



Vaccine market- shaping 1980-2010

Relevant insights to inform
digital market-shaping efforts



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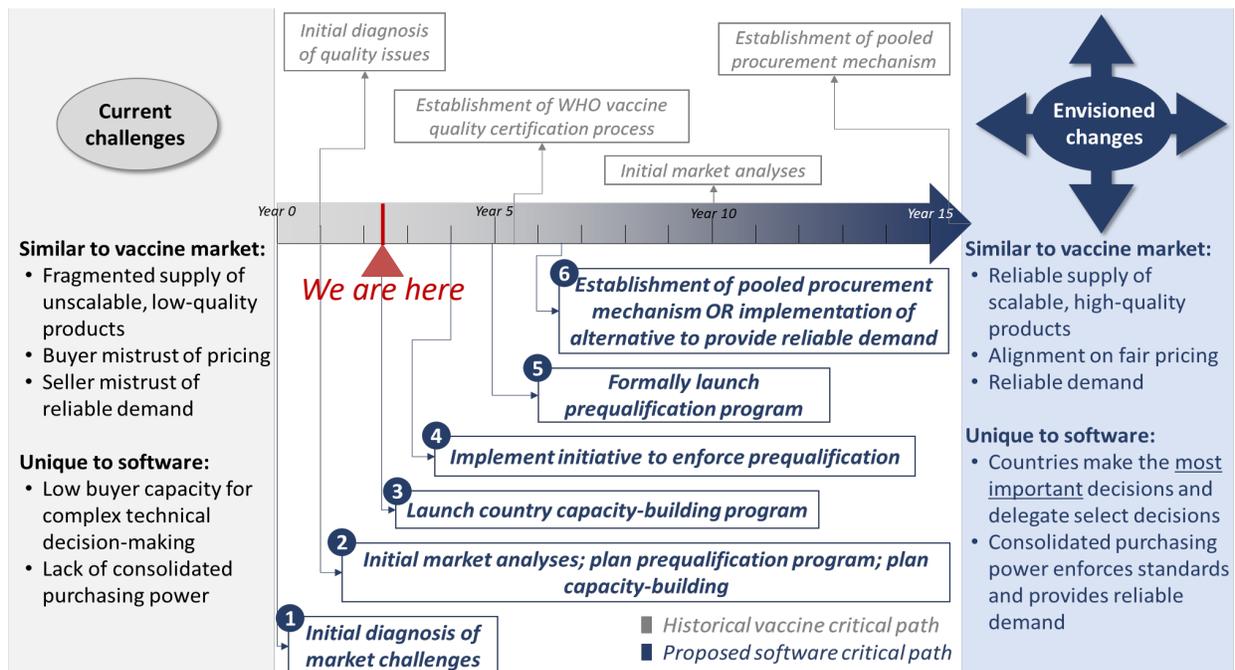
INTRODUCTION

One of global health's most remarkable success stories is the continuous progress towards greater vaccine equity. While many factors have contributed to more equitable vaccine distribution, several market interventions were crucial for making life-saving vaccines widely available to families throughout the world. These interventions include the launch of the World Health Organization's prequalification process to ensure global standards of safety, quality, and efficacy, and the creation of the international organization Gavi to unite the public and private sectors in accelerating equitable access to childhood immunizations.

Like vaccines, the use of digital technologies in the health sector can play an increasingly profound and transformative role in advancing health equity. As interventions like mobile-phone based disease surveillance improve health outcomes for communities, access to digital-enabled health care becomes an equity issue. In consideration of shared characteristics between the vaccine and digital health markets, there is value in examining experiences and developments from the vaccine market that can inform digital health's contribution to health equity. For example, the market challenges preventing the equitable distribution of vaccines in the 1980s bear some resemblance to those faced by digital health today, most notably high levels of mistrust among consumers. At the same time, digital health has important market characteristics that make it distinct from the vaccine market. Digital health has far greater product heterogeneity, for example, which can create novel regulatory challenges.

The figure below presents some of these market similarities and differences in relationship to current challenges and envisioned changes, while exploring where we are today within a 15-year pathway of proposed critical steps for software that takes its shape from the historical vaccine market timeline.

FIGURE A0. COMPARISON OF VACCINE AND SOFTWARE MARKETS, WITH MARKER INDICATING CURRENT STATE OF DIGITAL HEALTH

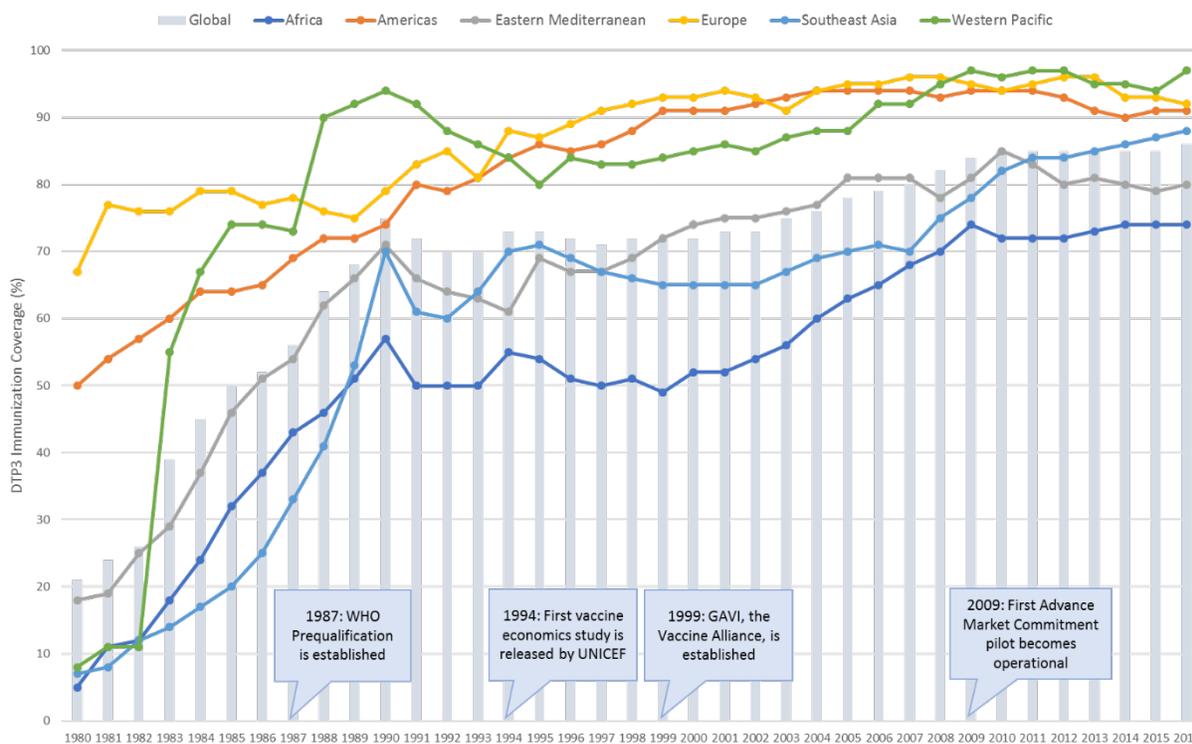


The following overview provides a summary of how market-shaping interventions transformed the vaccine sector, an assessment of which aspects of the vaccine market transformation are relevant to digital markets, and an articulation of some key differences that are important to consider as we pursue digital-enabled health care for all.

VACCINE MARKET OVERVIEW AND EVIDENCE

The vaccine market in low- and lower-middle-income countries (L/MICs) has benefitted from more than 30 years of market-shaping activities, some of which may be relevant to digital markets today. These market-shaping activities helped grow the market from approximately 21% of the world’s birth cohort in 1980 to 86% in 2016 (see Figure A1). From the establishment of a small-scale, regional pooled procurement mechanism in 1979 to the launch of a sophisticated Advance Market Commitment (AMC) in 2008, these mechanisms have helped to address a series of market failures that were preventing children from accessing lifesaving vaccines. This annex (1) provides an overview of the vaccine market at key points in time; (2) evaluates targeted market-shaping interventions that may have relevance to the wireless connectivity and software markets today; and (3) documents (at a high level) how key market-shaping interventions were operationalized.

FIGURE A1. DTP3 IMMUNIZATION COVERAGE FROM 1980 TO 2016, BY REGION (UNICEF, N.D.)



Abbreviations: DTP3, diphtheria-tetanus-pertussis; AMC, Advance Market Commitment; UNICEF, United Nations Children’s Fund; WHO, World Health Organization.

Throughout this assessment, the following thematic insights emerged.

Strategic (e.g., determining which solutions to pursue):

- **Countries did not demand or instigate solutions to market barriers; global donor, procurement, and policy-setting agencies consistently drove change.** Resource constraints, political incentives, and limited technical expertise of government agencies drove those agencies to refer to external expertise (e.g., World Health Organization [WHO]) and to align and follow the lead of global procurement agencies (e.g., United Nations Children’s Fund [UNICEF]). For example, WHO played a critical role in establishing minimum quality standards for vaccines. UNICEF effectively implemented these standards by procuring only the vaccines that met them. Countries trusted the technical conclusions of WHO and followed UNICEF’s lead, fast-tracking national acceptance of vaccines that had been ‘prequalified’ for procurement by UNICEF.
- **The vaccine community tackled market challenges sequentially, focusing first on the most acute issues with the simplest interventions.** WHO’s foundational product quality assessment program (prequalification) and key economic analyses were precursors to the Global Alliance for Vaccines and Immunisation (Gavi), a pooled financing mechanism for vaccines created in 2000. Gavi’s establishment, along with strong WHO recommendation for pneumococcal conjugate vaccine (PCV), were then precursors of the PCV AMC, a mechanism to incentivize manufacturers to supply low-income markets (The Boston Consulting Group [BCG], 2015; Gavi, n.d.^a). More sophisticated market interventions built off of earlier, foundational market interventions.
- **Economic analysis helped debunk long-standing assumptions—most notably that investment in local production of vaccines did *not* assure national access to high-quality, affordable vaccines.** In fact, through the Children’s Vaccine Initiative and other fora, WHO and UNICEF repeatedly educated the community that the global goal was access to an affordable, reliable supply of high-quality vaccines through any mechanism (international procurement, local procurement, local production), rather than the goal being local production. Vaccine manufacturers, countries, funders, the United Nations (UN), and implementing agencies have since relied on market research to deeply understand challenges, build consensus around problems, and successfully design and implement solutions. Studies on the economics that underpinned vaccine manufacturing were essential for educating public-sector partners and creating a common language and fact base for shaping market interventions. Market analyses underpinned simpler solutions, such as strengthening demand forecasts, to more complex solutions, such as the AMC.

Operational (e.g., determining how to implement a solution):

- **Successful vaccine market-shaping mechanisms depended on a trusted governance process, an accountable decision-making body, and high-level executive sponsorship.** Early support by high-level advocates (e.g., G8¹ finance ministers) drove wider support among donors, accelerating co-funding agreements and momentum (United States Agency for International Development [USAID], 2014). Governance was most effective when leadership included representation from donors (frequently a requirement for funding), country governments, multilateral agencies, and the private sector (e.g., Gavi Board).
- **For market-shaping governance to be trusted, it needed to be as neutral as possible, especially when suppliers and buyers had conflicting policies.** Market-shaping solutions often required compromises—or changes in behavior—from private-sector, global procurement agencies and countries. Hosting Gavi within private-sector companies would have created change resistance from

¹ Group of Eight (G8) refers to the group of eight highly industrialized nations, namely Canada, France, Germany, Italy, Japan, Russia, United Kingdom, and United States.

countries that would worry the private-sector companies were taking advantage. Hosting Gavi within countries would have reduced private-sector willingness to change due to fears that countries would promote unprofitable solutions for them. Hosting Gavi within a neutral, third-party organization had some initial merits, but neutrality is challenging over time.

- **The more experimental the intervention, the more time was required for alignment-building and implementation.** WHO established its product quality assessment program within one year; market analyses were uncommon in international development in the 1990s and took years before gaining acceptance from public health stakeholders. The AMC also required years to set up, and relied on lessons learned from slow *Haemophilus influenzae* type b (Hib) vaccine and rotavirus vaccine uptake.

The following pages provide a more detailed, chronological overview of specific vaccine market-shaping interventions that may have relevance to digital markets today. While these sections contributed to the insights highlighted above, additional, case-specific learnings are called out in each section.

- **1980s: Establishment of the WHO Prequalification of Vaccines Programme** addressed a quality assurance challenge in the vaccine market that shares select features with the software market today.
- **1990s: Sharing market information to build trust** highlighted major information asymmetry challenges between vaccine suppliers and buyers, ultimately laying the groundwork for pooled procurement and AMC mechanisms. Both the wireless connectivity and software markets struggle with lack of market information, though the specific information gaps vary across markets.
- **Late 1990s: Launch of a global pooled procurement mechanism**, Gavi helped to de-risk vaccine financing, aggregate demand, and streamline procurement processes, making the L/MIC market segment more attractive to suppliers. Pooled procurement solved challenges that appear in today's software market.
- **2000s: The PCV AMC** accelerated investment in production capacity and reduced prices for L/MICs earlier in the product life cycle. The wireless connectivity market faces a challenge with lag times between when wealthy and lower-income markets access networks connectively for innovations and upgrades.

A.1 1980s: Establishment of the WHO Prequalification of Vaccines Programme

- **In the 1980s, the vaccine market expanded dramatically, creating pressure for governments to meet growing demand** (as shown in Figure A1). The eradication of smallpox in the 1970s required the public health program to reach remote corners of the world and the impact of eradication was very clear; this helped build demand. Jim Grant, a visionary leader at UNICEF during 1980-1995, elevated universal immunization to be a serious UN priority, thereby building demand among countries and spurring a historic surge in childhood immunization rates (Adamson et al., 2001). Suppliers were able to manufacture the five core vaccines—bacillus Calmette–Guérin, diphtheria-pertussis-tetanus (DPT), tetanus toxoid, measles, and oral poliovirus vaccine—for cents, so the cost to fully immunize a child was less than US\$5. The results were incredible: from 1980 to 1990, Southeast Asia and Africa went from reaching less than 10% of their children to reaching more than 70% and more than 50%, respectively.

- **Governments invested in local manufacturers of vaccines to meet demand, which at times led to dangerously low-quality products.** Governments and many others in the vaccine community did not trust private industry pricing nor reliability of supply. Many believed that local production would allow governments to assure supply, exert control over pricing, and create jobs within the local economy. However, a combination of weak national regulatory authorities, inadequate investment, and poor understanding of running a manufacturing entity resulted in the proliferation of poor-quality, ineffective, and, in some cases, dangerous vaccines (WHO, 1992).
- **Global procurement agencies became increasingly concerned about their legal and reputational risk of procuring vaccines for use in L/MICs.** Both UNICEF and the Pan American Health Organization (PAHO) Revolving Fund—the two largest purchasers of vaccines at this time—wanted to ensure efficacy, quality, and safety of the vaccines procured and distributed by UN agencies (Dellepiane & Wood, 2015). The PAHO Revolving Fund, established in 1979, aggregated demand across North and South American countries (excluding the United States) and negotiated with vaccine manufacturers to receive the ‘lowest available price’ on behalf of its member countries. UNICEF’s program was established in 1977; by 1984, it was supplying \$7.5 million worth of vaccines to more than 80 countries (Institute of Medicine, 1993).
- **In 1987, in response to UNICEF’s request, the WHO Expert Committee on Biological Standardization published its first set of requirements for vaccine prequalification.** Since its establishment in 1947, members of the Expert Committee have always been scientists from national control agencies, academia, research institutes, public health bodies, and the pharmaceutical industry (WHO, n.d.^a). This governing body had the right expertise, authority, and global credibility to advise on the efficacy, quality, and safety of the vaccines that UNICEF was hoping to procure.
- **Prequalification directly addressed UNICEF’s acute needs by initially focusing its review on consistency of production and appropriateness of manufacturing site(s).** In 1987, seven vaccines were WHO prequalified, which collectively protected against tuberculosis, hepatitis B, and yellow fever (WHO, n.d.^b). One year later, publication was revised with an expanded mandate, specifying that WHO-prequalified vaccines must be licensed and under continuous regulatory oversight by an independent and fully functioning national regulatory authority in the country where the vaccine is manufactured (Dellepiane & Wood, 2015). As WHO added vaccines to its prequalification list, UN procurement agencies would subsequently invite tenders only for WHO-prequalified vaccine suppliers.
- **When global procurement agencies, most notably UNICEF, began adhering to the prequalification list and WHO softly pressured country regulatory authorities to close low-quality suppliers, the vaccine market slowly began to consolidate.** At this time, UNICEF was the largest single purchaser of vaccine (in doses) for L/MICs, buying approximately 850 million doses annually at a price of \$65 million (Institute of Medicine, 1993). When low-quality suppliers could no longer sell to UNICEF, and their local government customer was setting untenable price ceilings, many were forced to close. Countries became increasingly reliant on vaccines supplied by international manufacturers. However, they remained uncomfortable because of an ongoing suspicion, reinforced by inconsistent pricing, that vaccine manufacturers were manipulating markets for their own profits. Countries pressured UNICEF and vaccine manufacturers to provide vaccines at ever-lower prices, despite existing prices of only a few cents per dose. UNICEF’s purchasing power allowed it to drive vaccine prices to an all-time low.

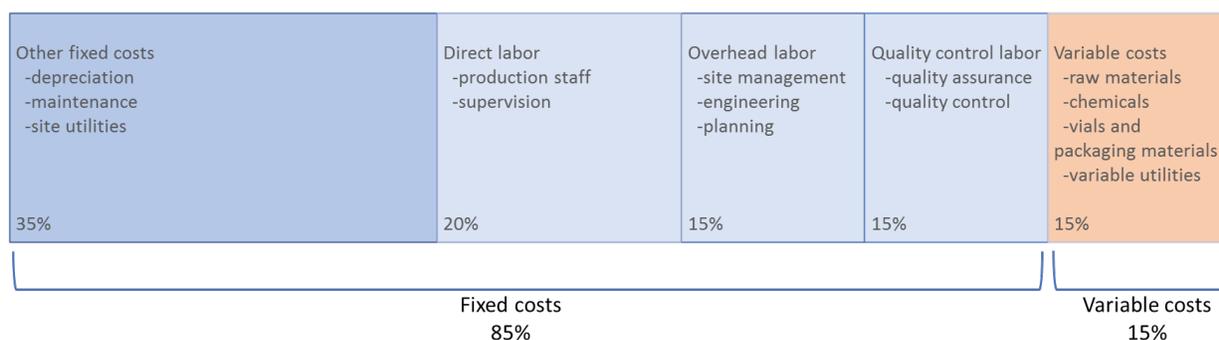
A.2 1990s: Sharing market information to build trust, laying the foundation for collaboration

- **In the 1990s, L/MIC customers continued to mistrust vaccine supplier motives, and pushed for reduced vaccine prices.** The vaccine market was now characterized by pricing tiers that varied as much as 100x between the lowest (L/MIC) and highest (US) tier prices for vaccine sales. UNICEF and the PAHO Revolving Fund each demanded the lowest-tiered price for all the countries they served. However, these agencies did not have a mechanism to increase vaccine prices for the countries transitioning to higher income levels. Wealthier countries, when they learned about the lower prices to UNICEF and PAHO, questioned why they were paying more.
- **As a result of pricing and quality pressures, the few remaining international manufacturers threatened to exit.** At this time, four vaccine manufacturers accounted for more than 70% of the market revenues and there were only 12 active international manufacturers in total (Batson et al., 2005). UNICEF's insistence on low prices did not allow these manufacturers to manage inflation well, so once-profitable price points became unprofitable. The attempts and failures to meet the needs of UNICEF procurement drove pricing fluctuations. For example, in 1992 a 23% increase over 1990 negotiated prices gave vaccine suppliers a few cents more per dose to manage inflation-induced cost increases, but raised significant concerns and eroded trust (Institute of Medicine, 1993). Relentless efforts to reduce prices by PAHO, UNICEF, and wealthier countries subsequently resulted in one major market exit and many companies warning that they could not continue to supply tens of millions of doses at the desired prices (Batson et al., 2005; Plahte, 2005).
- **The Children's Vaccine Initiative (CVI), established in 1990, provided a platform to raise awareness about vaccine supply challenges and new vaccine research and development (R&D) goals, but its mandate limited its ability to take action.** CVI was established with sponsorship from UNICEF, the United Nations Development Programme, WHO, the World Bank, and The Rockefeller Foundation. It addressed regulatory challenges, established new R&D targets, and began bringing donors together. Importantly, CVI provided a forum to widely disseminate findings from studies on vaccine economics, viability of local production, and supply changes. CVI's membership meetings, summits, and publications provided the right vehicle to share findings and ensure that information and advocacy led to change. However, CVI was limited by its awareness-raising mandate, which made it unable to execute on the findings that it disseminated and eventually led to the formation of Gavi.
- **The CVI Task Force on Situation Analysis for Vaccine Supply's documentation of vaccine production economics rebuilt trust in international vaccine manufacturer pricing and countries were willing to pay higher prices.** In 1993, UNICEF, a Task Force member, funded Mercer Management Consulting to document the underlying economic requirements and motivations of vaccine manufacturers (UNICEF, 1994). The analysis highlighted that roughly 85% of global vaccine manufacturers' expenses were fixed or semi-fixed² (see Figure A2). Thus, once a large plant was built, the average cost per dose declined as the volume of vaccine manufactured increased. However, the analysis also showed that producing tens of millions of additional doses to serve L/MICs required large additional capital investment because existing plants could not absorb the demand. Importantly, this analysis helped the public sector understand that increased production was not free. It also helped some private-sector partners explain how they could afford to supply UNICEF at a lower price.

² Labor was included as a fixed cost.

- **The cost structure confirmed that tiered pricing could be sustained as long as the lowest-tier price covered the marginal costs for the given volume of vaccines and the remaining pricing tiers covered fixed costs (Batson 1998).** The analysis dramatically changed the thinking of UNICEF and others in the public sector, helping them understand how UNICEF’s procurement of hundreds of millions of doses impacted availability and affordability of vaccines in the market. Ultimately, the study built comfort in tiered pricing models and vaccine pricing among L/MIC purchasers (UNICEF, 1994). UNICEF changed its procurement from focusing primarily on the lowest unit price to procuring for reliable supply, adequate capacity, and affordable price. The shift from lowest price to affordable prices was a very significant policy change. However, it took another ten years and the establishment of a more reliable pooled procurement and financing process before vaccine manufacturers redid manufacturing processes to take full advantage of economies of scale. And wealthier countries today continue to struggle with the tiered pricing model, particularly in the PAHO region.

FIGURE A2. TYPICAL FIXED AND VARIABLE VACCINE MANUFACTURER COSTS (ADAPTED FROM UNICEF, 1994)

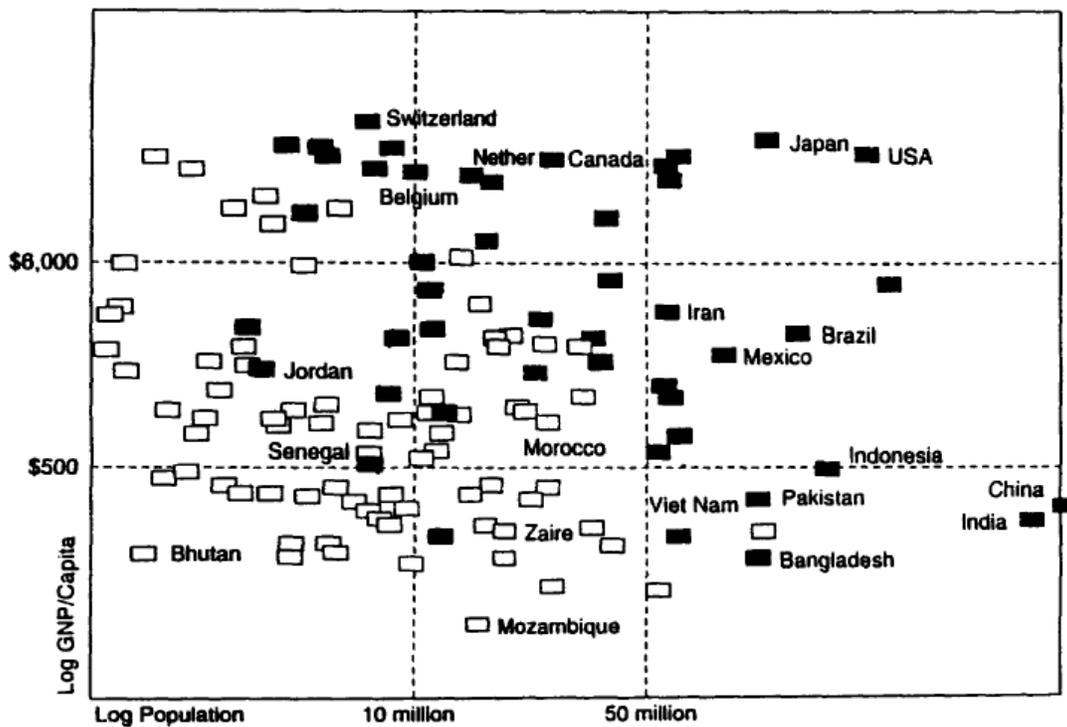


In addition to building visibility on the supply side, UNICEF recognized that strengthening demand forecasting would be critical to build vaccine supplier confidence in the L/MIC market. Suppliers had lost confidence in UNICEF’s demand forecasting, which was often inaccurate at the country level. Demand forecasting was weak for many reasons, including limited stock and demographic data rolling up from countries, a lack of supply chain data, and limited tools for analysis (e.g., global demand and supply for UNICEF was managed on a Microsoft Excel spreadsheet interpreted by a single person). While small in dollar terms, the pooled markets were for tens of millions of doses and so had a significant impact on production plans. In 1993, UNICEF identified the need for more credible demand estimates on which manufacturers could rely for their production plans (UNICEF, 1994). As partners worked to improve demand forecasts, basic issues came to light, such as the difference in forecasting against willingness to pay versus ability to pay (Batson et al., 2005). CVI’s Task Force initiated a revamp of forecasting with much-improved accuracy, building trust in the overall market for vaccine suppliers.

Tiered pricing based on purchasing power established a sustainable return on investment for vaccine manufacturers in the L/MIC market. Purchasing power was defined as a function of population size and Gross National Product per capita, based on publicly available metrics gathered and analyzed across a few UN agencies. UNICEF then classified countries into purchasing categories and identified different supply strategies for each category. This system better matched pricing with a country’s ability to pay (Batson, Evans, & Milstien, 1994). By 1994, UNICEF had also released a new strategy, which explicitly

focused its procurement on lowest prices for the poorest countries (Brooks et al., 1999). Small countries with low per-capita income were segmented into this specific category. These countries received UNICEF-procured vaccines with donor assistance. Countries with more purchasing power—driven by a large population, higher per-capita income, or both—were segmented into another category (see Figures A3 and A4). In some cases, UNICEF stopped procuring for countries in this category to uphold the tiered pricing model. These countries accessed UNICEF procurement, but financing came from national governments. UNICEF’s enforcement of the tiered pricing model sent a powerful signal to manufacturers, which had previously experienced a market with no pricing progression as countries grew in wealth. Tiered pricing, once enforced, built manufacturer confidence that they could afford to supply L/MICs. UNICEF’s pricing tiers were adopted by multiple actors, including by donors in their funding allocations, manufacturers setting their own tiered prices, and regional and local policy-setting (Brooks et al., 1999).

FIGURE A3. COUNTRY SEGMENTATION BY WORLD BANK INCOME GROUPINGS AND ESTIMATED POPULATION SIZE (BATSON, EVANS, & MILSTIEN, 1994)



Abbreviation: GNP, Gross National Product.

Note: Black boxes represent countries with local vaccine production.

FIGURE A4. STRATEGIES BASED ON COUNTRY SEGMENTATION FOR DONOR INTERVENTION IN VACCINE SUPPLY (BATSON, EVANS, & MILSTIEN, 1994)

Independent	INDEPENDENT	INDEPENDENT	INDEPENDENT
\$6000/ capita			
Services	PROCUREMENT SERVICES Provide supportive services in: - Procurement - Management - Financing	PROCUREMENT/ PRODUCTION SHARING SERVICES Evaluate feasibility of production sharing Provide supportive procurement services	PRODUCTION SERVICES Strengthen local production as necessary Strengthen quality assurance
\$500/ capita			
Financial Support	FINANCING Continue support Encourage vaccine allocation in national budget	PROCUREMENT/ PRODUCTION SHARING FINANCING Continue support Encourage vaccine allocation in national budget	PRODUCTION FINANCING Continue support Evaluate feasibility of production/ production sharing Strengthen/expand production as necessary Strengthen quality assurance
	Support Procurement	Support Production Sharing or Procurement	Support Production or Production Sharing
	10 million	50 million	

Tiered pricing was accompanied by strong advocacy to wealthier countries, which had to accept a higher price in order to offset the costs of supplying the L/MIC market. Development partners actively made the case that the value of lifesaving vaccines was worth far more than pennies per dose. The value-based argument, the social-based argument (e.g., achieving Millennium Development Goals and promoting health throughout the world), and the transparent methods for establishing the tiered structure all increased most wealthy countries' willingness to pay more. However, this willingness was not universal and tensions remain to this day, as humanitarian agencies (e.g., Doctors Without Borders) and procurement agencies (e.g., PAHO Revolving Fund) continue to advocate for receiving the lowest price.

Just as the tiered vaccine pricing model became the norm for core vaccines, a changing product landscape challenged this model and raised concerns about the pace of new product introductions. Tiered pricing worked for core vaccines because they were a global product used in both high- and low-income markets. Starting in the late 1980s and into the 1990s, pharmaceutical companies were releasing new and improved vaccines, some of which replaced the traditional core vaccines (e.g., DPT combinations that included hepatitis B and/or Hib antigens). However, these new vaccines were costlier to produce and thus much more expensive than the \$0.02 to \$0.15 prices for the traditional Expanded Programme on Immunization (EPI) vaccines. While wealthy countries immediately began switching to improved, more expensive vaccines, demand for these new products was low in L/MICs. This was partly because of higher prices but also because inadequate disease burden information in L/MICs made it difficult to prioritize 'which' vaccines to incorporate and 'when' to incorporate them. As wealthy countries switched over to the improved, more expensive vaccines, products diverged between wealthier and poorer countries. Prices increased for UNICEF because old-formulation vaccines no longer held a market in wealthy countries. The result was very slow uptake of new vaccines in L/MICs, and rising prices for old vaccines.

“It’s not just price”: Hib vaccine example

While high prices can be one cause of suppressed demand, solely focusing on pricing can mask deeper market issues. The Hib vaccine introduced in 1992 required newer, more expensive technology for production, and by 1999 still cost more per dose than the combined price in the core Expanded Programme on Immunization (Asian Development Bank, 2001). However, even when Gavi later offered it free of charge, other drivers slowed introduction into new markets. For example, a weak initial WHO position paper for Hib made countries skeptical of its value, which led to countries being unwilling to pay delivery costs even when there was no charge for the vaccine (Hajjeh, 2011). Additionally, Hib effectiveness studies were conducted only in high-income countries and governments doubted that the disease prevalence was as high in their countries. Finally, few local fora existed for immunization advocacy and policy decisions in L/MICs, making it difficult to share insights and information across countries.

A.3 Late 1990s: Launch of a global pooled procurement mechanism

In the 1990s, immunization rates stagnated in the developing world as childhood immunization was overtaken by other priorities (see Figure A1). By the start of the new millennium, children born in industrialized countries were receiving an average of 11 vaccines, including newer, more expensive vaccines like hepatitis B and Hib. In L/MICs, children generally received the same six EPI vaccines and struggled with high disease rates that were entirely preventable.

“Data isn’t everything”: Rotavirus vaccine and PCV ADIP example

Following the establishment of Gavi, countries were slow to apply to introduce new vaccines. Global policymakers were concerned that lag times in vaccine introductions between wealthy and poor countries would continue. In 2002, Gavi launched Accelerated Development and Introduction Plans (ADIPs) for rotavirus vaccine and PCV. Further investigation revealed that, as with Hib vaccine, countries struggled to understand the impact of the vaccine on disease because rotavirus is only one cause of child diarrhea, and PCV only covered certain serotypes that cause pneumonia. While the ADIPs generated powerful disease surveillance data, sophisticated lives saved forecasts, and other key advocacy pieces, the initiatives spent relatively less time understanding local country politics and contexts; earlier investment in understanding of decision-maker motivations and influencers might have resulted in reprioritization of certain analyses and accelerated country applications for the vaccines.

The introduction of new vaccines was delayed in large part due to higher vaccine prices, higher costs of delivery, and inertia. Adding new vaccines into the immunization pipeline required additional investments in the cold chain and health worker training. Vaccines including hepatitis B and Hib were largely absent from national immunization programs in most L/MICs. The immunization community was torn between focusing all its attention on increasing coverage of the basic six vaccines and introducing new vaccines. As a result of these and other factors, there was a growing gap between vaccines available to children in the poorest versus the wealthiest countries (Batson, 2005; Gavi, 2010).

A series of high-profile meetings built momentum to ensure all children had access to lifesaving vaccines. James Wolfensohn, head of the World Bank, convened a summit meeting of WHO, UNICEF, academics, health ministers, international agencies, and the pharmaceutical industry in March 1998 to

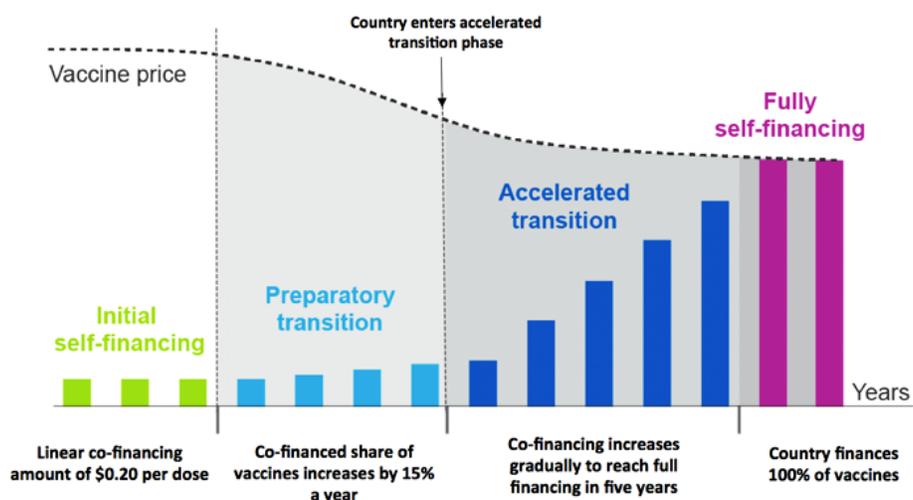
challenge leaders to find solutions to the stagnating coverage rates and slow introduction of new vaccines (Gavi, n.d.^g). In September 1998, Bill and Melinda Gates hosted a dinner for leading scientists to discuss how to overcome the barriers preventing children from receiving basic vaccines (Gavi, n.d.^g). In 1999, at a meeting in Bellagio, Italy, it was concluded (based on the findings of a working group comprised of WHO, UNICEF, the World Bank Group, the Bill & Melinda Gates Foundation, and The Rockefeller Foundation) that CVI, which throughout the 1990s had been the knowledge hub for the immunization community, should be replaced by a successor body that would be governed by its main sponsors rather than an independent entity. Sponsors would be involved at the highest levels to maximize commitment and provision of resources toward a partnership capable of generating more than any one organization could do alone (Clemens et al., 2010).

In January 2000, this partnership, the Global Alliance for Vaccines and Immunisation (now called Gavi, the Vaccine Alliance), was launched to create predictable, five-year vaccine financing for low-income markets. The launch occurred at the World Economic Forum, where many of Gavi's sponsors were regular attendees. Initially housed within UNICEF, Gavi and its funding arm, the Children's Vaccine Fund, pooled funds from bilateral, philanthropic, and private donors. The governance structure encompassed a 28-person board with representation from donors (six including the Gates Foundation), countries (five), independents (nine), partner organizations, Gavi CEO, and private-sector bodies (UNICEF, 2012). The five-year pledges improved upon annual procurement cycles that could be more volatile; five years provided stability for both countries and industry. Gavi also played a role in improving demand forecasting and prioritizing vaccine introductions, all of which built cross-stakeholder alignment and focused resources.

Gavi was designed to match donor financing with country-led demand. Countries that are eligible for support from Gavi take the lead in determining their immunization needs, applying for funding, and overseeing the implementation of their vaccination programs (Gavi, n.d.^h). Over time, Gavi changed its policy to require countries to co-fund vaccines, in part to chart countries on a course toward financial sustainability (see Figure A5). Through a 10% service delivery allocation, in-country development partners assist health ministries in strengthening and maintaining immunization delivery systems and offset the costs of expanding the immunization program.

As countries become wealthier, their co-pay increases until they become fully self-financing as a middle-income country. As per the Gavi website (Gavi, n.d.^b), "Countries co-financing obligations rise as their national income grows until they reach a threshold after which Gavi support is phased out over a five-year period. At the end of this process, countries are fully self-financing vaccines."

FIGURE A5. GAVI TRANSITION PROCESS (GAVI, N.D.^B)



Country access to Gavi resources is also conditional on ‘good behavior’ and ‘program readiness’ metrics to ensure support leads to impact. In addition to need, countries must meet a set of conditions to be eligible for funding. ‘Good behavior’ conditions include demonstrating will by directly submitting funding applications (rather than relying on partners) that commit to co-funding. Countries must additionally adhere to a strict accounting of expenditures and are subject to random audits. Finally, countries lose eligibility for certain types of support if they are behind on their co-fund payments. In terms of ‘program readiness,’ countries with poor immunization coverage can receive assistance to strengthen their immunization program, but they are ineligible to apply for new vaccines unless immunizations are reaching at least 70% of their birth cohort.

Gavi’s effective governance model allowed it to address new challenges as market conditions evolved. Gavi’s initial success led to increased bilateral donor commitments from an initial \$750 million in 1999 to more than \$1 billion in 2003 to another \$1 billion in 2006 and \$4.3 billion in 2011. To determine how to spend the additional funds, Gavi established an independent review committee of vaccine and development experts that reviewed vaccine portfolios against a series of seven criteria, highlighting vaccines whose coverage was disproportionate across socioeconomic status and gender (Gandhi, 2015). The committee recommended additional vaccines for approval by the Gavi Board. As Gavi’s mandate expanded, it evolved its policies and support to better meet its objectives.

“Effective governance enables adaptation to market changes”: PAHO Revolving Fund 2.0

Following the initial establishment of the PAHO Revolving Fund in 1979, a pooled procurement mechanism that aggregated demand across the PAHO region, diphtheria-tetanus-pertussis coverage in the region grew from 74% to 90% in ten years. However, procurement was consistently beset by policy-driven delays. These delays were due to conflicting policies between vaccine suppliers and countries. Suppliers insisted on payment before releasing goods, and many countries had a policy that required them to withhold payment until goods were received (DeRoeck et al., 2006). In 1993, PAHO’s Directing Council responded to this challenge by establishing a financing facility that provided short-term loans to governments to pay for vaccines. The short-term loan structure complied with government policies and supplier policies, and significantly reduced delays in procurement.

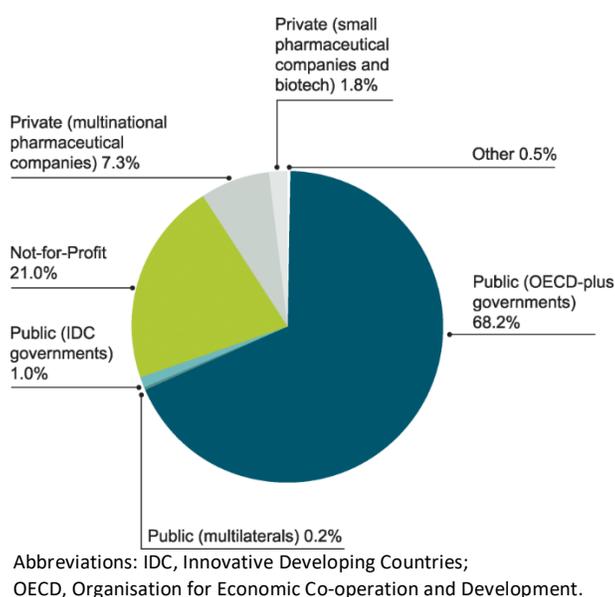
Since its inception, Gavi has become the most powerful market-shaping force in child vaccines. In 2010, the vaccines purchased with Gavi funding accounted for 5% of the value of the global market; though 5% may be viewed as small in terms of value, in terms of volume Gavi represented 30% to 70% of the total market volume in any given market (Gavi, 2011). Gavi support has contributed to the immunization of close to 640 million children, and 62 million children were immunized with Gavi-supported vaccines in 2016 alone. These vaccines resulted in the prevention of more than 9 million future deaths due to diphtheria, pertussis, hepatitis B, Hib, measles, meningitis, yellow fever, tetanus, and polio (Gavi, n.d.^d). Gavi's ability to aggregate large volumes of demand, and make that demand predictable, has prompted supply-side innovation that reduces cost per dose and enables lower prices. For example, within the first decade (2000-2010), the pentavalent vaccine against diphtheria, tetanus, pertussis, Hib, and hepatitis B dropped 18% in price (Clemens et al., 2010).

Almost 20 years after its inception, Gavi risks increasing irrelevance as high-population countries graduate. As more and more countries achieve middle-income status, the volume of vaccines procured by Gavi shrinks. The graduation of Nigeria and India to middle-income status will drastically reduce volume and thus Gavi's relevance to manufacturers. The changing nature of poverty may challenge the country-based model of providing aid; the majority of the world's poor currently reside in middle-income countries. Much as wealthier countries challenge the tiered pricing model, countries are testing the graduation model and pushing back against their price increases. Countries used to paying a price-per-dose are anchored on that price, and as their expected co-fund increases, country immunization programs struggle to articulate to more senior-level government officials why they need to reallocate budget from other areas. Additionally, countries may believe that global donors will intervene if they do not pay in full, and may test that. This ultimately has a negative impact on the poor populations of middle-income countries. The final challenge is ensuring Gavi remains relevant and value-adding to vaccine manufacturers' businesses, especially as countries graduate out of Gavi and its procurement volume decreases. Despite being the largest-volume buyer of vaccines, Gavi is *not* the most profitable customer for vaccine suppliers (the United States is).

A.4 2000s: Advance Market Commitment for pneumococcal vaccine

While market-shaping tools were increasing coverage of the core childhood vaccines, vaccine R&D remained focused on the needs of wealthy markets. The private sector perceived L/MICs as a small and risky market, and therefore commercially unviable. Consequently, there was little commercial investment to complement public-sector investment, as shown in Figure A6. This focus became more apparent in the 1990s as burden of disease diverged more dramatically between upper- and lower-income countries. In 1990, pneumonia and diarrheal disease contributed to 1.4% of disease burden in developed countries versus 17.2% in developing countries. Consequently, only 0.2% of R&D spending went toward these diseases (WHO, 1996). The Global Forum for Health Research (2004) estimated that 10% of the world's R&D investment was directed toward the diseases that affected 90% of the world's people.

FIGURE A6. LITTLE COMMERCIAL INVESTMENT TO COMPLEMENT PUBLIC RESOURCES (MORAN ET AL., 2009)



In the absence of a viable market to stimulate the development of new vaccines for diseases prevalent in L/MICs, there was a pressing need for an intervention to ensure that vaccines were developed, produced in adequate volume, and affordable and readily available for L/MICs. In 2003, the Global Health Policy Research Network at the Center for Global Development (CGD) established a working group comprising economists, lawyers, public health professionals, and public policy, pharmaceutical, and biotechnology experts, with an objective to accelerate the development of vaccines for diseases in L/MICs (Barder, Kremer, & Levine, 2005). The working group suggested various approaches (see Figure A7) and examined the AMC approach in detail after weighing the advantages against the potential risks and challenges. An AMC is an up-front, legally binding financial commitment by donors to support purchase of target vaccines for L/MICs if and when they are developed. The financial commitment is large enough to cover risk-adjusted costs of commercial investment for development of vaccines and scale-up of manufacturing capacity. The AMC can spur increased commercial investment for vaccines of interest to L/MICs, consequently accelerating the introduction of needed vaccines. Among the approaches suggested, AMC was the one approach that would simultaneously meet the goals of creating effective incentives for commercial investment in R&D, ensuring funding for rapid and affordable access to vaccines once they are developed, and creating incentives for competition among suppliers, and for further development of improved second-generation products (Barder, Kremer, & Levine, 2005).

In 2005, the CGD published *Making Markets for Vaccines: Ideas to Action* (Barder, Kremer, & Levine, 2005), which laid out a detailed framework for an AMC to bring new impetus to R&D in vaccines for diseases occurring mostly in L/MICs. This report not only helped make a compelling case for AMCs, but also outlined the steps and processes for developing a pilot. The report was highly instrumental in informing the design of the eventual PCV AMC.

FIGURE A7. SUGGESTED APPROACHES TO INCENTIVIZE COMMERCIAL INVESTMENT (BARDER, KREMER, & LEVINE, 2005)

Advance Market Commitment	Patent buyouts	Strengthened intellectual property protection
The sponsor promises to fund (fully or partially) the vaccine purchases that meet certain specified conditions.	The sponsor offers to buy patent rights to a vaccine that meets certain specified conditions, then puts the patent in the public domain and encourages competition in vaccine manufacturing.	The public sector commits to enforce or extend the intellectual property rights.
Sales tax credits	Prizes	Fast-tracked regulatory approval
The government offers a tax credit on total vaccine sales.	The sponsor offers a reward (including cash) to whoever achieves a prespecified goal.	Rewards pharmaceutical companies for developing vaccines for L/MICs by fast-tracking regulatory approval for those or for other medicines.
Patent extensions	R&D treaty	Virtual pharma
Gives a manufacturer the right to extend the patent on any product or allows for extension of the customary time period that a patent is protected.	A global treaty under which each signatory promises to devote a minimum percentage of its Gross Domestic Product to drug R&D through diverse mechanisms.	An R&D strategy in which a small management team acquires and monitors most of its R&D services from outside vendors.

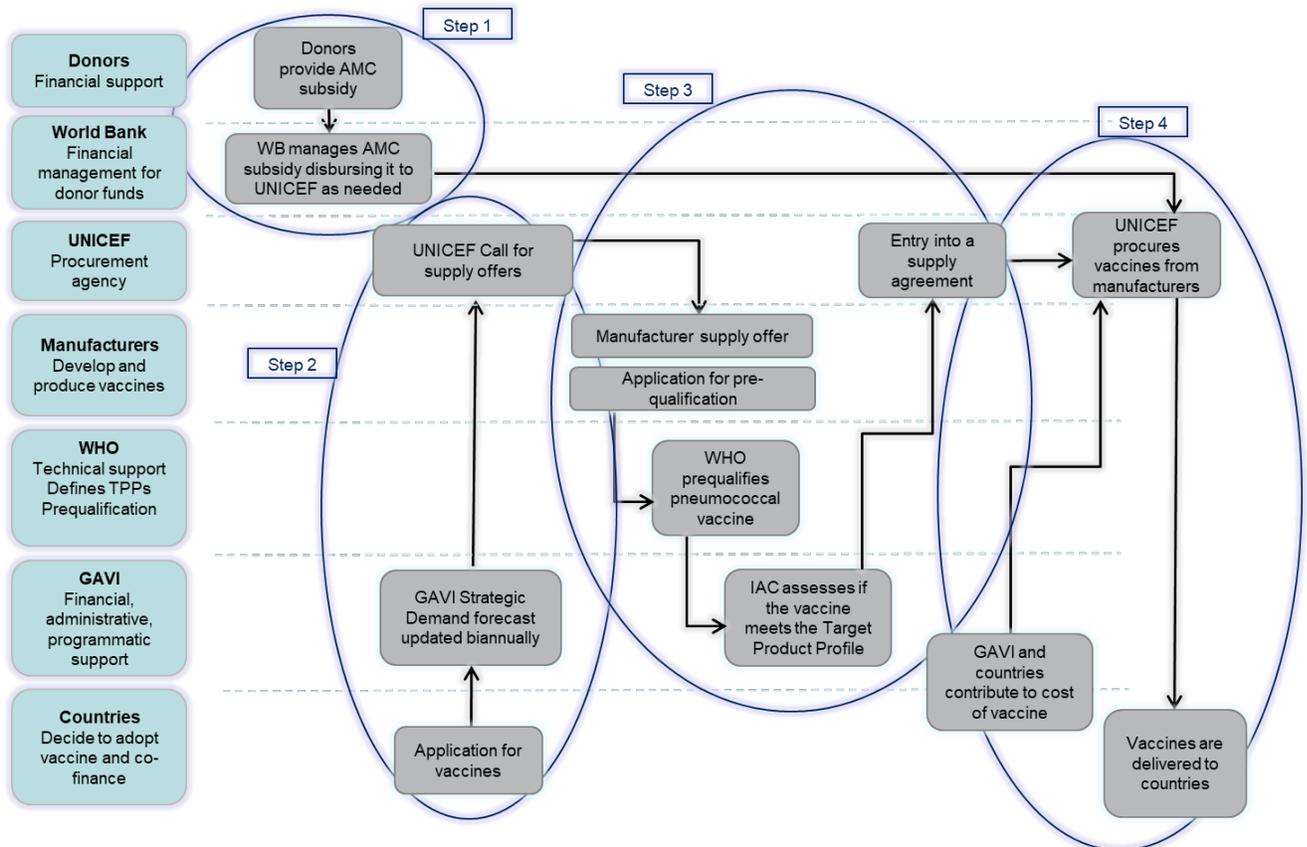
Abbreviations: L/MIC, low- and lower-middle-income country; R&D, research and development.

In the 2000s, pneumococcal disease was a leading cause of death among children younger than 5 years in developing nations, and pharmaceutical companies were not sure they could afford to manufacture doses for emerging economies, making PCV an ideal candidate for the AMC pilot. In the 2000s, pneumococcal disease, which causes pneumonia, meningitis, and sepsis, was the leading cause of death among children less than 5 years of age (approximately a million children each year), with 90% of these deaths occurring in developing nations. Though one pneumococcal vaccine did exist at that time, its formulation was not optimal against the major disease strains found in poor countries. The vaccine, manufactured by Wyeth (now Pfizer), was effective against seven strains of pneumococcus, but did not include the most common strains found in Africa and Southeast Asia. Both GlaxoSmithKline and Wyeth were completing R&D on a new PCV that would protect against pneumococcal disease in children. However, neither company was committing to investing in the additional production capacity needed to supply developing countries given the historically slow uptake of new vaccines in these countries. UNICEF's refusal to guarantee future orders made this capital investment even riskier for industry. Without an investment in capacity, supply shortages would delay vaccine introductions and even mechanisms like Gavi would be unable to reverse the standard 20-year delay between upper- and lower-income countries (BCG, 2015; USAID, 2014).

In June 2009, the PCV AMC became operational, and following advice from the CGD proposal, donors relied on existing institutions to implement the AMC. In 2006, an independent expert committee convened and recommended PCV AMC for the first AMC pilot. It was hypothesized that if these new pneumococcal vaccines were made widely available in L/MICs, they could save more than 7 million lives by 2030 (BCG, 2015). In February 2007, Canada, Italy, Norway, Russia, the United Kingdom, and the Gates Foundation committed \$ 1.5 billion to launch the first AMC, and later that year, a WHO ad hoc

expert advisory panel, in wide consultation, published a target product profile³ for PCV (BCG, 2015; WHO, 2007). An important design element for smoother rollout was engaging a diverse set of stakeholders and relying heavily on existing organizations and structures. Existing institutions were better able to manage and support the complexity of the mechanism. Donors chose Gavi to house the AMC Secretariat and administrative functions, the UNICEF Supply Division to manage the PCV procurement, and the World Bank to hold annual donor payments in a trust fund for Gavi (USAID, 2014). Long-term financing was secured via Gavi, whose independent review committee had approved PCV as a critical addition to the Gavi portfolio.

FIGURE A8. THE RELATIONSHIP MATRIX AND PROCESS BEHIND THE PCV AMC (CERNUSCHI, 2009)



Abbreviations: AMC, Advance Market Commitment; GAVI, Gavi, the Vaccine Alliance; IAC, Independent Assessment Committee; TPP, target product profile; UNICEF, United Nations Children’s Fund; WB, World Bank; WHO, World Health Organization.

³ A key strategic document that summarizes features of an intended product; it usually includes a list of features, with ‘minimum acceptable’ and ‘desired target’ described for each feature.

Figure A8 shows the PCV AMC process. Donors commit funds to guarantee the price of vaccines once developed (Gavi, n.d.^e). These financial commitments incentivize the manufacturers to invest in vaccine R&D, and to expand manufacturing capacity. In exchange, companies sign a legally binding commitment to provide the vaccines at a price affordable to L/MICs over the long term (Gavi, n.d.^e).

The most challenging aspect of the AMC was getting the pricing right. The AMC includes three features: (1) a long-term ‘target’ price that is affordable to L/MICs and covers the marginal costs of production; (2) a short-term price that gives suppliers sufficient margin to cover the capital investment required to expand vaccine manufacturing lines; and (3) a pricing structure that transparently, equitably transitions the market from the high to the low price over a specified time period (USAID, 2014). Under the AMC terms, Gavi will purchase and distribute 2 billion doses of PCV at an attractive, predetermined market price of \$7 per dose. For vaccine manufacturers to access this price, they must commit to continue to supply PCV at a price ceiling (the highest price paid by Gavi and countries after the subsidy funds are depleted/disbursed [USAID, 2014]) of \$3.50 per dose once the subsidy is fully depleted, over a ten-year period.

Partners conducted extensive modeling on the costs of production and required investment for additional capacity. Pricing was set to attract new manufacturers and to incent both low prices and large-volume manufacturing (see Figure A9). Large volumes were easier to reward; the supplier’s market share determined the overall subsidy received by that supplier. To incent low prices, per-dose subsidies increased if the manufacturer agreed to a long-term ‘tail price’ that was lower than the price ceiling. For example, if the manufacturer agreed to the maximum \$3 tail price, the short-term subsidy would be \$4 per dose. However, if the manufacturer agreed to a lower tail price of \$3.30, the short-term subsidy increased to \$3.70 per dose.

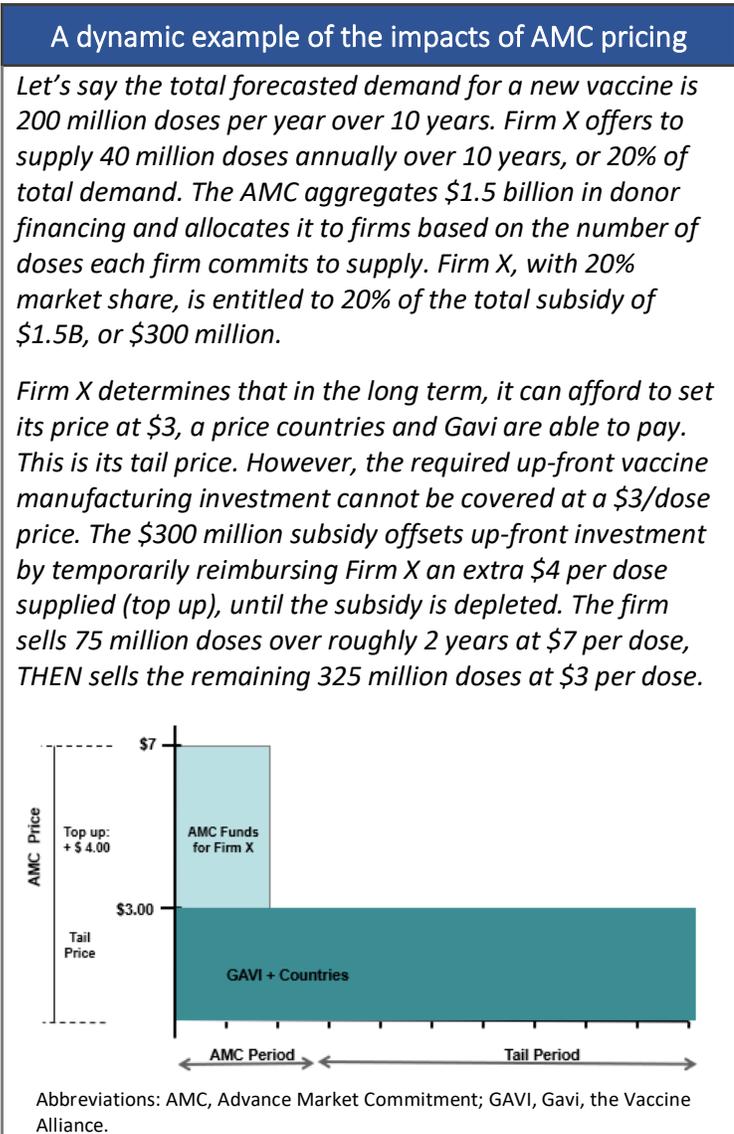
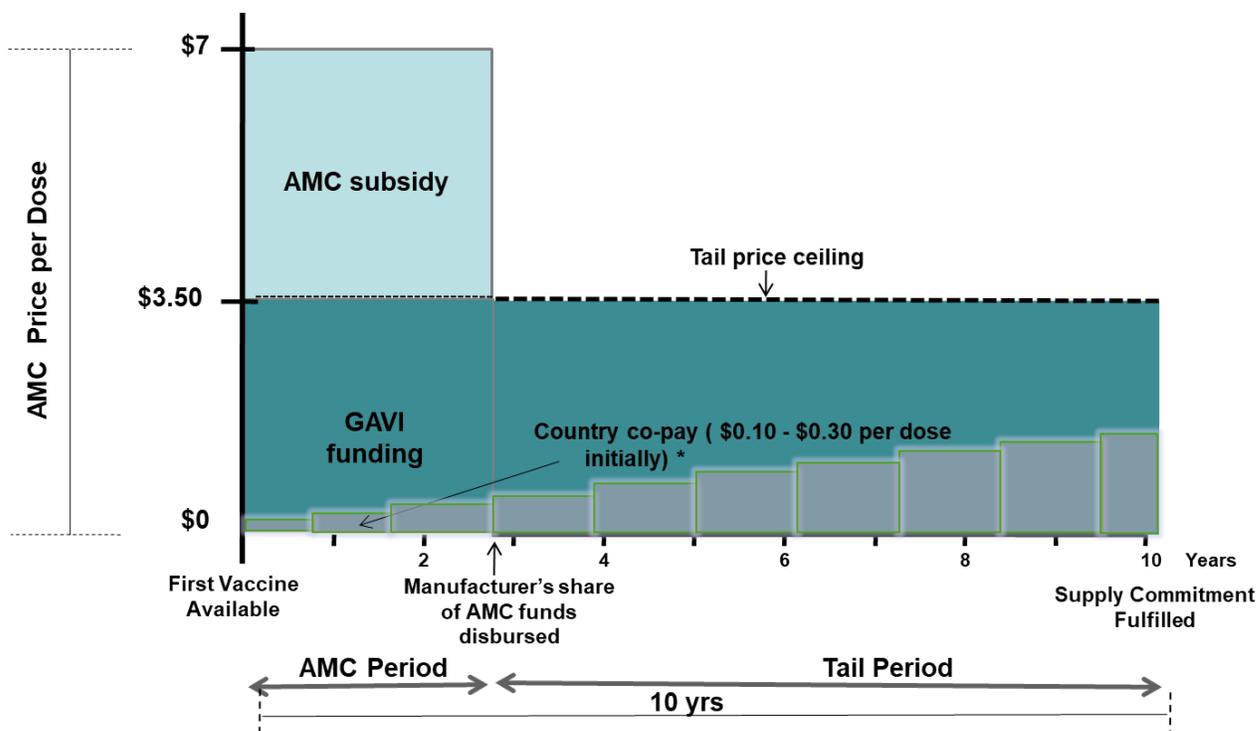


FIGURE A9. THE PNEUMOCOCCAL VACCINE AMC PRICING STRUCTURE (USAID, 2014)



* Co-financing levels will be in line with the applicable GAVI co-financing policy.

Abbreviations: AMC, Advance Market Commitment; GAVI, Gavi, the Vaccine Alliance.

The AMC pilot has been a great success, accelerating vaccine introductions across 57 countries. In December 2010, within one year of its introduction in wealthy countries, PCV was introduced in L/MICs, with Nicaragua experiencing the first rollout of the AMC (Gavi, n.d.^f). In 2015, BCG studied the achievements of the AMC pilot against its stated objectives and the overarching goal to “reduce morbidity and mortality from pneumococcal disease by accelerating the development, availability and uptake of pneumococcal conjugate vaccines” (Gavi, n.d.^e). In terms of this goal, more than 164 million doses had been procured as of December 2016 (Gavi, 2017), 49 million children were fully immunized with three PCV doses between 2009 and 2014, and 6 to 7.5 million pneumococcal disease cases were averted through 2015. PCV, through 2015, averted an estimated 230,000 to 290,000 deaths of children younger than 5 years, and it is estimated that more than 3 million deaths within this age group will be averted by 2030 (BCG, 2015). In terms of objectives, the AMC pilot had mixed results. Though it succeeded in accelerating the development timelines of manufacturers in later-stage development, the companies with earlier-stage candidates faced significant technical and regulatory challenges. On a positive note: the PCV AMC pilot proved that there is a large L/MIC market for manufacturers; it brought forward the availability of effective PCV for L/MICs; and it accelerated vaccine uptake by ensuring predictable vaccine pricing for L/MICs. It is important to note that complementary forces to the AMC, such as Gavi and WHO recommendations, proved vital for creating the enabling environment necessary for its success.

APPENDIX A.1: TIMELINE OF MARKET-SHAPING ACTIVITIES IN THE VACCINE MARKET

Year/Period	Description	Program
1974	The World Health Organization (WHO) established the Expanded Programme on Immunization (EPI), with the goal of developing and expanding immunization programs globally.	EPI
1979	The Pan American Health Organization (PAHO) initiated a US\$1 million Revolving Fund to provide timely access to EPI vaccines, vaccine supplies, and equipment by aggregating demand across the region and negotiating a lower price with manufacturers.	PAHO Revolving Fund
1981	The WHO Expert Committee on Biological Standardization published its first guideline on national control of vaccines, recommending the establishment of a national regulatory authority for all countries.	WHO Prequalification
1987	The United Nations Children’s Fund (UNICEF) requested WHO’s Expert Committee to advise on the efficacy, quality, and safety of the vaccines that UNICEF was hoping to procure.	WHO Prequalification
1990	The Children’s Vaccine Initiative was established with sponsorship from UNICEF, the United Nations Development Programme, WHO, the World Bank, and The Rockefeller Foundation to collaboratively solve increasing vaccine supply challenges.	Children’s Vaccine Initiative
1991	UNICEF established the Vaccine Independence Initiative by helping countries become more independent in financing and procuring vaccines, which freed up donor funding that could then be allocated to new vaccine introductions.	Vaccine Independence Initiative
1993	PAHO’s Directing Council established a short-term financing facility that allowed governments to borrow to pay for vaccines.	PAHO Revolving Fund
1994	UNICEF released the first study by the immunization community on vaccine economics, which established a common language and principles to lay the groundwork for future market-shaping initiatives.	Vaccine economics
1998	James Wolfensohn, head of the World Bank, convened a summit meeting of WHO, UNICEF, academics, health ministers, international agencies, and the pharmaceutical industry (Gavi, n.d. ⁸).	Gavi
1999	A meeting in Bellagio, Italy, concluded (based on working group studies drawn from WHO, UNICEF, the World Bank Group, the Bill & Melinda Gates Foundation, and The Rockefeller Foundation) that the Children’s Vaccine Initiative should be replaced by a successor body that would be governed by its main sponsors (Gavi, n.d. ⁸).	Gavi
2000	Gavi was officially launched at the World Economic Forum in Davos, Switzerland.	Gavi
Early 2000s	The Advance Market Commitment (AMC) gained traction among policymakers as a means of incenting private-sector research and development—or capital investment—to research, develop, and produce novel global health products.	AMC

Year/Period	Description	Program
2005	<p>In April 2005, the Center for Global Development provided a blueprint for creating an AMC, and was highly instrumental in informing the design of the eventual pneumococcal conjugate vaccine (PCV) AMC.</p> <p>In December 2005, the Italian minister of economy and finance, Giulio Tremonti, presented the report, <i>Background Papers to Advance Market Commitments for Vaccines: A New Tool in the Fight Against Disease and Poverty</i> (Gavi, n.d.^f).</p>	AMC
2007	<p>In February 2007, Canada, Italy, Norway, Russia, the United Kingdom, and the Bill & Melinda Gates Foundation committed \$1.5 billion to launch the first AMC to help speed the development and availability of a new PCV to target pneumococcal disease, a major cause of pneumonia, meningitis, and sepsis (Gavi, n.d.^f).</p> <p>In November 2007, UNICEF declared its interest in operating as procurement agent for the AMC.</p>	AMC
2009	<p>In June 2009, the AMC pilot project against pneumococcal disease became operational.</p>	AMC
2010	<p>In March 2010, GlaxoSmithKline and Pfizer made long-term commitments to supply new vaccines against pneumococcal disease (Gavi, n.d.^f).</p> <p>In December 2010, within one year of its rollout in wealthy countries, PCV was rolled out in Nicaragua, a lower-middle-income country.</p>	AMC

LIST OF ABBREVIATIONS

ADIP	Accelerated Development and Introduction Plan
AMC	Advance Market Commitment
BCG	The Boston Consulting Group
CGD	Center for Global Development
CVI	Children’s Vaccine Initiative
DPT	class of combination vaccines against diphtheria, pertussis, and tetanus in humans
DTP3	diphtheria-tetanus-pertussis
EPI	Expanded Programme on Immunization
Gavi	Global Alliance for Vaccines and Immunisation; Gavi, the Vaccine Alliance
GNP	Gross National Product
Hib	<i>Haemophilus influenzae</i> type B
IAC	Independent Assessment Committee
IDC	Innovative Developing Countries
L/MIC	low- and lower-middle-income country
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan American Health Organization
PCV	pneumococcal conjugate vaccine
R&D	research and development
TPP	target product profile
UN	United Nations
UNICEF	United Nations Children’s Fund
US	United States
USAID	United States Agency for International Development
WB	World Bank
WHO	World Health Organization

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