

Pull Mechanisms for Value-Added Technologies for Vaccines

An Evaluation of the Issues Influencing Vaccine Producer Willingness to Advance, Adopt, and Commercialize Value-Added Technologies for Vaccines for Low-Income and Lower-Middle-Income Country Markets

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Immunization systems and technologies for tomorrow



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The author and Optimize project representatives are sharing this report as a contribution to ongoing discussions about value-added technologies for vaccines and welcome comments from interested parties.

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Introduction

Low-income countries (LICs) and lower-middle-income countries (LMICs) have different needs for vaccines and value-added technologies for vaccines than those of industrialized countries because of the specific constraints that they face. In particular, because their infrastructure is often stretched to the limits, developing countries face challenges to deliver vaccines to the periphery within the confines of the cold chain that vaccines currently require. In addition, the tenuousness of waste disposal and waste management in some developing countries may introduce safety risks to the public (from re-use of injection materials) that are not experienced to the same degree in industrialized markets. Yet vaccine manufacturers have been reluctant or unable to adapt existing vaccines or apply value-added technologies for vaccines to meet the specific needs of the developing-country market.

To determine how to incentivize vaccine manufacturers to better meet the specific needs of developing countries, Optimize has commissioned a white paper to examine the factors influencing the willingness and ability of vaccine producers to advance, adopt, and commercialize value-added technologies for LICs and LMICs. Input for this white paper has been derived from a review of the existing literature, personal communications with representatives of the vaccine industry, and the experience of the author in the vaccine industry.

Objectives

A first objective of this paper is to fully examine and expose the issues influencing vaccine producers' abilities and willingness to advance, adopt, and commercialize value-added technologies for vaccines for low- and lower-middle-income country markets. The purpose of conducting this review is to ensure that all subsequent strategies and proposals for pull mechanisms for value-added technologies for vaccines best address the interests of both developing countries and the vaccine industry and make value-added technologies for vaccines accessible to LICs and LMICs as expediently as possible. Part of the review will be constituted by case studies of existing or available value-added technologies, such as vaccine vial monitors (VVMs), prefilled syringes, and formulation of vaccines for improved thermostability.

The purpose of conducting these case studies is to develop a list of lessons learned to inform future technological developments and possible collaborations with vaccine manufacturers. A second objective of this review is to develop concrete suggestions on ways for the public sector and industry to better ensure that key value-added technologies for vaccines are advanced, adopted, and commercialized for future vaccine products. Specific recommendations for pilot projects will then be made.

Outline

The paper will first provide some background to the recent developments in the vaccine industry and evolution of the global vaccine market. Then the specific characteristics of the developing-country vaccine market will be exposed. Within this chapter we examine some of the unique features of the vaccine industry such as:

- The uniqueness of the developing-country market.
- The laws of supply and demand in the developing-country vaccine market.
- The impact of intellectual property (IP) on access.
- The role of local production in access to value-added technologies.

Then the paper will develop three case studies of value-added technologies: one that was successfully introduced (VVM), another that has yet to be widely adopted (the Uniject[®] device), and another that has future potential (heat- and freeze-protection). The paper examines the reasons behind successes and failures for each.

Before proposing novel pull mechanisms for value-added technologies for vaccines, existing pull mechanisms for vaccines for LICs and LMICs will be examined and assessed for their impact on vaccine manufacturers' ability and willingness to advance, adopt, and commercialize value-added technologies for vaccines.

Finally, based on the findings of the review, some proposals will be made for possible new incentive "pull" mechanisms for value-added technologies for vaccines. Here we distinguish between vaccines that have a potential commercial return and those that are destined to be predominantly dependent on public-sector support. We also distinguish global manufacturers from local manufacturers and predict which types of incentives are most likely to be successful with each. Local manufacturers, unlike global manufacturers, may be fully or partially owned by the public sector. Local producers sell almost exclusively into LIC and LMIC markets, and they typically lag in innovation, by several years, behind global producers.

Background

At the time that the Expanded Programme on Immunization (EPI) was launched in the 1970s, there was little or no distinction between developing-country and industrialized-country vaccine markets. For the most part, all children were immunized with the same vaccines. But due to an explosion of innovation in the global vaccine industry in the 1980s and 1990s, vaccines became increasingly differentiated between rich and poor markets. Several new vaccines were developed and quickly adopted in industrialized countries, but developing countries, for the most part, stuck to the six original antigens that had been introduced through the EPI.^{1,2} Prices of "new" vaccines were considered high in contrast to EPI antigens, all six of the latter which could be purchased for less than \$1.00.³ Ironically, many of the newer vaccines had a much higher public health value in developing countries where burden of disease was considerably higher than in the industrialized world.^{4,5,6,7}

Further confounding the differences between industrialized and developing country markets was an increasing differentiation between same antigens: inactivated polio vaccine (IPV) for the industrialized market, oral polio vaccine (OPV) for developing countries; acellular pertussis for wealthy markets, whole-cell pertussis for poorer markets; combination measles-mumps-rubella (MMR) vaccine for the industrialized market, and monovalent measles vaccine for developing countries.^{8,9}

Today, industrialized and developing-country vaccine markets are even more distinct, with industrialized countries demanding thimerosal-free vaccines, in predominantly single-dose presentations (often prefilled glass syringes), and not demanding any temperature indicators such as VVMs.

The divergence of product offers for rich and poor markets created a dilemma for global vaccine manufacturers. Previously, production had simply been allocated according to the demand from the different markets. But demand for new products (or newer versions of products) did not materialize simultaneously in developing countries. This meant that the industrial capacity to serve the demand for “new” vaccines was often sized to meet the exclusive demand in the industrialized market (only a fraction of the size of the global demand). (The industrialized market was both easier to serve—because of its relatively smaller size—and more lucrative than the high-volume, low-price markets of LICs and LMICs).⁸

By contrast, in the late 1990s the local vaccine manufacturing industry still had little innovation to offer, although a few local manufacturers had become very high-volume producers for developing-country markets (both within and beyond their own borders). A few would produce stand-alone hepatitis B (Hep B) vaccine and develop combinations of diphtheria-tetanus-pertussis (DTP)-Hep B⁸ for the GAVI Alliance market. None were capable of offering *Haemophilus influenzae* type b (Hib)-containing combinations.⁸ None had “newer” vaccines (e.g., pneumo conjugate [pneumo], rotavirus [rota], human papillomavirus [HPV]) in their pipelines, and none had markets in industrialized countries.

By the time that donors had organized to purchase “new” vaccines for developing countries, global manufacturers had already been exclusively serving the industrialized world market with Hep B vaccine and Hib vaccines for 15 to 18 years.¹⁰ (Other vaccines had also become exclusive to industrialized countries: DTP containing combination vaccines; acellular pertussis; and, MMR was exclusive to high-income countries [HICs] and Pan American Health Organization [PAHO] countries.) When GAVI was launched in 1999, industrial capacity had been sized to the relatively small industrialized market, and it was obvious that it would be no easy feat for global manufacturers to scale to meet a “global” demand for “new” vaccines.

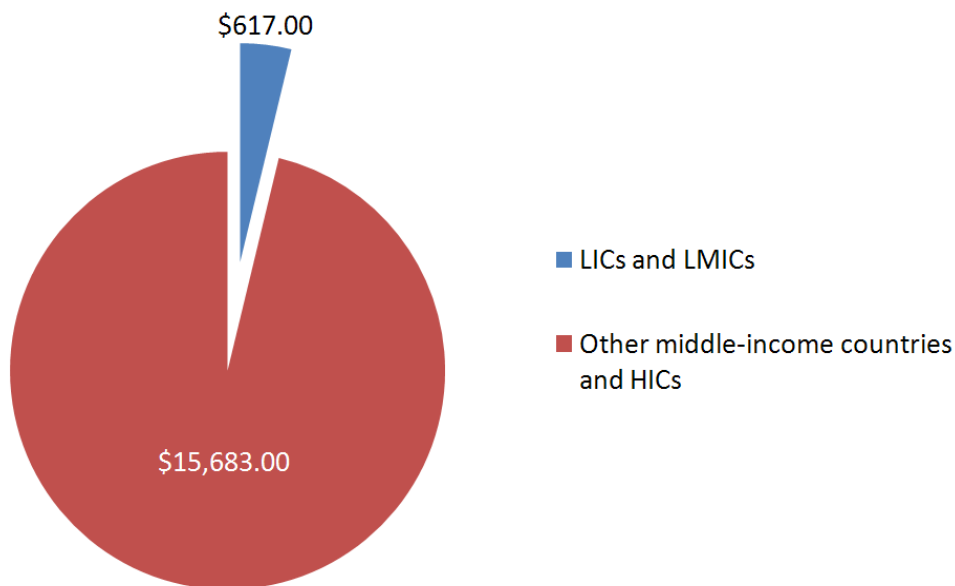
Demand uncertainty was touted as being the single largest impediment to serving the interests of developing-country markets with vaccines (and value-added technologies).¹⁰ For example, how large to scale? Furthermore, demand forecasts for developing countries were notoriously inaccurate. Until the advent of GAVI, the public-market vaccine demand forecasts for LICs and LMICs varied as much as 60 percent from actual

purchases, and contracting with manufacturers occurred on an annual basis. With GAVI, vaccine manufacturers now sign three-year supply agreements.

Now, with several new funding mechanisms in place and a demand forecasting system for developing countries functioning reliably, manufacturers (both global and local) may be less concerned with the uncertainty of demand and more concerned with the very modest attractiveness of the developing-country market, relative to industrialized markets (**Figure 1**).

Because of the limited attractiveness of the developing-country market, for the “newest” vaccines (pneumo, rota, HPV) producers want to avoid having to produce separate products for each market in order to contain costs and offer the most affordable product. This was in fact GAVI’s original premise, that global manufacturers would produce using “marginal production capacity” and that by scaling-up production, vaccines for developing countries would have a relatively low unit cost (economies of scale).¹¹

Figure 1. Value of the United Nations Children's Fund’s (UNICEF’s) vaccine market relative to the global vaccine market in US\$ millions, 2007^{12,13}



The challenge of producing a single product for both markets is to satisfy diverging demands for specific product characteristics from the two markets (industrialized and developing country). To serve the developing-country market by utilizing “marginal capacity,” a same (or similar) presentation and formulation would need to be offered in both markets (industrialized and developing). Since the product would have to conserve the characteristics of the highest-return market, the developing-country market could end up being served with products that are not specifically demanded. For example, thimerosal-free in single-dose (or small multi-dose) presentations—possibly even in prefilled syringes without an autodisable (AD) feature (technically not United Nations [UN] “prequalifiable”).

Theoretically, there is no compelling reason that specific value-added technologies for vaccines demanded by developing countries (heat- or freeze-protection technologies, VVMs) could not be incorporated into a “universal” product that would be sold in both industrialized and developing country markets. But historically, buyers have had little tolerance for undemanded features (i.e., PAHO has no demand for vaccines with VVMs) and each additional feature could add cost.

Without a clear willingness to pay and given the extreme price sensitivity of developing-country markets, there may be a real “need” for value-added technologies (e.g., technologies to facilitate higher temperature storage and transportation of vaccines — whether vaccine vial monitors, or changes to product labeling, or heat- and freeze-protection technologies) for vaccines; but without a parallel demand from the industrialized market for these technologies, there are few (or no) commercial incentives for global vaccine manufacturers to develop or adapt products for specific developing-country demand, and there are several deterrents.

Understanding the developing-country vaccine market

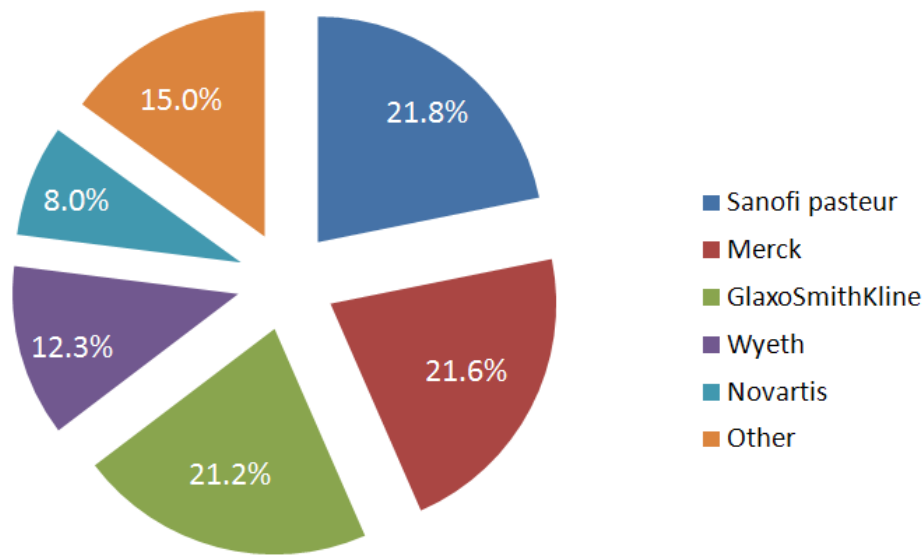
Given that the developing-country vaccine market is distinct and unique, why do vaccine manufacturers not adapt their products and value-added technologies to this market?

Unique characteristics of developing-country vaccine markets

Vaccine production is a capital-intensive, fixed-costs-based business.¹⁴ Today, licensing a vaccine can require clinical trials with up to 70,000 subjects¹⁵ and cost close to \$1 billion.¹⁶ This investment is made at risk, with no indication of success prior to the results from the largest pivotal clinical trials. Furthermore, post-marketing surveillance may ultimately reveal adverse events that force a withdrawal from the market; such was the case for Rotashield™.¹⁷ The ability to invest in innovation (the research and development [R&D] of new vaccines and value-added technologies) to meet the needs of developing countries is intimately linked to the revenue generated from worldwide sales of existing vaccines and additional investments from the private sector.

Entry into the vaccine business has very high barriers related to the complex nature of industrial operations, the regulated environment, the risks and costs of R&D, and the unpredictable nature of biologicals. This explains *the current make-up of the global vaccine market, an oligopoly*, made up of half a dozen global suppliers and a number of smaller local suppliers, the latter which sell primarily into their own domestic or other developing-country markets (**Figure 2**).

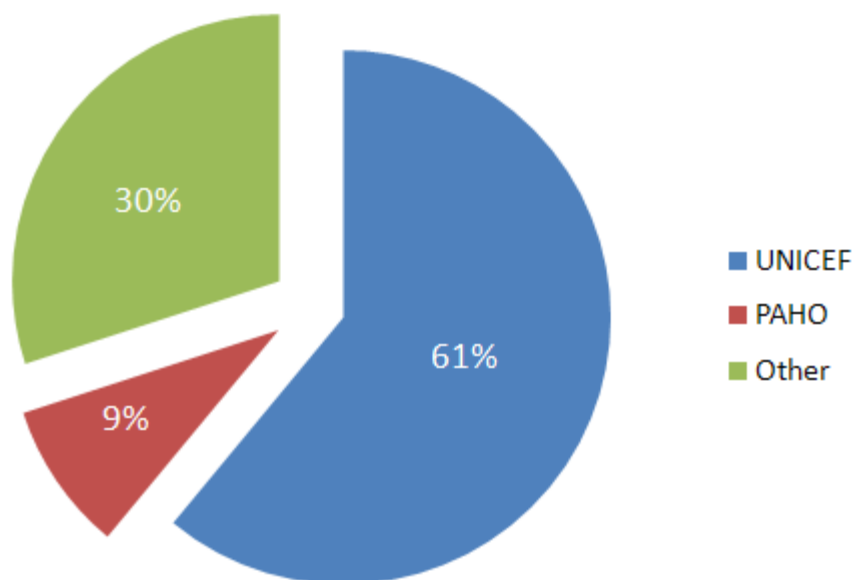
Figure 2. Vaccine market share 2008¹⁸



The developing-country market is also an oligopsonistic one (**Figure 3**). Two large procurement agencies alone purchase vaccines for over 70 percent of the developing-country birth cohort.^{13,19}

In the LIC and LMIC public market the demand for value-added technologies for vaccines is almost entirely donor dependent. Countries can only select value-added technologies for vaccines (e.g., formulations, presentations, or administration devices) for which donors are willing to pay, and buyers/donors may be disinterested in new or innovative products if prices are considered to be too high relative to historical prices for similar products.

Figure 3. Proportion of developing-country birth cohort covered by PAHO and UNICEF^{13,19}



Conversely, suppliers will have invested substantially in order to bring about innovation and will have an expectation of a reasonable return on investment (a minimum of more than just the additional cost of goods). Innovations that are not rewarded with a return on investment (e.g., an increase in unit price or increased market share), or that may even contribute to a lower unit price, reduced sales, or loss of market share, are counter to their interests.

Laws of supply and demand in the developing-country vaccine market

Under conventional law of supply, any growth in demand should lead to an increase in price, until such a time as the increase in supply offsets the increase in demand (**Figure 4, Figure 5**). In fact, the two enticements to enter the market when demand grows are additional market share and rising price.

When GAVI was launched, the mantra was that an increase in demand for vaccines would lead to increased competition amongst suppliers and consequently prices would fall (significantly over a span of five years). In fact, under normal circumstances this would only happen when supply outstripped demand (**Figure 6**). This may have occurred for Hep B vaccine; a number of monovalent Hep B vaccine producers were enticed into the GAVI market, and average selling price for Hep B vaccine did fall in the first few years of GAVI.¹³ But for “newer” vaccines (e.g., Hib and pentavalent vaccines) competition failed to materialize. Competition also failed to materialize for yellow fever vaccine (an old vaccine). Given the high barriers to entry into the vaccine market and the length of time required for competition to set in (it took six years for a first competitor of DTP-Hep B vaccine to enter the GAVI market,²⁰ seven years for a first competitor of pentavalent¹³), a short-term scenario (i.e., five to ten years) where competition for “new” vaccines or value-added technologies drives prices of products significantly downward seems highly improbable.

Today, five pentavalent vaccines have been UN prequalified,²¹ and it is possible that competition will begin to impact pricing over the next several years, but it is also possible that some suppliers will exit the market if prices fall below threshold (**Figure 7**). As price approaches threshold, the market is likely to be undersupplied, giving rise to supply security issues. Today, manufacturing problems with one supplier could lead to a global product shortage, and a sudden surge in demand—i.e., to respond to an epidemic—may make it impossible to meet demand.

For newer vaccines (e.g., rota, pneumo, and HPV), given the oligopolistic nature of the developing country market, growing demand could give rise to increasing prices, but more probably, individual vaccine manufacturers will choose to instead behave as “benevolent oligopolists.” This appears to have been the case for pentavalent vaccine for the first seven to eight years of GAVI where in the absence of competition, price rose only very slightly over time.²²

Figure 4. Greater demand should give rise to an increase in price, in the absence of greater supply

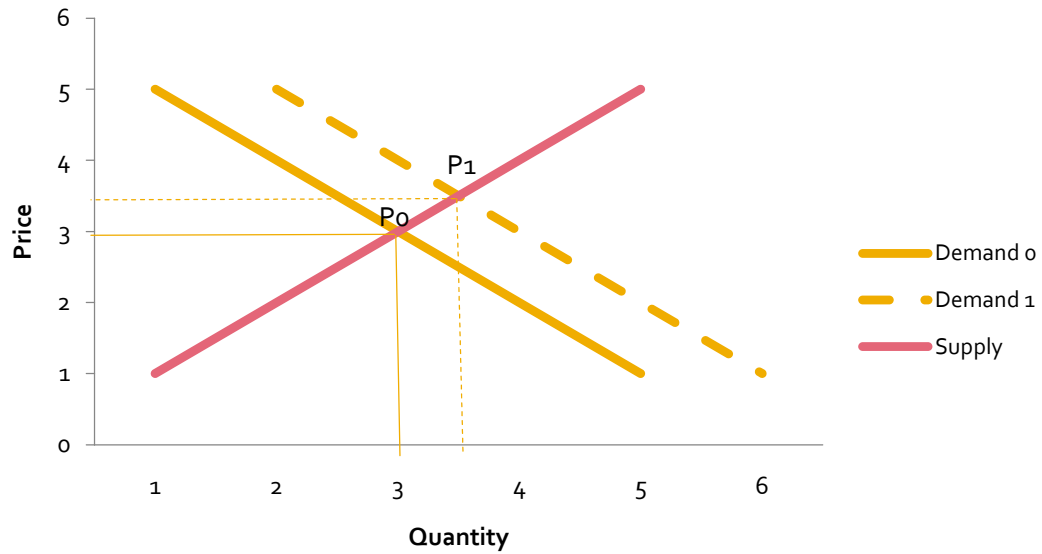


Figure 5. Only if the growth of demand is met by an equal growth of supply (i.e., more suppliers join the market) would price remain the same

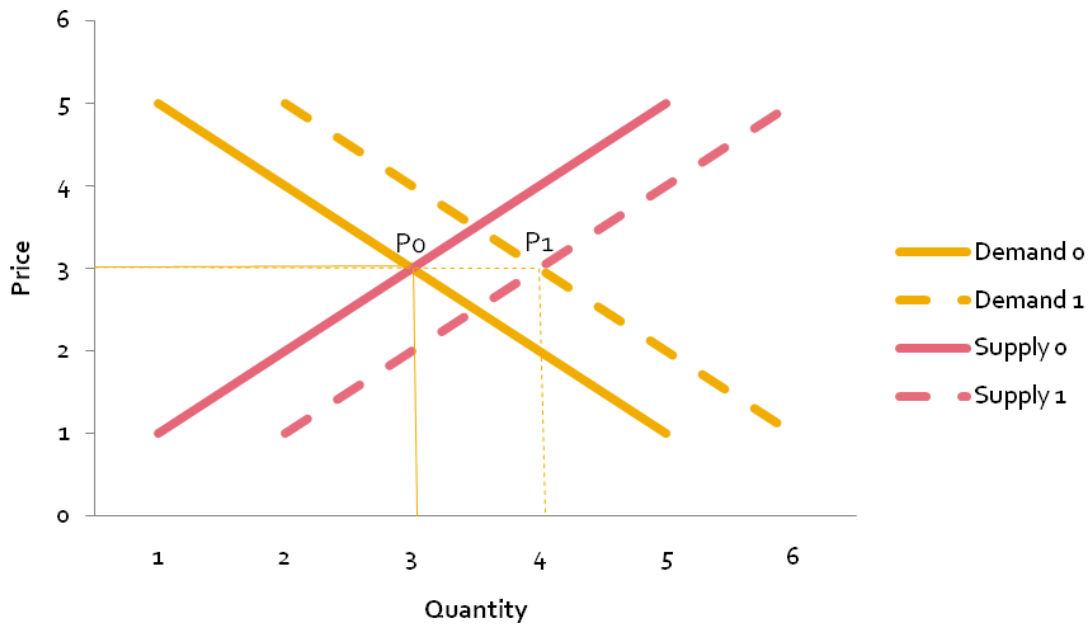


Figure 6. Only if growth of supply surpassed the growth in demand (i.e., too many suppliers join the market) would price fall

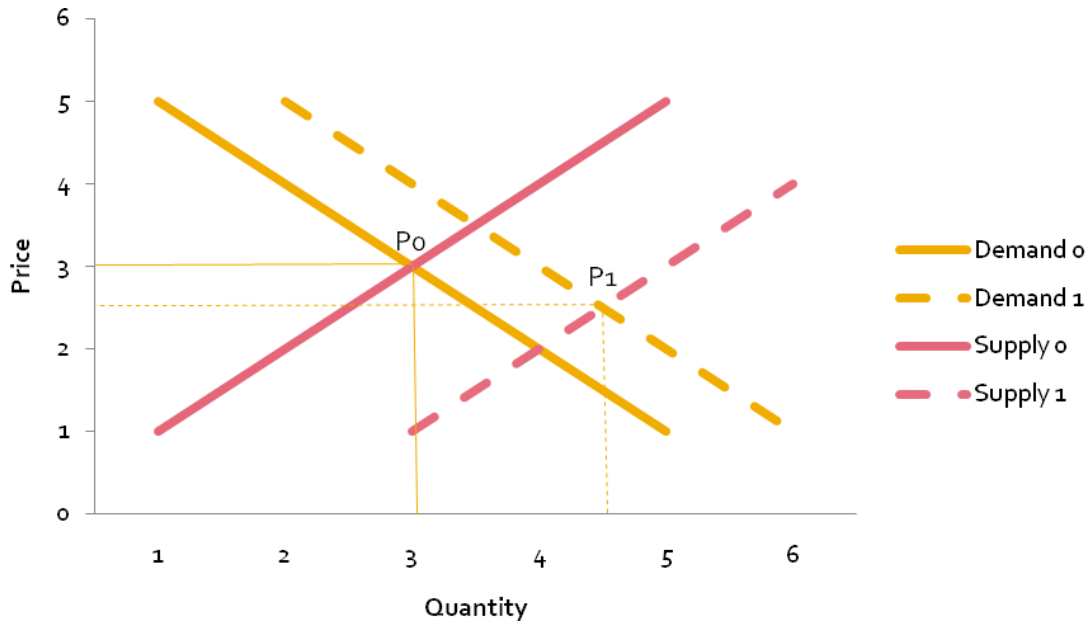
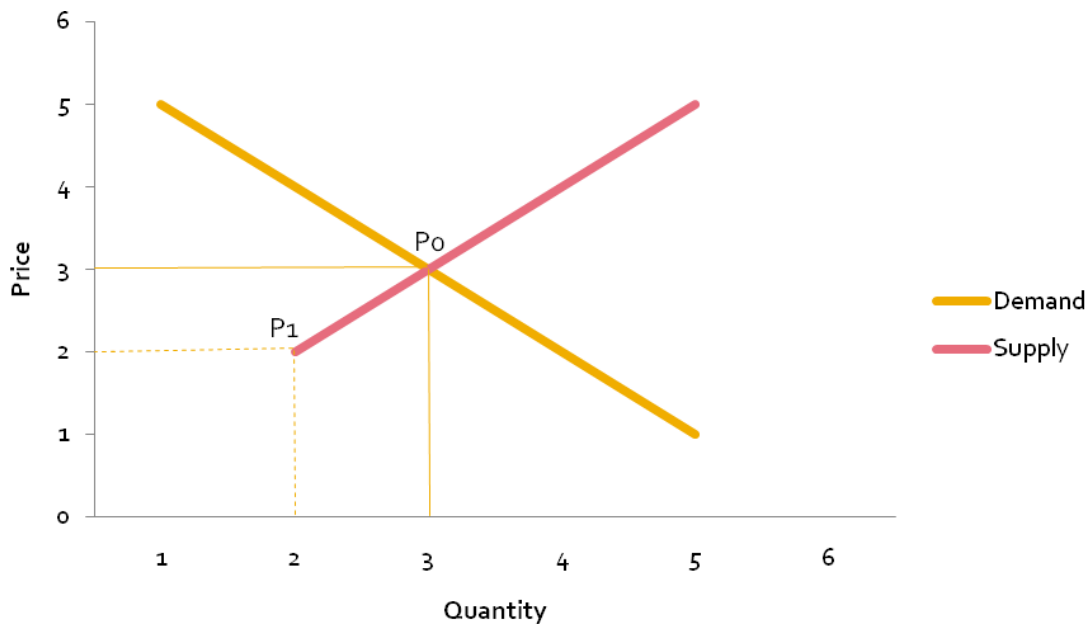


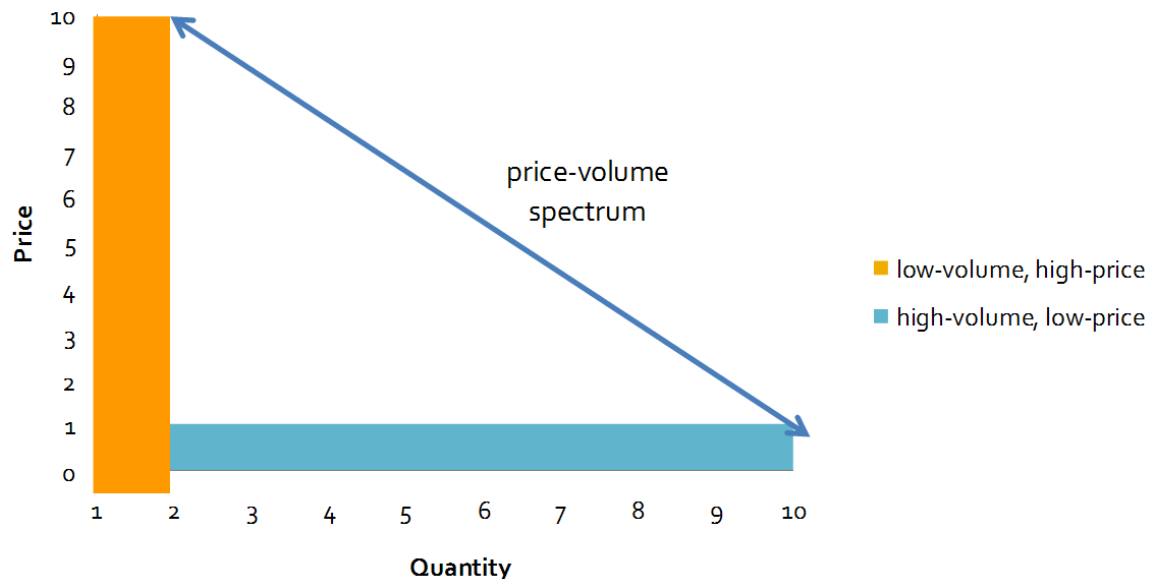
Figure 7. If price falls below threshold (P_1), suppliers exit the market



Differences between global and local manufacturers: the underlying vaccine economics are not different between types of suppliers. Local manufacturers may have greater tolerance for lower prices in the hopes of gaining greater market share,²³ but this is unrelated to cost of production, which, on average, will not be greatly different between global and local manufacturers (given the fixed-cost nature of the business).^{14,23}

Available industrial capacity may also be a stronger determinant of offer for local manufacturers than for global manufacturers (the latter whose capacity may already be saturated from sale of other products in other markets). In theory, the more valuable markets (for all suppliers) would be low volume/high price, and manufacturers would gravitate towards this end of the price-volume spectrum, given the opportunity (**Figure 8**). While the areas under the curves in **Figure 8** represent equal revenues, the high-price low-volume market generates higher profitability.

Figure 8. Price-volume spectrum



The role of IP in the developing-country vaccine market

For global manufacturers, there is no question that IP protection serves as an incentive (even a requirement) to invest in the developing-country market. Some local manufacturers, on the other hand, may be in search of IP that they would otherwise not have the means to develop (because of lack resources or because of scientific hurdles).

In general, if IP has been generated privately the innovator will want to generate a return on the investment. Sharing that property before investment has been recouped would compromise a reasonable return. But in practice, a desirable innovation will generate competition, which in turn should deliver the greatest value to the consumer (i.e., the best features at the best price). Sharing of IP should therefore not be necessary for access to an innovative value-added technology.²⁴

In instances where IP may impede progress (because of urgency or acceptance of one technology over all others), IP owners will typically license technology to competitors. This has occurred for the development of pandemic influenza vaccines where certain cell lines and IP for reverse genetics are deemed to be the most rapid way to develop pandemic vaccines.²⁵

If on the other hand the IP is in the public domain, the uptake of that innovation will be intimately linked to demand for the innovation (i.e., willingness to pay).

The role of local production of vaccines and value-added technologies in the developing-country vaccine market

Local manufacturers that are fully or partially subsidized through the public sector, or who are not innovators, may be willing to offer higher volumes of vaccine and value-added technologies at lower prices. This is of immediate benefit to the buyer for existing vaccines but will not improve affordability of the newest vaccines or value-added technologies. Only local manufacturers that are truly innovators can contribute to a sustainable supply of affordable “new” vaccines. The ability to innovate will be linked to the volume of sales and the profitability a company is generating from the sale of existing vaccines. The distinction between local and global manufacturers is therefore less one of geography and more one of ability to innovate and compete in the international marketplace for new vaccines.

Transfers of technology from global to local manufacturers are often touted as a means to make vaccine more affordable in developing countries. However, economies of vaccine production preclude manufacture for small local markets.²⁶ Because of the fixed-cost nature of vaccine production, local manufacture does not considerably reduce the cost of goods,²³ and other aggravating factors such as higher equipment maintenance and replacement costs, underperforming national regulatory authorities (NRAs), or civil and political unrest can offset any cost savings achieved in local environments. As for VVMs and AD syringes,²⁷ viability of a local vaccine manufacturer is not always assured.

Technically, transfers of technology are difficult to achieve and require a period of several years to complete. Global manufacturers may be loathe to give up technology when they can just as easily establish commercial ventures with local manufacturers (i.e., Panacea is an Indian bulk finisher for several manufacturers) or establish their own production facilities where there is a sound commercial rationale (i.e., sizeable market). Manufacturers may be fearful of giving up intellectual property that is utilized for some of their other products or processes (e.g., a conjugation technology).

Case studies of existing value-added technologies

How have the unique characteristics of the developing-country vaccine market impacted the uptake of value-added technologies for vaccines and what common themes have emerged from experience?

Here, the introductions of value-added technologies are examined to determine what lessons can be learned to inform future technology introductions. To better understand the reasons behind successes and failures, the three following value-added technologies were selected for case study:

- VVMs, a success story.
- Uniject, the jury is still out.
- Freeze-protection, a technology with promise.

Case study 1: VVMs

All vaccines delivered through the EPI must be stored and transported between 2°C and 8°C. Each antigen is heat labile to a different degree, but all have relatively short expiry dating (the World Health Organization [WHO] requires 24 months of shelf life for vaccines procured by UNICEF).²⁸ Exposure to heat over time reduces the potency of the antigen. Aluminum-adsorbed vaccines also flocculate when exposed to a freeze-thaw cycle and can be rendered impotent. Freeze-dried (lyophilized) vaccines can be stored frozen, but for pragmatic reasons (lack of freezers, and need to store diluents at higher temperatures) lyophilized vaccines are stored refrigerated—not frozen.

The cold chain has been problematic for the EPI since its beginning in the 1970s, a time when much of rural Africa and South Asia was not supplied with electricity. To ensure temperature monitoring of the shipment to countries, the EPI initially relied on a vaccine cold chain monitor (a heat-sensitive monitoring card—MonitorMark™) that was affixed to shipping cartons. In 1979, applying the same type of heat-sensitive indicator to each vaccine vial was first contemplated.²⁹

In response to the WHO/EPI's interest in a vial-level indicator, PATH began developing prototypes of vaccine vial monitors, under license from Allied Chemical Corporation, that would eventually be tested in ten countries between 1982 and 1985. Introductory trials in five countries were conducted between 1987 and 1990 with positive results. However, there were some technical issues with scaling up production, and when WHO selected OPV as the highest priority product for application of the indicator (given the accelerated activities around polio eradication—1988 World Health Assembly resolution), it was determined that the indicator was too slow to react for the highly heat-labile OPV. An improved technology, owned and manufactured by Temptime, was subjected to further trials by PATH and WHO, beginning in 1990, and deemed to be successful for use with all antigens.³⁰

Another five years of negotiations with vaccine manufacturers would follow, to overcome concerns and impediments to applying VVMs to OPV for the 1996 UNICEF tender. One of the initial impediments, since manufacturers are heavily regulated, was lack of clarity about what regulators in manufacturing countries would require (and permit) for the application of VVMs to labels and whether any claims related to temperature monitoring would have to be substantiated for the regulators. But the application of VVMs was undoubtedly expedited by both manufacturers and regulators because of the urgency that was attached to the polio eradication effort (the target for eradication was the year 2000). It was also, at the time, undoubtedly viewed as a one-time effort (i.e., exclusive to OPV).

Attempts to expand the use of VVMs to all EPI vaccines in 1998 faced a number of additional challenges: specifying the different types of VVMs for each individual vaccine and brand, overcoming the issue of having a single source for the technology, and ensuring that a requirement for VVMs would not limit the available supply of vaccines to UNICEF. But in 2001, VVMs became a minimum requirement on all UNICEF and GAVI tenders²⁹ (although in practice UNICEF continues to purchase some vaccines without VVMs for lack of alternate supply).

At a WHO meeting in 2002, manufacturers laid out the concerns that they had with the full-scale application of VVMs to all EPI vaccines (**Table 1**). Many of these concerns have now been allayed, but some remain, and at least one major manufacturer (sanofi pasteur) has yet to comply for all EPI vaccines.²⁹

Lessons learned

Despite the 15 years that it took to implement VVMs on OPV and the 30 years that it has taken to get VVMs applied to all EPI vaccines, the introduction of VVMs qualifies as a success story. More importantly, lessons learned from the introduction of VVMs can inform current and future value-added technology introductions. A full list of lessons learned is shown in **Table 2**.

Table 1. Concerns of manufacturers for implementation of VVMs on all vaccines²⁹

Nature of concerns	Concerns of manufacturers
Validation	VVM shelf life out of phase with vaccine shelf life
	Absence of data supporting correlation of VVMs with vaccine potency for all vaccines
	Consistency of VVMs in reflecting stability of each vaccine
	Absence of data that shows validation of VVMs
	Specifications for VVM adhesion
	High rate of false readings
Logistical	Dedicated labeling system for only a portion of production
	Management of inventory between VVM and non-VVM markets
	Different multilingual, multi-production, and multi-packed quantities
	Capital expenditures for implementing VVMs
	Conformity of preprinted labels with good manufacturing processes (GMP)
Regulatory	Requirement for NRA approval
	Responsibility and liability if VVMs indicate heat-exposed shipment
	Obligations of the manufacturer for shipment
Programmatic	Value of VVMs on heat-stable vaccines
	Interpretability of VVM conversion
Commercial	Single source of supply
	Period of warranty for VVMs
	Tolerance for quantities of VVMs delivered
	Requirement for minimum order of VVMs

Factors that favored VVM introduction, from the perspective of vaccine manufacturers

Rally around a common cause (the eradication of polio): Although it took five years of persuading vaccine manufacturers, the intensified efforts to reach polio eradication by the target year 2000, at the time, would have motivated both manufacturers and regulators to make a special effort to accommodate VVMs on OPV. No stakeholder would have wanted to have been seen as the obstacle to polio eradication. The fact that OPV was also being produced in massive quantities (hundreds of millions of doses) meant that a unique manufacturing processes for this antigen was easier to accept than it would have been for an antigen being produced in small quantity.

Agreement on a problem: Through the years of negotiating, all actors would have become acutely aware of the deficiencies in the cold chain and agreed that value-added technologies could play a valuable role.

Single-source technology: Ironically, the lack of competition for technology would have eliminated choice and avoided any dissention around which technology to select.

Following the lead: The actions of one manufacturer would have put pressure on others to adopt.

A minimum requirement for bidding on international tenders: Forcing bidders to apply VVMs in order to compete for international tenders left less room for noncompliance.

An externally driven initiative (see also “factors that may have impeded VVM introduction”): Vaccine manufacturers likely would have had little desire (or ability) to undertake the necessary validation of the VVM technology.

A phased approach: The piloting of VVMs on OPV, and the demonstration of feasibility and utility, would make it more difficult to challenge the expansion to all EPI antigens. Starting with a full-scale implementation on all EPI antigens would probably have doomed the project from the start.

Factors that may have impeded VVM introduction, from the perspective of vaccine manufacturers

No commercial incentive for vaccine manufacturers: In spite of the huge reduction in vaccine wastage, and the \$5 million per year in savings,²⁹ vaccine manufacturers accrued no benefit or reward in spite of the resources and time expended to implement VVMs.

Regulators were not involved in the validation phase: Because vaccine manufacturers are accountable to their NRAs, they rely heavily on the requirements of regulators to determine their course of action. Since regulators had not been approached for an opinion as to the necessary requirements for validation of VVMs, nor the regulatory steps needed for implementing VVMs, manufacturers would have felt both uncertain as to how to proceed and uncompelled to comply. The lack of “demand” from regulators for VVMs would also have added to the sentiment that the activity was not only somewhat frivolous but that it was adding complexity and risk.

VVMs were not being universally requested: Being subjected to a process that was unique for a particular client and that was segregating UNICEF (and later GAVI) inventory from general inventory created commercial risks for manufacturers that product could not be sold if demand did not materialize, or that product could potentially not be shifted to another client if a sudden and unexpected need arose (epidemic, product shortfall, etc). There were also capital and labeling system requirements that would have added costs and complexity to processes that were already sufficiently complex.

An externally driven initiative (lack of ownership): Individual manufacturers would have attributed less importance to an externally driven process, even if they fully

collaborated and engaged with partners, than an internally driven initiative. For lack of driving the process they would have failed to commit the way they might of had they been responding to a regulatory requirement.

Monopoly of Temptime: A single source of VVMs concerned manufacturers who feared having little to no leverage over pricing and purchasing conditions for VVMs.

Technical issues associated with the novelty: Because there was no experience with VVMs a host of technical issues had to be worked out before implementation could be successful. Manufacturers would have been most concerned with complying with GMP.

Table 2. Lessons learned from introduction of VVMs

Favored VVM introduction	Hurt VVM introduction
Common cause (help the polio eradication program)	No financial incentive for manufacturers, no rewards
Agreement on a problem (inadequate cold chain)	Regulators not requiring the technology
Monopoly for technology, so no dissension about the technology for which to opt	VVMs not requested by all developing-country market clients, creating separation between UNICEF and other inventories
Minimum WHO/UNICEF requirement for international tenders	Although vaccine manufacturers collaborated, validation was driven by PATH and WHO
Completing validation work prior to appealing to manufacturers	Monopoly of Temptime
A phase approach to demonstrate feasibility and utility first	Technical issues to be sorted out with VVMs

Summary of success factors

Taken altogether, the experience with VVMs suggests that success was attributable to:

- A compelling cause that stakeholders supported.
- A piloted approach that sold stakeholders on the feasibility and utility of the technology before full-scale implementation.
- A single-source technology which contributed to a harmonized approach and avoided dissensions over choice of technology.
- A requirement from the largest procurement agencies for full-scale application of the technology (in the UNICEF and GAVI market).

Case study 2: Uniject

Injections for immunization represent only a small fraction of all injections (less than ten percent).³¹ But LICs and LMICs often have inadequate capacity for medical waste management. Without attention to proper waste management, injection devices currently used in most immunization programs (conventionally hypodermic needles and plastic or glass syringes) may increase the safety risk to the public in developing countries, through inappropriate re-use of the injection device (as high as 75 percent in some countries).³² Single-use AD syringes are currently recommended for use with vaccines in developing countries, to reduce the risk of re-use.

The cost of vaccine wastage can also be enormous for some developing-country programs, as vaccine wastage rates can be as high as 80 percent for some antigens.³³ In some localities, professional health care providers may not have easy access to remote populations. In such instances village health care workers or birth attendants with limited skills may be expected to deliver immunizations.

A simpler and safer injection device for immunizations could both increase immunization coverage and safety, and reduce wastage. This was the thinking in 1987 when Uniject, an AD, single-use, prefilled, integrated needle/package device, was developed by PATH. The device was an improved version of a prototype developed by Merck who then ceded the IP to PATH who worked to further improve the device up until 1993.³³ PATH demonstrated the compatibility and stability of vaccines in the device and then field tested it with tetanus toxoid (TT) and Hep B in 1995 and 1996. The technology was subsequently licensed to BD.

Vaccine manufacturers were encouraged to offer relevant antigens for the developing-country market in Uniject, but as of today only four Hep B manufacturers and one tetanus vaccine manufacturer have opted for Uniject. To present vaccines in Uniject, manufacturers must follow a conventional regulatory pathway which includes validation of compatibility and stability of the vaccine in the device, validation of the filling process, clinical trials, and license application to a regulator (all of which requires a period of up to three years).³³ The device is also prequalifiable with UN procurement agencies.

Both vaccine manufacturers and donors have resisted a wholesale adoption of Uniject for varying reasons not the least of which is a higher per-unit cost than for a conventional syringe and vaccine in multi-dose vials. Other reasons include competition for technologies and exclusive relationships with syringe (or device) manufacturers. Countries have also experienced issues with higher storage volumes, requiring increased frequency of transport in Indonesia,³³ and manufacturers have highlighted that Uniject requires several times more equivalent filling capacity than for multi-dose vials (because the unit-fill time is much more rapid for multi-dose vials, and because the filling line speed for Uniject is slower than for vials).

PATH and BD have worked with manufacturers and countries to overcome the technical issues, and BD reports that speed of filling for Uniject is now comparable with vials.³⁴ But there is little demand from donors for vaccines presented in Uniject. And unlike for VVMs, although there have been tenders for vaccines in Uniject, there is no UNICEF requirement to supply vaccines in Uniject.

Country demand may also be limited. Since the per-unit cost of vaccines in Uniject is higher than in vials, even though Uniject may be cost-effective in settings where vaccine wastage is high,³⁵ it seems unlikely that donors will tolerate higher unit prices unless there is a strongly expressed preference from countries. (Indonesia delivers Hep B vaccine in Uniject,³³ but is the exception to the rule). The higher per-unit cost of Uniject was relative to previously used multi-dose vaccines and to a more expensive novel container.

Lessons learned

Uniject was developed over 20 years ago and has yet to enjoy widespread adoption for immunization (although other applications may hold greater promise).³³ The adoption of Uniject for immunization can thus be qualified as highly restricted. The literature describes a technology that was “ahead of its time” in that the relatively higher per-unit cost of a Uniject, compared to an AD syringe, does not lend itself to combination with inexpensive vaccines (e.g., tetanus toxoid). But it is not clear today if Uniject would have a brighter future if used with more expensive vaccines.

Lessons learned from the introductions of Uniject can inform current and future value-added technology introductions. A full list of lessons learned is shown in **(Table 3)**.

Factors that favored adoption of Uniject, from the perspective of vaccine manufacturers

Prefilled device with multiple benefits: simplifies use and logistics, improves safety (dose accuracy, prevention of re-use), minimizes wastage because of single-dose format: Multi-dose vials have long posed concerns over cross-contamination and vaccine wastage. At the extreme, some antigens were being wasted at rates of up to 80 percent.³³ It was clear that the better option for certain settings (e.g., for use in outreach, for use by lower-level health personnel, for use with high-value vaccines) was a single-dose prefilled presentation (“new” vaccines for LICs and LMICs are all presented in one- or two-dose presentations). The multi-dose vial policy also raised fears with manufacturers over liability in the event of cross-contamination. The aspiration of vaccine from a vial into a syringe also left room for human error. The act of vaccination requires training, and in resource-poor LICs and LMICs, dependency on trained health personnel for immunization can limit vaccination coverage, especially in remote areas. In an ideal world a single-dose, easy-to-use administration device and a preservative-free vaccine (already used in single-dose presentations in HIC markets) would be the best alternative.

An externally driven initiative (see also “factors that may have impeded Uniject adoption”): The use of plastic final containers for vaccines was not conventional, and the demonstration of feasibility by PATH forced some manufacturers to consider the possibility of prefilling plastic containers. The field testing of the device preempted refuting the device on practical grounds.

Reputation of industrial partner (BD): The solid reputation of BD as a leader in the syringe and device industry lent credibility to the technology and would have forced manufacturers to, at minimum, assess the technology (and the competitive threat).

Relatively inexpensive: Given that the technology was intended for use in LICs and LMICs, the cost of the device could not add significantly to the cost of immunization. Relative to other technologies and devices that were being contemplated at the time (e.g., jet injectors and other prefilled syringes), the cost of Uniject was relatively inexpensive (compared to the capital expense for injector guns), and it was conceivable that demonstrable cost-effectiveness would generate a willingness to pay.

Appropriate selection of antigens which required a birth dose or were delivered through outreach (TT and Hep B vaccine): The selection of antigens requiring a birth dose and often delivered in outreach (TT for the mother and Hep B vaccine for the infant) made perfect sense from a programmatic point of view, where it was understood that birthing often occurred outside of the health care setting and access to immunization services would be limited. The selection of these antigens, over any other antigens, minimized concerns that Uniject was designed to usurp the role of health professionals.

Factors that may have impeded the adoption of Uniject, from the perspective of vaccine manufacturers

Higher per-unit cost: In a highly price-sensitive market there would have been little confidence that the market would bear a higher-cost product. Vaccine manufacturers could have done little more than to pass on the additional cost of goods to the customer, and thus would not have accrued any benefit or reward in spite of the considerable resources and time expended to institute filling in Uniject.

An externally driven initiative (lack of ownership): Individual manufacturers collaborated to conduct stability testing and validate processes but would have attributed less importance to an externally driven process, even if they fully collaborated and engaged with partners, than an internally driven initiative. For lack of driving the process, they would have failed to commit the way they might have had they been responding to a regulatory requirement.

Array of competing technologies and competition amongst manufacturers for exclusivity: Each manufacturer was likely trying to seek a competitive advantage over the other through product differentiation. One of the avenues for product differentiation is device technology. At the time that Uniject became available, manufacturers were already exploring other technologies including jet injectors in attempts to offer LIC and LMIC markets an easier-to-use product at an affordable cost. Manufacturers that were investing in specific technologies with device manufacturers (e.g., BD) would have wanted guarantees that their investment would not profit competitors through exclusivity or other means. The challenge for all manufacturers was the price of the conventional syringe which was so low it seemed impossible that any other device could be developed and commercialized at an equivalent cost. In the face of a highly price-sensitive market, even cost-beneficial innovations were not guaranteed a place in the market.

Technical issues related to specialized filling: Challenges related to tooling for Uniject, given the other deterrents, discouraged the pursuit of the technology. The unit-dose presentation also limited the industrial capacity of manufacturers, and ultimately would have resulted in less capacity to serve the market. The lower capacity would not have been offset by higher price (i.e., a ten-fold decrease in capacity could not have commanded a ten-fold increase in price).

Little to no demand—no procurement agency requirement: Unlike with VVMs, where the demand became universal and donor driven (i.e., a requirement of WHO for UNICEF purchases), the same demand has not yet materialized for Uniject. The private sector, even in LICs and LMICs, was just as happy to be served with high-end prefilled devices.

Even if some significant demand had materialized, the challenges of managing two separate inventories (in Uniject and not in Uniject), running two separate types of filling lines, and maintaining sufficient industrial capacity for a same market (which was already strained for many antigens) may have been too great.

Limited to liquid vaccine: The inability to fill lyophilized vaccines in Uniject limited the appeal of the device.

Marketing messages too numerous?: Uniject had a lot of selling features, and it is possible that a single primary purpose was not evident. Had there been greater unity of message around a single purpose it might have been easier to develop a consensus around a common problem and market Uniject as the solution. Unlike for VVMs, which could be sold as the solution for monitoring the cold chain for OPV and saving the polio eradication effort, too many purposes for Uniject may have diluted a unity of purpose.

Trust: Some manufacturers became concerned that the development of Uniject may have been intended to unlevel the playing field between manufacturers. A breakdown in trust, in some instances, contributed to resisting adoption of the technology.

Table 3. Lessons learned from efforts to get Uniject adopted

Favored adoption of Uniject	Hurt adoption of Uniject
Prefilled, AD, single-use device with multiple benefits	Marketing messages too numerous?
Externally driven initiative that demonstrated feasibility and compelled manufacturers to consider seriously	Higher per-unit cost, especially relative to vaccines in multi-dose vials
Reputation of industrial partner (BD)	Compatibility and stability testing and field trials completed before appeal to vaccine manufacturers—vaccine manufacturers not driving the development
Relatively inexpensive compared to other technologies	Array of competing technologies, and competition amongst manufacturers for exclusivity
Appropriate selection of antigens (Hep B and TT), which required birth dose	Technical issues related to specialized filling equipment, filling time, and filling lot size
	Little to no demand—no procurement agency requirement
	Limited to liquid vaccines (e.g., not measles, yellow fever, Hib)
	Breakdown in trust between stakeholders

Summary of lessons learned

Taken all together the experience with Uniject suggests that the primary reasons that the technology has failed to be widely adopted are:

- It introduced an additional cost that the price-sensitive LIC and LMICs market were not prepared to bear.
- It competed with other technologies that were concurrently under development and was not exclusive to a vaccine manufacturer.

- Technical challenges reduced capacity to fill.
- Demand failed to materialize in the form of contracts with the UN procurement agencies.
- Limited applicability of the technology to liquid vaccines only.
- No single compelling argument to galvanize the will of the donor community and manufacturers.

Case study 3: Formulations for improved thermostability

Because of the heat sensitivity of vaccines (exposure to heat over time reduces the potency of the antigen) and although heat sensitivity is variable between antigens, all vaccines do require refrigeration for storage and transportation. The relatively short shelf life for vaccines (about two years) means that inventory must be ordered frequently and expired product must be discarded. In LICs and LMICs, refrigeration can be problematic, particularly in remote areas that may not have access to electricity or alternate sources of energy. LICs and LMICs may not have sufficient capacity for refrigerator maintenance and repair.³⁶ Inadequately set and maintained fridges can also expose vaccines to freezing which can damage aluminum adsorbed vaccines. On the other hand, there is little demand in upper-middle-income countries (UMICs) and HICs to do away with the cold chain for vaccines, even if UMICs and HICs also do periodically experience difficulties as a result of cold chain breaches.^{37,38}

Researchers have looked at ways of stabilizing vaccines at ambient temperatures to make the vaccines more robust should cold chain breaches occur and/or to alleviate the constraints imposed by the requirement of a cold chain for immunization. Approaches include polymer-based formulations,³⁹ trehalose,⁴⁰ micro-crystals,⁴¹ or polyol⁴² and other formulations of vaccines that stabilize them over a wide range of temperatures (e.g., -10° to 45°C) and prevent damage from freeze-thaw cycles.

Manufacturers have been researching and developing formulations that would impart greater stability for new vaccines, and the stability of some vaccines has been improved upon, but so far no revolutionary breakthroughs have reached licensure. This is a highly competitive area of R&D given that success should lead to a significant competitive advantage. As such it is a considerably secretive activity.

For mature vaccines, “retrofitting” with new heat-stable formulations could require extensive clinical development, and, therefore, would have to be justified by the hope of some economic return. In particular, in addition to immunogenicity and effectiveness studies to demonstrate equivalence with existing formulations, regulators would undoubtedly require safety studies to demonstrate no increase in immediate or long-term adverse events. On the other hand, when vaccines are in the early stages of development, it is entirely fitting to explore possible advantageous formulations to impart the greatest thermostability.

With an extremely price-sensitive LIC and LMIC vaccine market, it is not clear what additional value buyers would attach to heat-stable vaccines. In the absence of any indication from purchasers, it may be that manufacturers are not convinced by the value

that purchasers would attach to this property although improved stability has an inherent value to the manufacturer (e.g., improved bulk production efficiencies, reduced risk of recalls when cold chain is breached during storage/distribution while the vaccine is under the manufacturer's responsibility, and reduced shipping/storage costs).

The history of cooperation between vaccine manufacturers and international agencies has not always been positive. In the 1990s, Pasteur Merieux Connaught (now sanofi pasteur), under the urging of WHO and Centers for Disease Control and Prevention (CDC) experts, undertook the development of a heat-stable OPV using deuterium oxide (conceptually feasible). But development was eventually aborted after WHO and CDC began to doubt the need and feared some negative repercussions on the eradication program. The mid-course change in strategy suggested to manufacturers that the public sector could be indifferent to the risks borne by the vaccine manufacturers and that their strategies could misguide R&D in the vaccine industry.⁴³

Concurrent experiences with other technologies (e.g., jet injectors) may also have contributed to an atmosphere of doubt (over technical feasibility, donor commitment, or other).

Manufacturers also seek out exclusivity. If there is a wholesale adoption of a technology, like there was for VVMs, individual manufacturers reap no competitive advantage.

Lessons learned

Heat- and freeze-stable vaccines could improve the effectiveness and dramatically simplify the delivery of vaccines in LICs and LMICs. Yet today, in spite of technologies that hold promise, no new (or existing) vaccine is licensed for storage outside of a 2°C to 8°C range (exceptions: NeisVac-C™ can be stored for up to nine months at 25°C,⁴⁴ and Dukoral™⁴⁵ can be stored for up to two weeks at <27°C). Manufacturers do understand the competitive advantage that they would gain with a viable heat- and freeze-stable technology, but there is uncertainty about the reward for the innovator, and the expected rewards are today likely insufficient to accelerate development in this area. Lessons learned from failed developments can inform current and future developments. A full list of lessons learned is shown in **(Table 4)**.

Factors that favor the development of heat- and freeze-stable technologies, from the perspective of vaccine suppliers

Need in LICs and LMICs: All stakeholders understand the constraints imposed by the requirement of a cold chain for the storage and transportation of vaccines. Manufacturers have and continue to conduct R&D of heat- and freeze-stable technologies in an attempt to improve on existing stability and gain a significant competitive advantage.

Stabilization processes available in the public domain (see also “factors that may have impeded development of heat- and freeze-stable technologies”): The availability of stabilization processes in the public domain facilitates the R&D effort and encourages further exploration of reported experiences.

Relatively easy to do when researching and developing a new vaccine: When a new vaccine is still under development there is an opportunity to test the compatibility of a new antigen with a number of new heat- and freeze-stable technologies.

Factors that may have impeded the development of heat- and freeze-stable technologies, from the perspective of vaccine suppliers

Uncertainty of true demand and willingness to pay: In a highly price-sensitive market there is little that vaccine manufacturers could do other than to pass on the additional cost of goods to the customer, which the market might not bear, and little benefit or reward would be gained in spite of the considerable resources and time expended in developing a new technology.

No expressed need from UMICs or HICs: In a global market it is often the case that recovery on R&D investment comes, for the most part, from high-income markets. In the absence of a demand from high-income markets for a technology that would make the cold chain redundant, there is little opportunity to recover R&D costs from an exclusively low-income market.

Stabilization processes available in the public domain: To get manufacturers to improve vaccine stability, the buyer would have to impose a minimum requirement for purchase (like for VVMs). Some product differentiation might result from the application of a same stabilization process, given that achieving stability is highly know-how dependent, but in the absence of true product differentiation, manufacturers would rather seek competitive advantages through the application of proprietary processes.

Array of competing technologies and competition amongst manufacturers for exclusivity: Each manufacturer seeks a competitive advantage over the other through product differentiation. Numerous technologies are being researched, but this is not a driver of differentiation in high-income markets where there is little demand for storage of vaccines outside of the typical 2°C to 8°C range. Were heat- and freeze-stable technologies to be developed, manufacturers would want to guarantee their investment through exclusivity or other means.

Different stabilization processes may be required for different antigens: It is possible that one process will not be compatible with all antigens, in which case either multiple processes would be required for the LIC and LMIC market or only some vaccines could be made available with improved stability. The non-universality of a stabilization process would make it less appealing.

Trust between stakeholders: The unfortunate backtracking by WHO and CDC experts on deuterium-oxide stabilization of OPV created a profound chasm in trust between private and public sectors. Vaccine manufacturers are weary to engage in long-term development projects in the absence of true public-sector commitment. The absence of willingness to pay from buyers is an indicator for lack of public-sector commitment.

Table 4. Lessons learned from failed vaccine stabilization technology efforts

Favors development of stable vaccines	Impedes development of stable vaccines
Need in LICs and LMICs	Uncertainty of true demand and level of willingness to pay
Technologies available in the public domain	No expressed need from UMICs and HICs
Relatively easy to do when researching and developing a new vaccine	Technologies available in the public domain—no competitive advantage
	Array of competing technologies, and competition amongst manufacturers for exclusivity
	Different technologies may be required for different antigens
	Breakdown of trust between stakeholders

Summary of lessons learned

Taken all together, the experience with the development of heat- and freeze-stable technologies suggest that barriers to development of stabilization technologies include:

- The absence of a UMIC and HIC market for these technologies, creating a commercial barrier that discourages development for an exclusively LIC and LMIC market.
- The absence of a confirmed willingness to pay from purchasers.
- Manufacturers’ desire to have exclusivity (in whole or in part) over their preferred technologies to gain a competitive advantage.
- No single stabilization process that purchasers could impose as a minimum requirement for purchase.

Compilation of lessons learned from all three case studies

In total, the principle factors that influence the behavior of vaccine manufacturers to develop and adopt value-added technologies are summarized in **Table 5**:

Table 5. Compilation of lessons learned from three case studies in value-added technology introductions

Favor value-added technologies	Impede value-added technologies
Compelling and rallying cause	Uncertainty of true demand and level of willingness to pay, and no expressed need from UMICs and HICs
A phased approach with demonstration of feasibility	Technical challenges of producing at a similar level of cost
A single source of technology	Competing technologies and desire for exclusivity
A requirement of the largest purchasers	No minimum requirement from largest purchasers
Universality of the technology	Limited applicability of the technology
	Breakdown in trust between stakeholders

Pull mechanisms to incentivize the development of value-added vaccine technologies

Existing pull mechanisms for vaccines

New innovative financing mechanisms have been developed to both secure the longer-term commitments of donors and also to entice vaccine manufacturers to better serve the LIC and LMIC vaccine markets. The principal “pull” incentive to date that has influenced manufacturers’ attitudes to LIC and LMIC markets is long-term donor support to countries for purchase of vaccines (the GAVI Alliance—formerly GAVI Fund). GAVI has grown the value of the LIC market from approximately US\$100 million to over US\$600 million in the space of seven or eight years.¹³

Another pull mechanism for pneumococcal conjugate vaccine is the Advanced Market Commitment (AMC), which has yet to be implemented. The AMC may have less “pull” than GAVI because the reward is artificially set (unlike GAVI which relies on market forces), and the reward may be too small and too limited in time to have the same pull effect or to generate competition.

The fundamental problem remains the low value of the LIC and LMIC vaccine markets relative to the UMIC and HIC markets and, to a lesser degree, the sustainability of demand. This is attributable to at least two factors, the donor dependency of the LIC and LMIC markets and donors’ undervaluation of new vaccines due to historical low pricing for vaccines.

In fact, because of the chronic donor dependency of the LIC and LMIC vaccine markets and because of an expectation for costs-savings, vaccines are held to a cost-effectiveness standard by which few (if any) other national LIC or LMIC investments are made.

Given the high (or higher) cost of innovation, donors must come to accept and understand the need to commit more resources to immunization if they expect LICs and LMICs to access value-added technologies for vaccines. LICs and LMICs must themselves give greater priority to value-added technologies for immunization.

What types of pull mechanisms would entice vaccine manufacturers to invest more in value-added technologies for vaccines?

Distinction needs to be made between two types of vaccine development:

1. Vaccines that have a primary market (i.e., high value) in industrialized markets and a secondary market (i.e., lower value) in developing countries (e.g., pneumococcal conjugate, rotavirus, HPV).
2. Vaccines that are primarily intended for use in developing countries (e.g., malaria, tuberculosis, HIV).

For (1), few incentives can redirect the course of development because these vaccines are targeted first and foremost at well-known and studied markets. For (2), much greater opportunity exists to influence the course of development because true markets for these

products do not exist, or the market is almost entirely donor dependent. For an exclusively donor-dependent market, vaccines are more likely to be designed to meet the specifications of the donors (who often contribute significantly to the development of the product through “push mechanisms”).

This paper focuses primarily on incentives for vaccines that are not exclusive to a donor-dependent market and that will require some form of pull incentive to redirect development to include value-added technologies.

Distinction also needs to be made between global vaccine producers and “local” manufacturers (who may be private, public, or para-public). Local manufacturers sell almost exclusively to LIC and LMIC markets (exception: Serum Institute of India recently licensed measles vaccine in Switzerland, and its website suggests that it exports vaccines to half a dozen Western European countries).⁴⁶ Local manufacturers also predominantly follow the lead of global manufacturers in innovation, with a lag of several years between the two (exception: PT BioFarma who has adopted Hep B vaccine in Uniject for its local market, due to a pull from its ministry of health).³³ Because of this and because local manufacturers may still be competing more for higher-volume markets than high-value markets, it may be appropriate to consider different “pull mechanisms” or “pull thresholds” for the two types of manufacturers.

Principles of incentive measures:

Any incentive measure should include the following.

1. Reward added value—not lowest price. Cost-benefit analyses should aid in decision-making for the appropriate selection of value-added technologies.
2. Generate competition for the reward by sufficiently compensating for the high cost of R&D, cost of goods to produce, and the high risk assumed by the innovator.
3. Allow for competing technologies, as individual manufacturers often seek to distinguish themselves from the competition through innovation; competition will also provide consumers with choice and create the conditions for the best value for the money.
4. Allow the value-added technology manufacturer full ownership over development of the technology.
5. Be linked to a specific objective (e.g., improving safety), not a specific technology.
6. Be of sufficient duration to reward the risk assumed by the innovator (i.e., at least 15 to 20 years) recognizing that donor dependency for value-added technologies for vaccines is going to be protracted, and donors must be prepared to commit for at minimum this period of time.
7. Be equitable to all vaccine producers and not create conditions that favor some over others.

Types of pull mechanisms to be considered:

Based on the LIC and LMIC market dynamics and the lessons learned from the case studies on VVMs, Uniject, and heat- and freeze-stable technologies, the types of incentives to the vaccine industry that could address the principle barriers to adoption of value-added technologies are shown in **Table 6**. The single greatest issue that needs to be addressed is the limited market attractiveness and the lack of valuation for innovation.

Table 6. Incentives to address specific barriers to adoption of value-added technologies

Barriers to adoption	Possible Incentives			
	Local Manufacturers		Global Manufacturers	
	Primary market: domestic public and private	Primary market: international public market in LICs and LMICs	Primary market: HICs Secondary market: LICs and LMICs	Primary market: LICs and LMICs Secondary market: None
Limited willingness to pay	Higher price for product with value-added technology	Higher price for product with value-added technology	Higher price for product with value-added technology	“Push” mechanisms to develop value-added technology
Technical challenges	Provision of technical assistance	Provision of technical assistance	Higher price for product with value-added technology	“Push” mechanisms to develop value-added technology
Competition	Provision of technical assistance	“Push” mechanisms to develop value-added technology	Higher price for product with value-added technology	“Push” mechanisms to develop value-added technology
Not a purchaser requirement	Higher price for product with value-added technology	Higher price for product with value-added technology	Higher price for product with value-added technology	“Push” mechanisms to develop value-added technology
Not universal	Higher price for product with value-added technology	Higher price for product with value-added technology	Higher price for product with value-added technology	“Push” mechanisms to develop value-added technology
Lack of trust	Committed funding for purchase of value-added technology	Committed funding for purchase of value-added technology	Committed funding for purchase of value-added technology	“Push” mechanisms to develop value-added technology

In addition to incentives to overcome barriers to adoption, a number of other incentives can be conducive to the adoption of value-added technologies (**Table 7**). The strongest conducive incentive is a clear and compelling story to motivate both manufacturers and donors to rally to fix an urgent problem (e.g., failure of polio eradication without VVM for OPV).

Table 7. Conducive incentives that promote adoption of value-added technologies

Conducive incentives
Compelling and rallying cause
<i>A priori</i> demonstration of feasibility of specific value-added technology
Consensus on use of a single technology
Condition for procurement by largest purchasers
Broadly applicable technology

Based on these findings, the following “pull” mechanisms could be considered for each specific value-added technology:

- 1. Higher price for product with value-added technology through a procurement policy that rewards innovation:** Distinct from the pneumo AMC, this “pull mechanism” would offer a higher price for any product with a value-added feature, and not set a “tail” price, but instead allow the market to set the “tail” price. Likewise, the commitment would not be limited in time. Instead this procurement policy would allow UNICEF to award contracts on the basis of value-added features and to tolerate prices that are up to twice as high as for current similar products. Demand from countries would ultimately determine the amounts of each type of product (value-added feature, or no value-added feature) purchased. As such no specific fund from donors would need to be established (although donors would have to agree to a policy of rewarding value-added products).

To act as a true incentive, the value of the reward (the price) would have to be such that it creates competition for the reward. A two-fold increase in current price might act as a sufficient incentive. (Because new value-added technologies may require substantial clinical testing, and in all cases regulatory approval, the process will be time-consuming and resource intense for the manufacturer. For this reason, manufacturers may not be willing to innovate even for marginal profit gains. Therefore the gain would have to be deemed sufficient to warrant reallocating resources to invest in a lengthy process).

To justify the price level, economic assessments should be conducted to determine the value of the innovation (in lives saved, wastage prevented, cold chain capacity made redundant, etc). But ultimately the demand for the product (i.e., uptake by countries) should determine its value.

- 2. Provision of technical assistance to local manufacturers for formulation and finishing of vaccines from bulk:** If market attractiveness fails to incentivize global vaccine manufacturers, some local producer/bulk finishers might be contracted to formulate bulk vaccines in innovative formulations or to fill formulated product in innovative devices. This would alleviate any economic burden on the originator, and the bulk finisher might deem the current market to be sufficiently attractive to sell into.

This would require formalized agreements between bulk vaccine producers and bulk finishers (as exists today for polio and Hib antigens, e.g., between several global producers and Panacea). However, there are several reasons why both bulk vaccine manufacturers and local producers may not wish to pursue this option, and so this mechanism should be given a low probability of success.

- 3. Grand-Challenge-like awards for after-market innovations:** The possibility of adapting technologies to existing vaccine should not be excluded, and inventors of devices or formulations that make use of existing vaccines could be considered for one-time awards.

Possible pilot projects for Optimize

Based on this review, Optimize should consider two pilot projects:

- 1. A review of the proposed pull mechanisms and a complete assessment with vaccine manufacturers of the attractiveness of the LIC and LMIC vaccine markets** to assess the level of attractiveness that would elicit their interest in marketing value-added technologies. Specifically, manufacturers should be asked to indicate at what price points they would enter the market for specific technologies (assuming technical feasibility). At the same time, bulk manufacturers should be asked about their willingness to consider contracting with bulk finishers to determine the degree of likelihood for such an option.
- 2. An advocacy effort to develop clear and simple messages about the urgency and importance of each value-added technology/specific objective** that can be used to convince donors of the value of novel technologies.

Additional cost-benefit analyses (additional to those already done) could be contemplated for the purpose of valuing the incremental price that donors should be willing to pay for each value-added technology.

Conclusion

An assessment of the current vaccine market dynamics in LICs and LMICs reveals that today there is insufficient incentive for vaccine manufacturers to further invest or accelerate developments of value-added technologies.

Experience shows that a compelling and urgent cause, such as the eradication of polio, can motivate vaccine manufacturers to innovate (i.e., apply VVMs to OPV), but there is little to no reward to vaccine manufacturers for complying.

Trust issues between public and private sectors have at times hindered progress towards making value-added technologies available.

A specific incentive to fairly reward manufacturers who innovate could succeed in making value-added technologies (existing or future) accessible, provided donors are willing to commit additional resources.

Greater advocacy and social marketing are also required to galvanize interest around urgent and compelling public health issues that can be addressed through value-added technologies.

Optimize can undertake some key research to determine the best ways forward.

References

1. Munira SL, Fritzen SA. What influences government adoption of vaccines in developing countries? A policy process analysis. *Social Science and Medicine*. 2007;65(8):1751–1764.
2. Miller M. Vaccine Research, Availability...and Reality Perspectives of International Health & Humanitarian Assistance Communities [PowerPoint online]. Available at: www.usminstitute.org/presentations/mill0301.ppt. Accessed September 10, 2009.
3. Kane M, Brooks A. New immunization initiatives and progress toward the global control of hepatitis B. *Current Opinion in Infectious Diseases*. 2002;15(5):465–469.
4. World Health Organization (WHO). *The Global Burden of Disease: 2004 Update*. Geneva: WHO; 2008.
5. Obaro SK, Palmer A. Vaccines for children: policies, politics and poverty. *Vaccine*. 2003;21(13–14):1423–1431.
6. Riddell A, Pollard AJ. Tropical disease vaccines. *Expert Review Vaccines*. 2003;2(1):105–112.
7. Scott JA. The preventable burden of pneumococcal disease in the developing world. *Vaccine*. 2007;25(13):2398–23405.
8. McKinney S, Jarrett S. Update on Vaccine Security [PowerPoint online]. Available at: http://www.who.int/immunization_supply/vaccine_security_jarrett_mckinney.pdf. Accessed September 9, 2009.
9. Greco M. Development and supply of vaccines: an industry perspective. In: Levine MM, Kaoer JB, Rappuoli R, Liu MA, Good MF, eds. *New Generation Vaccines*. 3rd ed. 2004:75–88.
10. McKinsey and Company. *Accelerated Development and Introduction of Priority New Vaccines: The Case of Pneumococcal and Rotavirus Vaccines*. New York: McKinsey and Company; 2002. Accelerated Development and Introduction Plans? Document, No.5B.
11. GAVI Alliance. *Key Concepts: Economics of Vaccine Production. Understanding Vaccine Prices*. Geneva, Switzerland: GAVI Alliance; 2001.
12. Allary C, Riche M, Edwards M. Global vaccine commercialization part one: competitive challenge. *BioProcess International*. 2008;6(9):S4–S11.
13. Procuring supplies for children—immunization page. The United Nations Children's Fund (UNICEF) website. Available at: http://www.unicef.org/supply/index_immunization.html. Accessed September 9, 2009.

14. Batson A, Glass S, Whitehead P. Vaccine economics: from candidates to commercialized products in the developing world. In: Levine MM, Kaoer JB, Rappuoli R, Liu MA, Good MF, eds. *New Generation Vaccines*. 3rd ed. 2004:57–74.
15. Institute for Vaccine Safety. *FDA Issues Information Update on Rotavirus Vaccine*. Baltimore: Institute for Vaccine Safety; 2007. Available at: <http://www.vaccinesafety.edu/cc-rota.htm>.
16. Pennsylvania Biowatch (2004). Big Pharma? Think Again. Available at: <http://www.pennsylvaniabio.org/BIOWATCH/October2004/guestcolumn.htm>.
17. Handysides S. Vaccine manufacturer voluntarily withdraws rotavirus vaccine. *Eurosurveillance*. 1999;3(43):1311.
18. Sanofi Aventis. Full Year 2008 Results and Outlook [PowerPoint online]. Available at: http://en.sanofi-aventis.com/binaries/FY2008_EN_V5_tcm28-23943.pdf. Accessed September 13, 2009.
19. UNICEF. *State of the World's Children 2009: Maternal and Newborn Health*. New York: UNICEF; 2008.
20. Affolder R, Rizzo I, Burgess C, Bchir A, Lob-Levyt J. A prescription for drug delivery. *Nature*. 2007;449(7159):170–172.
21. Vaccine supply and finance page. The Hib Initiative website. Available at: <http://www.hibaction.org/vaccine.php#products>. Accessed September 13, 2009.
22. UNICEF. Historical Average Weighted Price of Pentavalent Vaccine Offered to GAVI Eligible Countries [PowerPoint online]. Available at: www.who.int/nuvi/hib/Financing02.ppt. Accessed September 13, 2009.
23. Mercer Management Consulting. *Lessons Learned: New Procurement Strategies for Vaccines*. New York: Mercer Management Consulting; 2002.
24. Mahoney RT. Public-private partnerships in the development of hepatitis B vaccine in Korea. *Science Technology and Society*. 2005;10(1):129–140.
25. MedImmune licenses reverse genetics technology to GlaxoSmithKline. *The Free Library* [serial online]. 2007. Available at: <http://www.thefreelibrary.com/MedImmune+licenses+reverse+genetics+technology+to+GlaxoSmithKline.-a0174074947>.
26. Milstien J, Batson A, Meaney W. A systematic method for evaluating the potential viability of local vaccine producers. *Vaccine*. 1997;15(12–13):1358–1363
27. Lloyd JS, Milstien JB. Autodisable syringes for immunization: issues in technology transfer. *Bulletin of the World Health Organization*. 1999;77(12):1001–1007.

28. WHO. *Procurement of Vaccines for Public Sector Programmes*. WHO/V&B/99.12. Geneva: WHO; 1999.
29. Frost LJ, Reich MR. *How do Good Health Technologies Get to People in Poor Countries?* Cambridge, MA: Harvard Series on Population and International Health; 2008.
30. PATH. *HealthTech Historical Profile: Vaccine Vial Monitors*. Seattle: PATH; 2005. Available at: www.path.org/files/TS_htiv_vvms.pdf.
31. WHO. *Guiding Principles to Ensure Injection Device Security*. Geneva: Safe Injection Global Network; 2003. Available at: http://www.who.int/injection_safety/WHOGuidPrinciplesInjEquipFinal.pdf.
32. Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. *International Journal of STD and AIDS*. 2004;15(1):7–16.
33. PATH. *HealthTech Historical Profile: the Uniject™ Device*. Seattle: PATH; 2005. Available at: www.path.org/files/TS_htiv_uniject.pdf.
34. BD Uniject™—now or never. Presented at: 4th Annual Global Immunization Vaccine Presentation and Packaging Advisory Group Lunch Break Side Meeting, February 17, 2009; New York.
35. Levin CE, Nelson CM, Widjaya A, Moniaga V, Anwar C. The cost of home delivery of a birth dose of hepatitis B vaccine in a prefilled syringe in Indonesia. *Bulletin of the World Health Organization*. 2005;83:456–461.
36. Immunization Basics. New documents and tools on routine immunization and sustainable financing. *Immunization Basics SnapShots*. 2008;8:1–4. Available at: http://www.immunizationbasics.jsi.com/Newsletter/Archives/snapshots_volume8.htm
37. Bell KN, Hogue CJR, Manning C, Kendal AP. Risk factors for improper vaccine storage and handling in private provider offices. *Pediatrics*. 2001;107(6):e100.
38. Matthias DM, Robertson J, Garrison MM, Newland S, Nelson C. Freezing temperatures in the vaccine cold chain: a systematic literature review. *Vaccine*. 2007;25:3980–3986.
39. Coeshott C. *Thermostable Vaccines with Improved Stability at Non Refrigerated Temperatures*. Seattle: Grand Challenges in Global Health; 2008. Available at: <http://www.grandchallenges.org/ImproveVaccines/Challenges/HeatStable/Pages/Thermostable.aspx>.
40. Liu J, Wang P, Li G, et al, inventors: Changchun Institute of Biological assignee. Freeze-dried hepatitis A attenuated live vaccine and its stabilizer. US patent 6 884 422. April 26, 2005.

41. Murdan S, Somavarapu S, Ross AC, Alpar HO, Parker MC. Immobilisation of vaccines onto microcrystals for enhanced thermal stability. *International Journal of Pharmacy*. 2005;296(1–2):117–121
42. Braun LJ, Tyagi A, Perkins S, et al. Development of a freeze-stable formulation for vaccines containing aluminum salt adjuvants. *Vaccine*. 2009;27:72–79.
43. A heat-stable oral polio vaccine—waiting for a decision. CVI goal: vaccines that withstand heat. *CVI Forum*. 1995;10:19–20.
44. GlaxoSmithKline. NeisVac-C vaccine [product monograph]. Mississauga, Canada: GlaxoSmithKline; 2009.
45. Sanofi pasteur. Dukoral [product monograph]. Toronto, Canada: Sanofi pasteur; 2007.
46. Serum Institute of India website. Available at: <http://www.seruminstitute.com/>. Accessed September 13, 2009.