transfer agreements such as this, has improved legislation to protect and incentivize innovation in the country (Homma, 2009). Vaccine technology transfers have been ongoing with GSK since the mid 1980s. Last year, the Butantan Institute signed a technology transfer agreement with Sanofi for their pandemic influenza vaccine. This was the second agreement with a MVC, and marked a growing recognition by large manufacturers of the value of middle-income vaccine markets, especially ones with exclusive access. We see this model as being highly successful for countries with nationalized vaccine manufacture. It may be successful for countries like China where the country size is large enough that the market is still attractive even without exclusivity.

One limitation of current technology transfer agreements is that they do not allow exports to third party countries. It would be ideal if a country such as Brazil could transfer these vaccines to other countries in the region with similar endemic diseases and average income.

This presumably could be a 'win-win' for the vaccine manufacturer as well, since it might allow them access to countries that would delay buying the vaccine otherwise.

7.4 Innovation Partnerships

Innovative partnerships are an effective mechanism to transfer technologies to the emerging country vaccine developers and manufacturers. Collaborations between two smaller companies with equal risk sharing benefits both entities. Smaller companies in the developed markets are actively seeking market opportunities in developing countries. Joint ventures (JV) are becoming a free-market method of gaining entry to the market while the developing countries gains access to innovations that may leapfrog the efficiency of current technologies.

7.4.1 Cadila- Novavax Joint Venture

In 2009, Novavax Inc. and Cadila Pharmaceuticals entered into a joint venture to develop and manufacture vaccines and other biologics using technologies developed by both companies. The JV, named CPL Biologicals, will build additional research and manufacturing capacity in India (Topnews, 2009). This strategic venture brings in unique vaccine technologies to the Indian industry.

Novavax Inc. is a US-based clinical-stage biopharmaceutical company that had developed unique virus-like-particle (VPL) technology to produce vaccines. The company has developed novel efficient procedures to develop potent VLP-based recombinant vaccines (Novavax, 2010). Cadila Pharmaceuticals Lt. is one of the largest private pharmaceutical companies in India. Cadila manages an integrated portfolio of healthcare solutions, which includes cardiovascular, gastrointestinal, infectious, and respiratory disease. Products are manufactured in India and sold in over 50 countries worldwide (Cadila Pharma, 2010).

On June 10th 2010, CPL Biologicals announced completion of the state-of-the-art vaccine manufacturing facilities in Dholka, India. Validation of the facilities is ongoing and expected to produce up to 60 million doses of novel vaccines per year (Biospace, 2010). Initially, the facilities plan to produce influenza vaccines based on Novavax's VPL technology. As Indian counterparts gain experience with the new technology, it is expected that other innovative vaccines will be produced.

Through technology transfer JVs, developing countries can prepare to address regional vaccine needs. This is a win-win scenario to both private companies. However, the cost of vaccines produced with new technologies is still unknown. One possibility could be government-funding programs to help local companies form JVs to bring in newer technologies, which could allow cheaper overall cost of manufacturing. As competition increases with more companies adopting VLP technologies, vaccine prices will decrease to market equilibrium.

7.5 Not-for-Profit Vaccine Manufacturing

As we discuss in our section on the vaccine value chain, vaccine development is a complex and expensive process. PDPs have been successful in advancing new vaccine development, but are usually dependent on the private entity for manufacturing capabilities. Even in the high-income countries, it has been our personal experience that access to pilot manufacturing for clinical candidates is limited. There is often a wait list. For approved vaccines that predominantly address emerging economy needs, increasing price pressure placed on vaccine manufacturers' risks long-term sustainability of supply. As in the early 1990s, manufacturers may again withdraw from the market. In most cases, the negotiated price is the cost of goods and a small mark-up for profits. Price pressure also makes funds for re-investment in next generation vaccines or newer vaccines unlikely. Hence, the question is whether there is

alternative model that can provide long-term opportunities for vaccine production and innovation.

Philanthropic organizations that have embarked on vaccine development through PDPs have typically built infrastructure in emerging economies for several of the components in the vaccine value chain. However, vaccine manufacturing is a segment that has not been built into these partnerships. Filling this gap is the next logical step for capacity building. Therefore, we propose a new model where NFPs build manufacturing and fill/finish infrastructure within emerging economies with no manufacturing facilities. This manufacturing capacity within developing county markets will help to build a sustainable industry responsive to regional needs.

We propose two types of manufacturing facilities be constructed by NFP consortiums. The first would be a pilot plant for the production of vaccine candidates. The second would be a facility for the manufacture of licensed vaccines for regional needs. Both proposed facilities would be constructed with donor funds and managed by global NFP consortiums. The strategy is to build a NFP-board with diverse financial and political base with a global presence. This will allow for a global focus and access to geographically unrestricted funding for the manufacturing facility (Berkley, 2006).Quality would be maintained to international GMP standards.

Following are examples of some of the costs or recent manufacturing plants.

1) Panacea has completed a multi-use bulk manufacturing facility in Lalru, Punjab in 2010. This included a train for mammalian cell culture vaccine production, another for microbial products, and a third for viral vaccines. The entire facility will produce to WHO and FDA standards of GMP. The total investment was estimated at Rs. 1 B (~US 22 M).

2) A proposed vaccine-manufacturing facility for the Canadian HIV Vaccine Initiative (CHVI) was estimated to cost CAD $88 M. According to the authors of the original proposal, this facility would have had the capabilities to manufacture clinical trial size lots using three different

technologies. He further estimated that a clinical trial lot would cost $250,000 to $1 M, 50% less than what would be charged by a private manufacturer (CMAJ, 2010).

3) In May of this year, Novavax completed a VLP vaccine facility in the US for the cost of $5 M. Because the process is simpler than for many traditional vaccines, the facility is 1/3 smaller and uses about ¼ of the electricity of a conventional plant. The capacity of the facility will be about 10 million doses a year. Based on these successes, it is cost effective to build manufacturing facilities in developing countries.

Developing country manufacturers are already adapting the latest manufacturing technologies to increase safety and efficiency in vaccine production. The Novavax Inc-Cadila Pharmaceuticals joint venture is a good example. The proposed facilities should also incorporate the latest technologies that will be demanded for newer vaccine production. VLP technology is used in many of the current vaccines candidates; incorporating this technology will be strategically important. Newer aseptic automated filling/finish equipment like that manufactured by VanRx technologies can be utilized to cost effectively control production capacity.

The pilot plant would be situated proximally to a region with a significant number of ongoing clinical trials. As clinical trials are being run in Kenya for IAVI, the TB Aeras Foundation, and the RTS,S malaria vaccine candidate, we propose pilot plant construction in this country. South Africa would be another option for proximity to clinical trial sites, and would offer the advantage of having a NRA assessed as functional by the WHO.

There are many advantages for having well managed, publicly owned vaccine manufacturing facilities in developing countries. PPPs have successfully negotiated with private manufacturers to charge low vaccine prices for the developing world. However without a profit making incentive, NFP-owned CMO facility can supply at COGS plus a small margin that can

further lower price. Having access to cheaper, high quality vaccine when needed is primary importance for the developing country markets. Collectively, procurement agencies will have access to cheaper vaccines extending accessibility.

Regional production of vaccines will reduce the strain on cold chain management and transport system. The cost associated with vaccine supply increases with cold-chain transport distance prior to reaching the end user. Customs clearance, storage, cold-chain breakdown, transport cost and vaccine spoilage can result in significant wastage. Lead-time from a distant supplier can also hinder access. The proposed regional manufacturing facilities will circumvent many of these problems. By providing services to a specific region, the manufacturing facility can monitor the demand for specific vaccines and tailor production levels for quick access. Regional facilities can work in conjunction with regional procurement agencies to determine the demand for each vaccine and control production levels. These are factors already affecting MVCs, whose products are reaching low- and middle-income countries. Once a fully manufacturing facility is in operation, MVCs may be compelled to use such facilities given the benefits; however, the facility will have to build a strong record of accomplishment before this can happen. Lack of manufacturing oversight that could result in poor production and product liability will be of concern for MVCs.

There are multiple PPPs operating in developing countries aiming to develop new vaccines for neglected diseases. With this NFP-CMO model, PPPs can collaborate to produce clinical trial batches of vaccine close to clinical trial sites. This facility can support the manufacturing need of other NFP organizations and PPPs reducing trial cost. Sharing the facilities by other public organizations will help to maximize the value of donor financing. With multiple PDPs using one manufacturing facility, economies of scope will result. There should be less idle time in a plant that produces multiple vaccines, which will reduce per project costs;

knowledge from one manufacturing process can also benefit others. Capacity building for manufacturing will help African and Asian countries to achieve economic autonomy. Reduction of unemployment rates, increased workforce skills, and decreased dependence on foreign suppliers will result from local increased capacity. There will be indirect job creation from infrastructure support for the CMO, especially if raw materials are supplied locally that is supporting or supported by the CMO.

One of the major barriers to entry for small biotechnology companied is the lack of biologics manufacturing capacity. GMP facilities and regulatory expertise are not readily available. Building and maintaining GMP facilities are cost-prohibitive for these companies. The proposed facility will encourage new vaccine development programs for the region. NFP run CMOs will act as a catalyst for local innovations and provide cost-effective vaccine production for clinical trials and later on, full manufacturing capacity. These private sector contracts will generate additional revenues to maintain, expand, and continually modernize capacity. The revenues generated from contract services can be invested into development programs, expanding manufacturing capacity and integration of newer technologies.

A NFP-CRO will become a major catalyst for building manufacturing knowledge capacity. International experts can train locals in all aspects of scientific techniques, development and implementation of new technologies, maintenance and upgrade of equipment, and regulatory knowledge required to operate a GMP facility. When a critical scientific and technical knowledge mass is reached, these local experts can disseminate training further into local industry. Furthermore, such experts could begin private manufacturing facilities that contribute to the local supply. Innovation diffusion through knowledge networks can help in-country academic and biotechnology sector as well as regional sectors. These networks are essential in bringing local solutions to neglected diseases of the region.

Table 7: Advantages and Challenges for NFP-CMOs

Global Health Stakeholder	Potential Roles	Advantages of NFP-CMO relationship	Challenges of NFP-CMO relationship
Developing countries	- Communicate demand	- Potentially lower cost product - Shorter product lead times - Local capacity building - Potential upgrade of NRA	- Underdeveloped NRA - Lack of political will and motivation - Trained personal - Transparency
PPP-PDP	Vaccine R&D and establish line within CMO for developing country markets	- Leverage CMO facility for new projects - Leverage for clinical trial lots	- May require new manufacturing experts to join CMO - Limited to existing CMO technologies w/o funding for manufacturing
Local biotech/ regional biotech	- Build knowledge capabilities - Provide R&D and raw materials for CMO - Marketing of the product	- Increase access to developing counties - Eliminate fixed costs associated with manufacturing facility	- Underdeveloped biotech sector - Lack of expertise
MVCs	- Provide R&D and raw materials for CMO, - Marketing of the product	- Increase access to developing counties - Eliminate fixed costs associated with new facility	- Lack of product oversight - Liability for product - Unknown and variable contract manufacturing costs
Global health donors	- Investment cost exceeding that of JE Project	- Potential to leverage investment across many vaccines - Additional insight into COGS and developing country needs	- Large upfront investments - Unknown sustainability of manufacturing model

Source: Authors

There are number of barriers to overcome for this model to work (See summery Table 7). Specifically, gaining support from developing country governments will be challenging. In countries such as India, where a robust local manufacturing industry exists, an NFP-CMO would not be valued or valuable. However, support from global organization such as WHO as to the

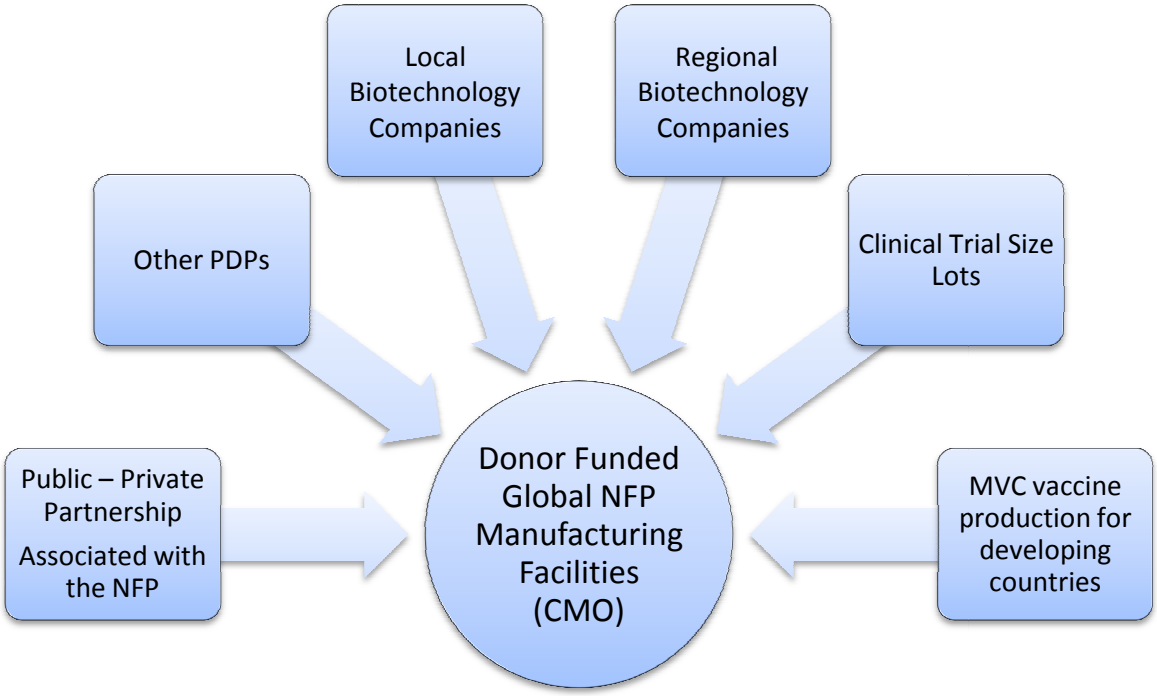
benefits can influence the appropriate host country government. The goal of these facilities should not be to compete against vaccines in the free market. Instead, emphasis has to be on new vaccines for neglected diseases and equilibrating speed of access to vaccines for emerging markets. Secondly, the donor community will need convincing of the long-term potential benefits of the investment. For example, there are number of Gates Foundation funded PPPs that lack internal manufacturing capabilities. Investment from multiple NFPs will be required to maximize the efficiency of a manufacturing site and so buy-in must be broad. The message that a NFP-CMO can provide long-term support for disease prevention must be conveyed. The most successful method would be through evidence-based demonstration.

We suggest a pilot project to collect initial data and examine the feasibility of a NFP-CMO. Pilot manufacturing facilities can be built, tested and validated for clinical trial-size lot manufacturing. Building regional production capacity for clinical trials will help to better estimate timelines and reduce vaccine developmental cost. Manufacturing can flexibly align with the demand for test vaccines. In cases where subject recruitment is sporadic, proximity of the manufacturing facility can determine efficient operations of trial sites. Less dependence on MVC or for-profit CMOs will be both time and cost-efficient.

Newer modular manufacturing technologies will help tailor production volume to meet demand. Smaller facilities will cost less and risk tolerance will be higher. Facilities in emerging countries have been estimated to cost 25%-50% of those in high-income settings, though this gap may be closing as GMP standards become increasingly stringent (Wilson, 2010). However, it is still cost-effective to build and operate in a low- or middle-income country as the property, construction and labour costs are significantly lower (Brooks, 2010; Popova, 2010). Global public health organizations will need to work together closely to set clear expectations of the facility's use priorities, allocation of responsibility and plan for self-sustainability of the site. A

successful demonstration of an NFP-CMO will help garner support from the donor community to expand into full-scale regionally based manufacturing facilities. If the pilot facility can generate stable demand, operate with low costs and contribute to the donor community's vaccine development goals, there will be support for funding a full manufacturing facility. As funding per program becomes limited by increasing numbers of different programs and financial constraints from the recession, we believe donors will respond positively to a multi-user manufacturing facility that provides multiple cost efficiencies. Our vision for a NFP-managed licensed vaccine manufacturer is one where the facility would work closely with a regional procurement organization to prioritize manufacture. The facility would be situated in a region that does not currently have an NRA. The absence of vaccine production in entire regions of the world exacerbates the concentration of the industry and threatens stable supply. Support would be given to the host nation to build a WHO recognized NRA, initiated prior to construction. An "IFFIm like" funding mechanism for the facility may even be appropriate. Donors would commit long-term funds to the site; investors buy bonds based on the commitments, accelerating funding for construction to the early phase while providing some potential for financial return if the endeavour is successful.

Figure 9: Proposed Not-for-Profit Manufacturing Model



Source: Authors

7.6 Summary

In this chapter, we have reviewed key models by which access to vaccines, especially new vaccines, has been improved for the developing world. Most of these models have the potential for long-term sustainability and each of them have unique characteristics that are beneficial for specific types of vaccine development. Moreover, there are promising signs that models that have required public funding in the past, such as partnerships between low- and high-income country manufacturers, are now supported in the free market. PDPs for vaccine development have only been operational since the late 1990s. Given a 15-20 year vaccine development cycle, it is difficult to assess fully the success of these partnerships. Nevertheless,

there are incremental improvements and innovations happening that are benefitting vaccine markets at both the company and country level.

The development of vaccine candidates through partnerships with GSK and Biomanguinhos, as well as the Cadila-Novavax JV are especially innovative and importantly facilitate new technology transfer to emerging countries. India and Brazil have robust vaccine industries and they will continue to grow independently. Countries such as China are gaining regulatory and manufacturing scale-up capabilities through partnerships, which will enable sales outside of China.

PDPs and other pull and push mechanisms will continue to be required for the rest of the developing world. We have proposed a new donor funded NFP-CMO based model for vaccine manufacturing that would reduce vaccine development and manufacturing cost to PDPs and, in its second phase, increase regional production.

8: SUMMARY AND RECOMMENDATIONS FOR SUSTAINABLE NEW VACCINE ACCESS

The industry analysis, evaluation of the strategic importance of innovation, and description of the differences in the vaccine markets all indicate that vaccine innovation is almost exclusively motivated by sales in high-income countries. The majority of vaccine related innovations occur in developed countries. Over time, developing country manufacturers incorporate them. However, emerging economies are beginning to engage directly in vaccine development through JV and technology transfer agreements with MVCs. As these agreements are based in the free market, often the ventures are motivated by profits rather than the local public health needs. The rise of Product Development Partnerships (PDPs) has begun to enable vaccine innovation that meets the needs of countries most affected by infectious disease. Some new vaccines from PDPs have reached licensure and others are in late-stage trials.

In many instances, PDPs have also helped to build value-chain capacity with private enterprise partners in the developing world. Capacity building has occurred throughout the value chain from R&D through to commercialization. The current success of these vaccine PDPs are can be attributed to the public partner owning the development risk, thereby encouraging private companies to develop products for low- and middle-income markets.

While the many efforts for vaccine development and their successes are heartening, there are also valid concerns about the sustainability of vaccine partnerships over the long-term. A number of “push” and “pull” funding mechanisms have been successful. However, many of these efforts are dependent on donor funds from wealthy nations or foundations whose net

worth have been severely impacted by the recent global recession. The majority of PDPs receive funds through a single organization, the Bill and Melinda Gates Foundation.

Furthermore, recent natural disasters and other global catastrophes are diverting the resources of the donor community. GAVI is already reassessing their vaccine support for the next 5 years due to financial concerns (Usher, 2010). PDPs have much less certain returns on investment than for vaccine purchase and may therefore find their support even more reduced. While many PDPS have succeeded precisely because of their disciplined focus on the development of a single vaccine, the capacity that has been built may not translate to knowledge that will be useful for the success of another vaccine. PDPs have partnered with existing vaccine companies in the developing world rather than starting *de novo* efforts. However, it has meant that vaccine manufacture has been strengthened in a region that already had a competitive industry. Vaccine security remains a major concern for UNICEF and limits its negotiating power. There are still regions that have no regional manufacturing infrastructure.

For this reason, we propose a donor funded, NFP managed pilot plant for vaccine manufacture. As discussed in Chapter 7, this would be situated in a region where other PDP capacity types have already been built, such as clinical trial network in South Africa and Kenya. Initially, this facility will provide clinical-trial lots to regional PDPs. The facility will have the capacity to produce new inexpensive vaccine types like DNA, so that it can support future manufacturing demands. If the pilot is successful, it would be possible to expand to a post-licensure facility that is able to manufacture commercial scale product. This proposed NFP-CMO is meant to increase availability of new vaccines at a lower cost. Because the facility will be modular, production can be tailored and long term vaccine demand forecasting will be less important. The strategic selection of location will help to build local capacity, economic and social development.

All the vaccine access models we examined have an important role in delivering vaccines to developing countries. The resources and knowledge of MVCs are still necessary to develop complex vaccines. Technology transfer and JVs with these organizations enable developing country suppliers to address regional demand. PDPs are needed to continue to the development of neglected disease vaccines. However, mechanisms for vaccine access must be initiated within PDPs that do not require external funds, to ensure the continued improvements to vaccine access for developing countries.

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